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Nitro-Assisted Brønsted Acid Catalysis: Activation of C(sp^3)–O and C(sp^3)–F Bonds

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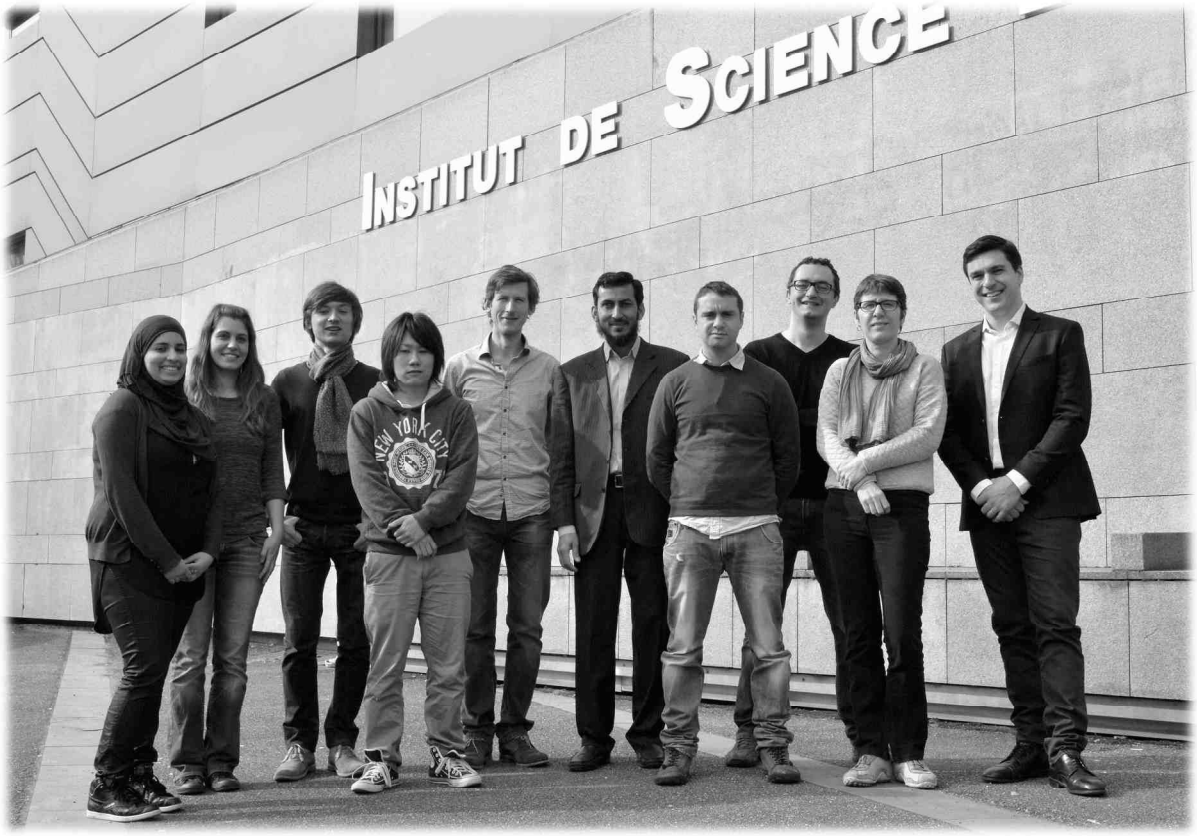
«Nearly everything is really interesting if you go into it deeply enough.”
– Richard Feynman



The Laboratory of Chemical Catalysis (March 16, 2015) enlightens this otherwise unused page.

Acknowledgements

No one knows what is going to happen with a young PhD student who is about to join an organic chemistry research group that did not exist yesterday. In this situation, the high level of curiosity and an ambition to prove yourself mixes with the uncertainty about chemistry working out properly. This was the feeling when my journey in the Laboratory of Chemical Catalysis started about 3 and a half years ago and now it feels like that was the best opportunity I've been given so far.

Meeting Joseph was, of course, the rate-determining step. Inspired by his enthusiasm about chemistry and his personal charisma, I readily decided to stop my searching elsewhere and join a mysterious adventure of starting up a new chemistry lab with him. Looking back to that time, now it is a pleasure to see the success of our project, as from an empty laboratory with preliminary research plan we grew up to the fully equipped lab which is able to produce first class results.

All throughout my PhD, Joseph was a thoughtful supervisor with very soft pedagogical methods. To his credit, despite the well-known fact that fast and exciting results are highly desirable straight away at the early life-stage of a young research laboratory, he encouraged me to also spend time on complementing our studies with my own tentative ideas and learn from their results. Often at the end of our frequent discussions about chemistry, I wanted just get straight to the lab and try that guess on practice. Guiding me when suggestion was necessary, he helped me to grow up personally and scientifically, challenged my intellect and provided me with the tools to answer the questions. This longstanding cooperation has resulted in a high level of involvement in what we were doing for the past years and now I wish to be able to transfer this outstanding experience in my future projects. For the rest of science, our published, as well as upcoming research is a testimony to collective work.

Outside of the Laboratory of Chemical Catalysis, I was willing to maximize my scientific experience and have been lucky to acquire knowledge from, be an invited attendee and speaker at the group seminars of other research laboratories. In this regard, I wish to thank Prof. Sauvage, Prof. Lehn, Prof. Ebbesen and Dr Klymchenko for allowing me to have these interactions, for sharing thoughts and delivering suggestions. Importantly, the outcome of this experience has been marked by our scientific collaborations with the groups of Dr Cecchini (Joel) and Prof. Ebbesen (Jino and Atef).

Before going into the detail, as the deepest memory of my PhD, "tous simplement", I want to say "Thank you, Strasbourg". Although I have briefly visited cities on the five continents, Strasbourg is so far the best place I have ever stayed for a while. He met me with the rainy autumn, cold winter and grilling summer at first so I was afraid that we would never get along. But then, easy and naturally, I discovered so many aspects of this lovely town: walking all the beautiful and safe streets, crossing the Cathedral almost every evening on my way home from the lab, spending calm time next to the channel on Quai Desaix and Petite France. My stay within his borders was often accompanied with music, delicious food and tasteful Alsatian wine. For the best, I thank Strasbourg for an opportunity to meet and work with many nice people, who are now my colleagues and friends.

Thus, working with the competent colleagues, who become also your friends, was always what I wanted. In this context, Edward (St Andrews), in addition of being a perfect lab mate, will stay in my memory as a nice friend, excellent beer/whisky drinker as well as a true advocate of Bruce Springsteen's music. His contribution to proofreading this manuscript deserves a particular acknowledgement.

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lines, my dealing with occasional difficulties, including the résumé in French of this thesis, would be hard to imagine without her support and open willing to help.

Otherwise, I was lucky to work in a team of dedicated researchers, with whom we were able to dilute the seriousness of our academic pursuits by much fun. Florian (Karlsruhe), Leandro (La Laguna), Malik (Strasbourg), Ismat (Islamabad) made the routine life days and evenings in the lab full of memorable stories, while making experiments.

A new generation of postdocs and PhD students, Kamila (Edinburgh), Vuk (Strasbourg) and Sreejith (Pune), were my lab mates for only 6 months or less, but already created confidence that laboratory will carry on in good hands. On the top of it, I am sure that this refreshed team will enrich the group with new traditions and cultures after my leave.

Among others, I had a chance to work with, and often learn from, a group of motivated master and visiting students: Kazuki, Junya, Nour, Anaëlle and Jing have marked their intriguing, although short, stays in the group with the high degree of dedication. Margot and Guang, M2 and M1 students at their time, up until now stay the good friends with us, illuminating the group with their kind and interesting personalities.

The names I have mentioned above belong to those with whom the interactions during my PhD thesis were the strongest: sharing projects, scientific discussions, travelling the world and simply enjoying time together outside of the work regularly. Nevertheless, I was lucky to have made outstanding friendships and ties with many others in ISIS, whose names it is my pleasure to mention here: De Cola group (Youssef, Claire, Dedy, Ricardo, Eko), Hermans group (Akihiro and Vincent), Lehn group (Jack, Martin, Jan, Tum, Jean-Louis, Ghislaine, Lutz, Nema), Samori group (Mirella and Alessandro), Torbeev group (Vladimir and Régis). I am grateful to Muriel and Nathalie, who did a lot to make my routine life in ISIS to be a pleasant adventure.

Although by the middle of my PhD I had already fallen in love with France, my Ukrainian heart would feel a bit cold if not experiencing the warmth of my Ukrainian friends from all over the world: I will not be able to list all of you, who made my homeland a bit closer to me at the moments of joy and nostalgia, but here are the people with whom I enjoyed time from the early stage of my scientific endeavors and up until nowadays: Iuliia (Strasbourg), Andrey (Groningen), Roma (Darmstadt), Marianna (Strasbourg), Igor (Paris polytechnique), Igor (Kyiv), Ilya (Kyiv).

Maybe also beyond the scope of these acknowledgements, I would like to mention people outside of research with whom I was lucky to made a close friendship and who often accepted me in their routine life to share thoughts and ideas (Nina, Elvira, Anne, Masako, Alexander). My closest friend of this time, Dima (Novosibirsk), often made me feel lucky for his presence in my daily life. My spatial appreciation is dedicated to Minako Yashiro for her almost 3 years-long support from overseas, an experience that proved to be determining in my life.

Much more could be said, but none of this would be possible without my parents, Alla and Eugen, and my grandparents, Katya and Grygoriy, who, despite having only one (grand)son in the family, left me free to pursue my scientific endeavors abroad. With my deepest gratitude, I want Vika and her husband Sasha to appear on the pages of this manuscript, as their house has been a second home since my early childhood, and they did more than enough for me to become my family. I love you.

Nitro-Assisted Brønsted Acid Catalysis: Activation of C(sp^3)–O and C(sp^3)–F Bonds

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List of abbreviations

Å	angström(s)	4-DMAP	*N*,*N*-dimethyl-4-aminopyridine
Ac	acetyl	DMF	dimethylformamide
ACS	American Chemical Society	DMSO	dimethyl sulfoxide
AcOH	acetic acid	DPPA	diphenyl phosphoryl azide
acac	acetylacetone	dppf	1,1'-bis(diphenylphosphino) ferrocene
aq.	aqueous	dr	diastereomeric ratio
Ar	aryl	ε	dielectric constant
B3LYP	Becke-3-Lee-Yang-Parr	E	*Ger.*, engegen; electrophile
BDE	bond-dissociation energy	ee	enantiomeric excess
Bmim	1-butyl-3-methylimidazolium	equiv	equivalent
Bn	benzyl	EI	electron impact
Boc	*tert*-butylcarbonate	ESMS	electrospray mass spectrometry
BzOH	benzoic acid	Et	ethyl
°C	degree Celsius	g	gram(s)
cat	catalytic quantity	GCMS	gas chromatography mass spectrometry
Cbz	carboxybenzyl	h	hour(s)
cod	1,5-cyclooctadiene	H-bond(ing)	hydrogen bond(ing)
const	constant	HFIP	1,1,1,3,3,3-hexafluoro-2-propanol
CSD	Cambridge Structural Database	HPLC	high-pressure liquid chromatography
DABCO	1,4-diazabicyclo[2.2.2]octane	HRMS	high-resolution mass spectrometry
DAST	diethylaminosulfur trifluoride	Hz	Hertz
ddpm	1,1-bis(diphenylphosphino) methane	*i*	iso
DCE	1,2-dichloroethane	IR	infrared
DCM	dichloromethane	k	reaction constant
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone		
DEAD	diethyl azodicarboxylate		
DFT	density functional theory		
DMA	dimethylacetamide		

L	liter	quant.	quantitative
LA	Lewis acid	r_W	van der Waals radius
LCMS	liquid chromatography mass spectrometry	r.t.	room temperature
		s	second(s)
μ	micro	sat.	saturated
m	meta	S_N1	nucleophilic substitution unimolecular
M	molar; metal		
Me	methyl	S_N2	nucleophilic substitution bimolecular
mg	milligram		
min	minute(s)	*tert*	tertiary
mL	milliliter	TBDMS	*tert*-butyldimethylsilyl
mmol	millimol	TBDPS	*tert*-butyldiphenylsilyl
mp	melting point	temp.	temparature
MS	molecular sieves	TES	triethylsilyl
MsOH	methanesulfonic acid	TFA	trifluoroacetic acid
MW	microwave	TfOH	trifluoromethanesulfonic acid
n	“normal”; straight chain	Troc	trichloroethyl chloroformate
Bu	butyl	THF	tetrahydrofuran
Nu	nucleophile	TIPS	triisopropylsilyl
NMR	nuclear magnetic resonance	TLC	thin layer chromatography
o	ortho	TMS	trimethylsilyl
p	para	TPP	tetraphenylporphyrin
p-NBSA	4-nitrobenzenesulfonic acid	TPPMS	sodium diphenylphosphinolbenzene-3-sulfonate
PCy_3	tricyclohexylphosphine		
PFPAT	pentafluorophenylammonium triflate	Ts	tosyl, *p*-toluenesulfonyl
		TS	transition state
Ph	phenyl	TsOH	*p*-toluenesulfonic acid
PivOH	pivalic acid	xantphos	4,5-bis(diphenylphosphino)-9,9-dimethylxanthene
PIFA	[bis(trifluoroacetoxy)iodo] benzene		
PMB	4-methoxybenzyl	wt%	percentage by weight
PMIm	1-methyl-3-pentylimidazolium	X	heteroatom or pseudohalide
		χ	electronegativity
PNP	4-nitrophenol	*Z*	*Ger.*, zusammen

Résumé

Résumé

Cette thèse, divisée en 5 chapitres, décrit le développement d'un système catalytique général et doux à l'aide d'un acide de Brønsted pour adresser les limitations clés dans la transformation d'alcools π-activés et aliphatiques, aussi bien que dans la transformation des composés fluorés aliphatiques tertiaires et révèle la nature complexe de la catalyse acide en solution où des co-catalyseurs nitro sont capables d'accélérer la catalyse par un acide de Brønsted.

CHAPITRE 1

Pour répondre à la demande constamment croissante de transformations catalytiques fortement efficaces, les alcools ont longtemps été considérés comme des partenaires électrophiles attractifs pour la substitution nucléophile directe puisque l'eau libérée est, en principe, le seul sous-produit de la réaction en présence de nucléophiles protiques. Traditionnellement, la substitution nucléophile d'alcools est réalisée soit par une pré-fonctionnalisation supplémentaire du groupement hydroxyle ou par ionisation dans des solutions concentrées d'acides minéraux forts. Au cours de la dernière décennie, les alcools π-activés (des substrats portant un π-système; c'est-à-dire un groupement aryle, alcène, alcyne ou la combinaison de cela) ont pu être, avec succès, couplés avec des nucléophiles réagissant à travers l'atome de carbone ou l'hétéroatome à l'aide de quantités substœchiométriques d'acides de Brønsted ou d'acides de Lewis.

Bien que de bons rendements synthétiques aient été obtenus avec certains catalyseurs, la portée des transformations exécutées par un catalyseur donné reste en grande partie limitée à certaines classes de nucléophiles et aux alcools π-activés. Les combinaisons réussies de substrat/catalyseur/nucléophile/solvant doivent toujours être révélées expérimentalement par une sélection avisée et souvent laborieuse pour permettre la réactivité désirée. Ainsi, la découverte d'un ensemble général de conditions pour les réactions de substitution des classes diverses d'alcools activés et non-activés avec une variété de bons et de moins bons nucléophiles reste fortement élusive. A nos yeux, un système catalytique permettant la réactivité générale des alcools, devrait respecter les critères énoncés ci-dessous (Figure 1).

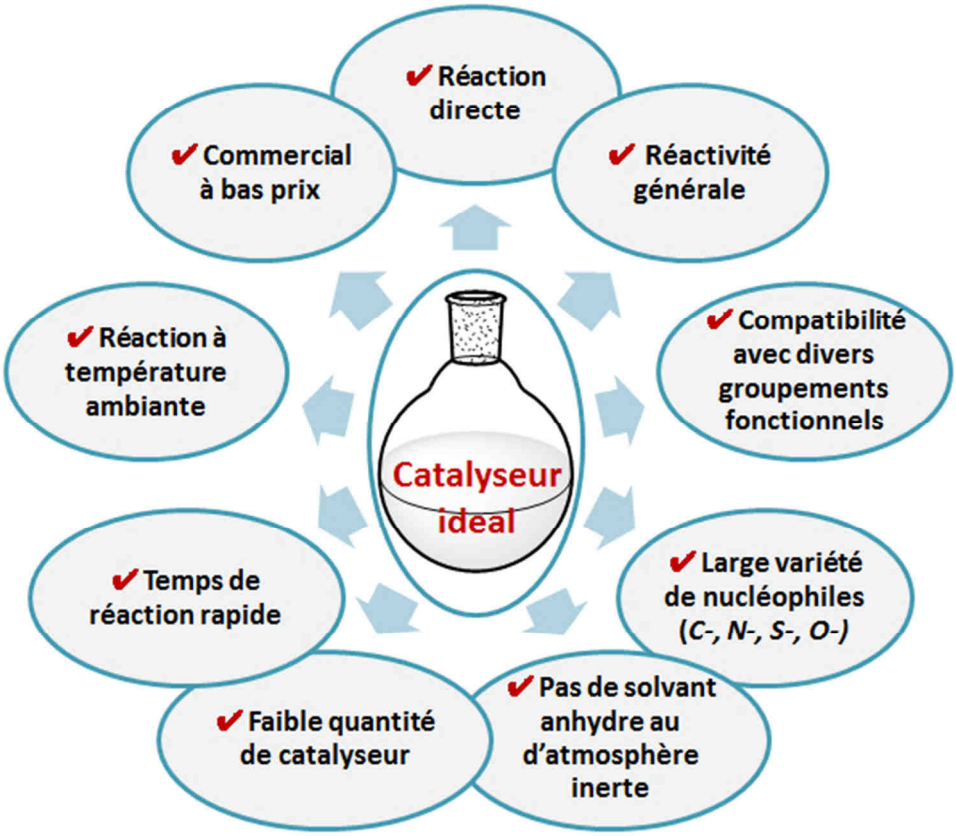


Figure 1. *Représentation graphique de l'efficacité désirée du catalyseur idéal pour l'activation d'alcools.*

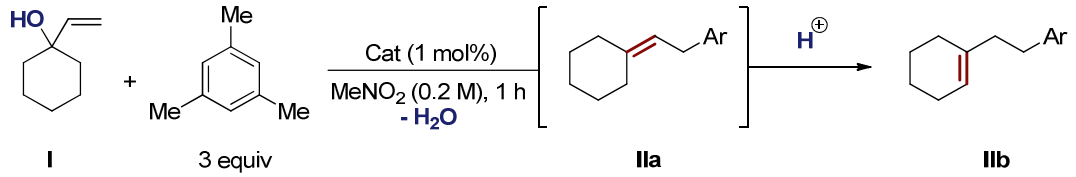
La recherche d'un système catalytique idéal pour résoudre le problème de la limitation clé dans le domaine est détaillée dans les chapitres 2 à 4 de cette thèse.

CHAPITRE 2

Dans le chapitre 2, nous abordons le problème du compromis entre la réactivité et la chimiosélectivité dans les transformations déshydratantes d'alcools π-activés. L'investigation du caractère chimiosélectif/réactivité du catalyseur testé a été conduite dans la réaction test de Friedel-Crafts intermoléculaire entre l'alcool allylique **I** et le mésitylène comme nucléophile où le ratio des régioisomères **IIa/IIb** formés au cours de la réaction a été étudié en parallèle du rendement global de la réaction (Table 1). Dans ce système, le composé alcène exocyclique **IIa** initialement formé a tendance à s'isomériser pour former l'alcène endocyclique **IIb** thermodynamiquement favorable en présence d'un acide de Brønsted fort, qui est potentiellement produit par l'hydrolyse du catalyseur par l'eau qui est un sous-produit stœchiométrique ou par l'alcool lui même. Une vue générale systématique de différents

acides de Brønsted et d'acides de Lewis a révélé que le catalyseur trispentafluorophényleborane hydraté $B(C_6F_5)_3 \bullet H_2O$ dans le nitrométhane est un système catalytique idéal dans les réactions de substitutions nucléophiles d'alcools.

Table 1. *Criblage de catalyseurs pour l'activation chimiosélective de l'alcool* ***I***.



I 3 equiv **IIa** **IIb**

Entrée	*Catalyseur*	*T, (°C)*	*Rendement[a] IIa + IIb, (%)*	*Ratio IIa/IIb*
1	none	80	<5	N/A
2	TfOH	80	77	1:10
3	HBF_4	80	88	1:9
4	H_2SO_4	80	78	1:5
5	*p*-TsOH	80	74	4:1
6	TFA	80	68	>20:1
7	$Ca(NTf_2)_2/Bu_4NPF_6$	80	74	1:9
8	$Bi(OTf)_3$	80	83	1:12
9	$Sc(OTf)_3$	80	83	1:9
10	$Yb(OTf)_3$	80	62	4:1
11	$FeCl_3$	80	82	1:3
12	$AuCl_3$	80	85	6:1
13	BF_3•THF	80	82	1:10
14	$B(C_6F_5)(OH)_2$	80	<5	N/A
15	BPh_3	80	<5	N/A
16	$B(C_6F_5)_3 \bullet H_2O$	80	92	>20:1
17	$B(C_6F_5)_3 \bullet H_2O$	22	60	>20:1
18[b]	**$B(C_6F_5)_3 \bullet H_2O$**	**22**	**77**	**>20:1**
19	TfOH	22	47	2:1
20	*p*-TsOH	22	32	>20:1
21	TFA	22	<5	N/A

[a]Rendement isolé. [b]Temps de réaction étendu à 4 h.

$B(C_6F_5)_3 \bullet H_2O$ dans le nitrométhane représente un excellent compromis entre forte réactivité et forte chimiosélectivité dans la réaction de substitution déshydratante d'alcools: une gamme de substrats π-activés a été couplée avec succès à une variété de nucléophiles de type *C*-, *N*-, *S*- et *O*- (Schéma 1, a). De plus, les nucléophiles portant un groupement protecteur de type éther silylé (Schéma 1, b) ainsi que des alcènes, habituellement sensibles aux conditions acides, se sont avérés tolérants aux conditions standards.

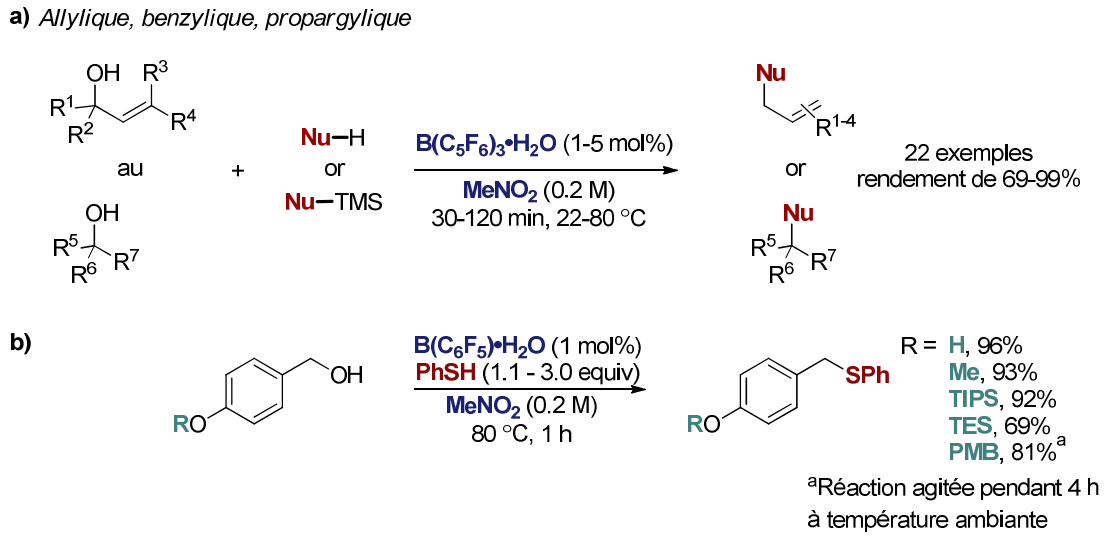


Schéma 1. *Catalyse par $B(C_6F_5)_3$•H_2O dans le nitrométhane permettant la substitution chimiosélective d'une large gamme d'alcools π-activés.*

De plus, l'effet drastique du solvant dans ces transformations a été noté. Le nitrométhane a démontré son efficacité et s'est avéré crucial dans nos futures investigations.

CHAPITRE 3

Dans le chapitre 3, avec le système catalytique puissant découvert précédemment, nous nous intéressons aux alcools aliphatiques tertiaires particulièrement difficiles à activer. Les défis d'une substitution catalytique substœchiométrique douce d'une telle classe de substrats incluent l'ionisation difficile formant le carbocation qui conduit rapidement à l'alcène stable ainsi que la plus forte basicité des alcools aliphatiques tertiaires comparés aux alcools π-activés. Des quantités substœchiométriques de $B(C_6F_5)_3$•H_2O dans le nitrométhane ont démontré, de manière efficace, qu'une large variété d'alcools aliphatiques tertiaires a pu être activée avec succès dans des réactions d'alkylation de type Friedel-Crafts ainsi que dans des réactions de thiodéshydratation avec une gamme d'arènes riches en électrons et de thiols respectivement (Schéma 2).

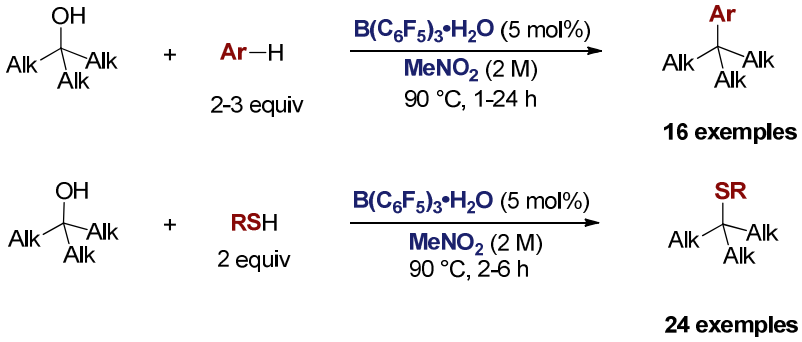
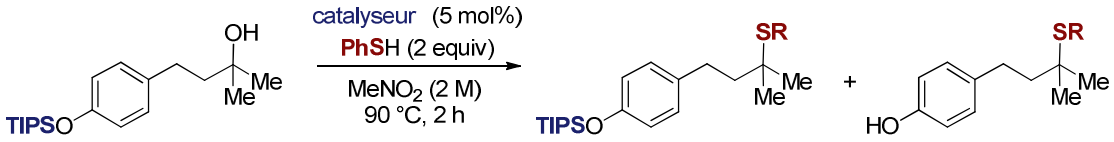


Schéma 2. *Catalyse par $B(C_6F_5)_3•H_2O$ dans le nitrométhane permettant l'utilisation substœchiométrique dans la substitution d'alcools tertiaires aliphatiques.*

Encore une fois, en contraste avec l'activation par des acides de Brønsted ou par des acides de Lewis communément utilisés, $B(C_6F_5)_3•H_2O$ en présence de nitrométhane, permet la réactivité désirée tout en préservant une chimiosélectivité envers des fonctions habituellement sensibles aux conditions acides (Table 2).

Table 2. *Comparaison de $B(C_6F_5)_3•H_2O$ avec d'autres catalyseurs pour la réaction de thiodéshydratation chimiosélective dans le nitrométhane.*



III **IV** **V**

Entrée	*Catalyseur*	*Rendement GC IV*	*Rendement GC V*
1	$B(C_6F_5)_3•H_2O$	92 (77)[a]	<5
2	TfOH	35	59
3	H_2SO_4	58	32
4	TsOH	58	7
5	TFA	49	<5
6	$FeCl_3$	65	23
7	$AuCl_3$	<5	<5
8	$Sc(OTf)_3$	39	54
9	$Bi(OTf)_3$	13	24
10	$Ca(NTf)_2/Bu_4NPF_6$	20	77
11	$B(C_6F_5)(OH)_2$	<5	<5

[a]Rendement isolé après une colonne chromatographique sur gel de silice.

CHAPITRE 4

Dans le chapitre 4, nous détaillons un effet co-catalytique sans précédent entre des composés nitro et le catalyseur $B(C_6F_5)_3•H_2O$ dans la réaction d'azidation d'alcools aliphatiques tertiaires, permettant ainsi, pour la première fois, un turnover catalytique. En plus de l'utilisation de quantités substœchiométriques de catalyseur, ces conditions ont montré leur efficacité envers de nombreux substrats. Dans nos investigations préliminaires, l'effet du solvant sur le résultat de la réaction a clairement souligné la réactivité supérieure de la réaction d'azidation dans le nitrométhane (Figure 2): bien qu'une quantité non négligeable d'azide **VIII** (<10%) a été détéctée dans les solvants DCM et DCE, tous les autres solvants communs polaires et apolaires testés (du benzène au DCM dans le tableau ci-dessous) n'ont pas abouti au composé attendu ou ont abouti au composé intermédiaire silylé **VII** comme unique produit de la réaction. En outre, l'aspect curieux supplémentaire de l'effet de solvant a été observé, quand tous les cinq autres solvants nitro ont abouti à la haute conversion de l'alcool **VI** formant l'azide **VIII** correspondant, malgré le fait que, dans certains cas, la constante diélectrique était beaucoup plus basse de celle du nitrométhane.

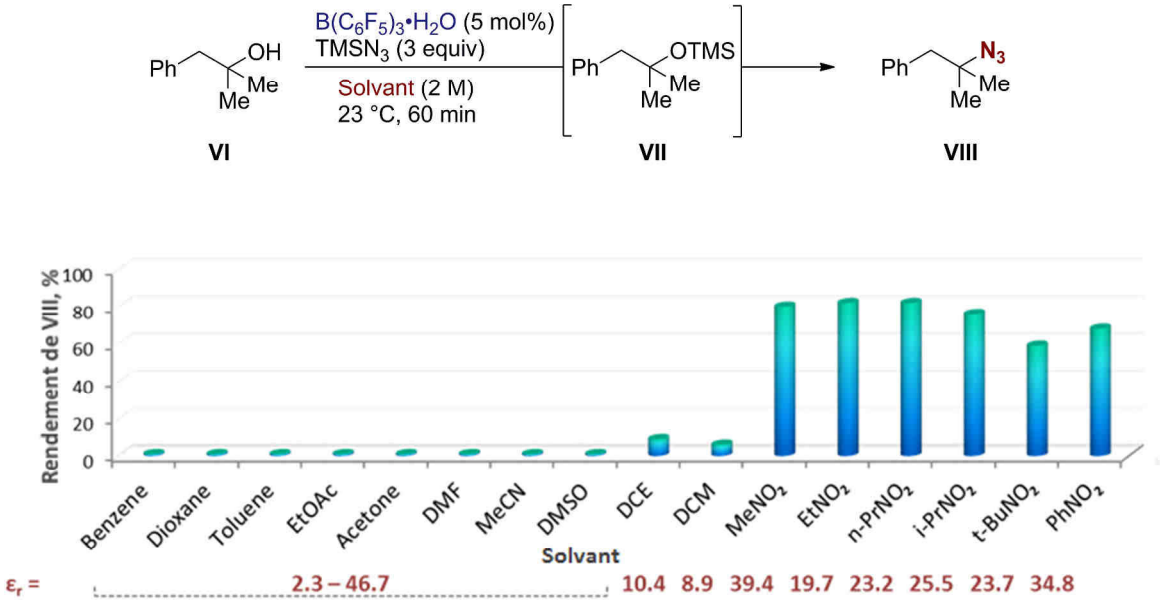


Figure 2. *Criblage de solvants pour la réaction d'azidation.*

Bien que la réactivité particulière dans le nitrométhane ne pourrait être initialement que vu comme étant la résultante d'un effet de solvant, des études cinétiques ont montré que le nitrométhane incite un changement de dépendance de concentration de premier ordre de

l'acide de Brønsted à une dépendance de deuxième ordre de l'acide de Brønsted ainsi qu'une dépendance de deuxième ordre des composés nitro. Cela démontre que le composé nitro est en fait un co-catalyseur et induit un changement de dépendance de concentration de l'acide de Brønsted.

Une étude de la vitesse initiale de la réaction d'azidation du composé éther de silyle **IX** comme une fonction du co-catalyseur nitro (100 mol %) dans le benzène, montre que les nitrobenzènes qui sont riches en électrons ont un plus grand effet sur la vitesse de la réaction que les analogues pauvres en électrons (Figure 3).

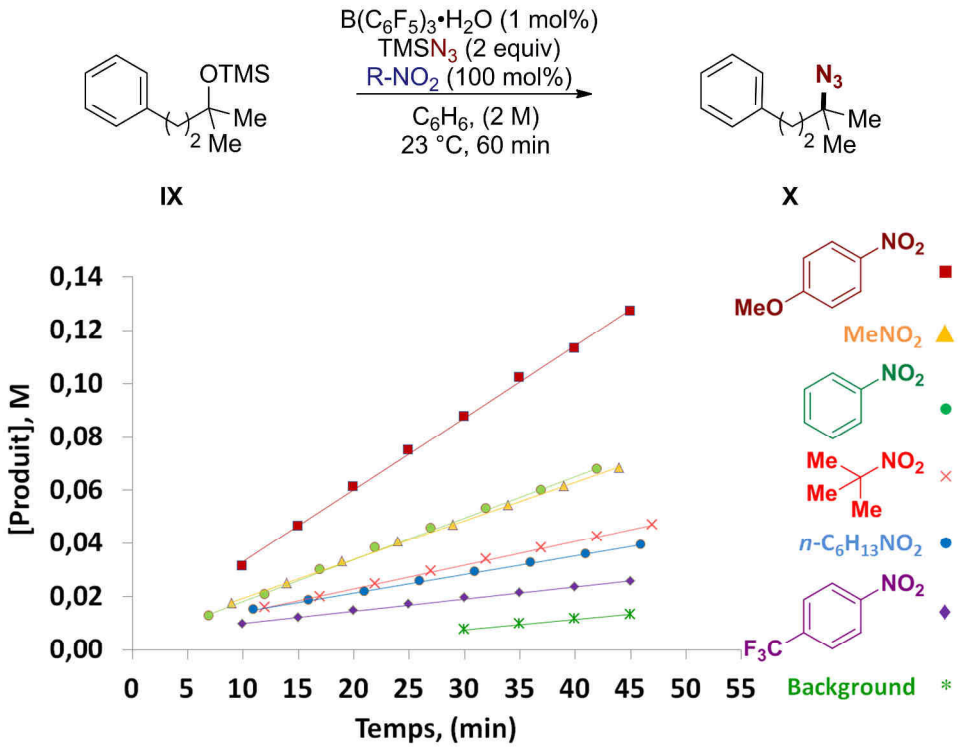


Figure 3. *Etude de la dépendance de la vitesse initiale en fonction des variations électroniques entre les composés nitro.*

Les expériences cinétiques, électroniques et spectroscopiques suggèrent que des agrégats de composés nitro et d'acides liés par des interactions hydrogènes sont, les espèces catalytiques responsables de la cinétique de la catalyse observée. Nos résultats ont souligné qu'une « simple » catalyse par un acide de Brønsted peut être étonnamment complexe en solution, illustrant le besoin d'investigations mécanistiques détaillées.

La catalyse par un acide de Brønsted assistée par un composé nitro a abouti à une méthode d'azidation directe, douce et chimiosélective d'alcools tertiaires aliphatiques en

utilisant le nitrométhane comme solvant ou en utilisant 50 mol% de *p*-nitroanisole dans le benzène (Schéma 3). L'utilité de la méthode est soulignée par le fait que 18 des 25 composés azides formés sont de nouveaux composés avec des fonctionnalités élaborées telles que des éthers silylés, des alcènes, des hétérocycles comportant un atome d'azote, qui seraient difficiles à obtenir par les conditions dures et stœchiométriques alternatives décrites dans la littérature.

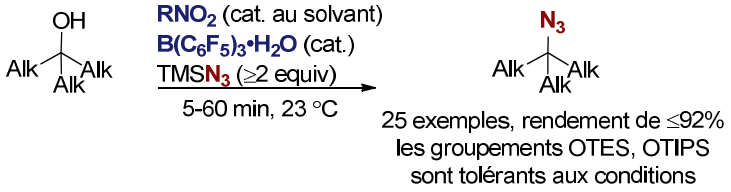


Schéma 3. *Catalyse par un acide de Brønsted assistée par des composés nitro dans la réaction d'azidation d'alcools aliphatiques tertiaires.*

CHAPITRE 5

Dans le chapitre 5, la catalyse très efficace par $B(C_6F_5)_3•H_2O$ dans le $MeNO_2$ a été étendue, au delà de l'activation d'alcools, à une autre classe d'électrophiles: les composés aliphatiques tertiaires fluorés. Ces conditions ont entraîné le clivage de la liaison forte C-F et ont permis des réactions catalytiques de Friedel-Crafts pour la première fois. Dans des conditions expérimentales optimisées, la diversité des nucléophiles aryles ou hétéroaryles et des composés fluorés pouvant être utilisée a été examinée (Schéma 4). Des aryles riches en électrons ont montré une bonne efficacité. De même, les hétérocycles contenant des atomes d'oxygène, de soufre et d'azote se sont révélés être de bons nucléophiles pour cette transformation. La plupart des électrophiles fluorés se sont avérés très réactifs dans ces conditions et ont permis d'obtenir les composés correspondants avec de bons ou d'excellents rendements. L'utilité de la méthodologie est mise en évidence par le fait que, malgré près de 140 ans d'histoire dans le développement de la réaction de Friedel-Crafts, plus de 90 % des produits dans cette étude sont de nouveaux composés.

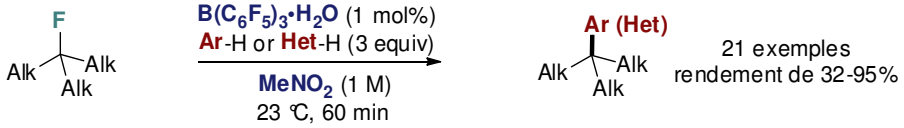


Schéma 4. *Arylation de composés aliphatiques fluorés par la réaction de Friedel-Crafts permise par $B(C_6F_5)_3$•H_2O dans le nitrométhane.*

Des études RMN dépendantes du temps ont été effectuées dans le but d'avoir un aperçu de la nature de l'espèce catalytiquement active dans la réaction de Friedel-Crafts. Dans tous les cas, les réactions montrent une période d'induction et un profil cinétique de type sigmoïde, caractéristique de systèmes autocatalytiques (Figure 4). Toutes les observations collectées suggèrent que l'espèce monomérique HF est un catalyseur peu efficace, mais que l'homoassociation de HF ou l'association de HF avec le catalyseur initial dans des concentrations plus importantes génèrent un catalyseur supérieur. Ainsi, malgré le fait que la réaction soit autocatalytique en présence d'HF, le catalyseur initial joue un rôle majeur.

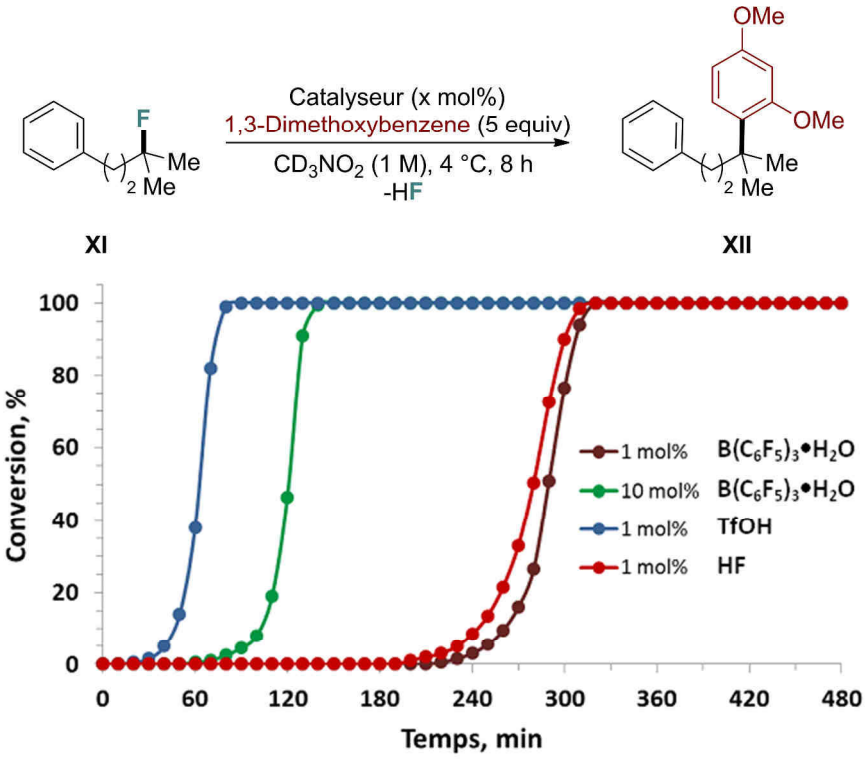


Figure 4. *Etude RMN dépendante du temps à 4 °C révélant un profil cinétique autocatalytique.*

Le chapitre 6 récapitule nos efforts vers une approche plus générale de la substitution nucléophile d'alcools ainsi que des composés alkyles fluorés. Il met en évidence le besoin

d’investigations mécanistiques détaillées même dans le cas de processus catalytiques considérés comme “simples” qui ont prouvés ici pouvant être étonnamment complexes en solution. Les perspectives de ce travail sont aussi discutées.

La dernière partie est la partie expérimentale, qui présente le détail de chaque expérience, les protocoles de synthèse ainsi que les procédures de caractérisation des produits synthétisés.

CHAPTER 1[1]

General Introduction

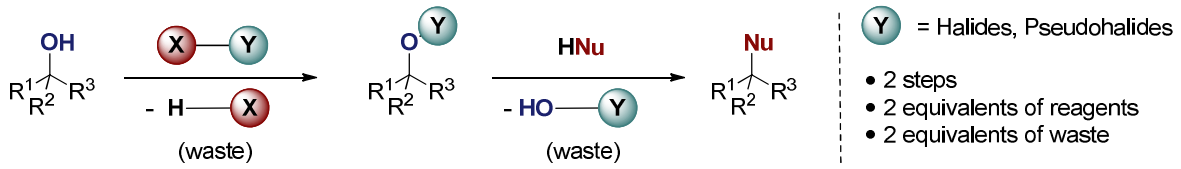
[1] Portions of this chapter have been published: Dryzhakov, M.; Richmond, E.; Moran, J. *Synthesis* **2016**, *48*, 935.

1.1 Introduction to alcohol activation

The widespread abundance of hydroxyl compounds in nature and industry has positioned them as attractive synthetic targets and valuable building blocks for complex molecule synthesis.[2] Being widely available or easily produced compounds, alcohols are objectively seen as ideal electrophiles for a variety of substitution reactions. Since water is, in principle, the only by-product when paired with a protic nucleophile, direct alcohol substitution appears to be very appealing from the point of view of atom economy.[3] Thus, in 2005, the ACS Green Chemistry Institute Pharmaceutical Roundtable identified the direct substoichiometric nucleophilic substitution of alcohols as a priority area of research.[4]

1.2 Alcohol substitution via preactivation of OH group

Although alcohols have long been recognized as attractive electrophilic partners for direct nucleophilic substitution reactions, the relatively poor leaving group ability of the OH unit traditionally required such alcohols to be derivatized to the corresponding halides or pseudohalides prior to the actual substitution step. This preactivation produces waste at two stages and increases the amount of steps required to achieve a given synthetic sequence (Scheme 1.1).

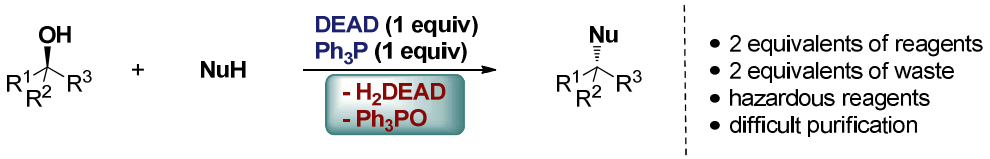


Scheme 1.1. *Two step nucleophilic alcohol substitution via preactivation.*

An alternative method to convert unprotected alcohols to the corresponding substitution products directly in "one pot" and with inversion of stereochemistry would be the Mitsunobu reaction and its related variants.[5] Although the Mitsunobu reaction avoids the isolation of an activated species in a separate step, the overall transformation is highly

[2] Kalliokoski, T. *ACS Comb. Sci.* **2015**, *17*, 600.
[3] (a) Trost, B. M. *Science* **1991**, *254*, 1471. (b) Wender, P. A.; Verma, V. A; Paxton, T. J.; Pillow, T. H. *Acc. Chem. Res.* **2008**, *41*, 40. (c) Newhouse, T.; Baran, P. S.; Hoffmann, R. W. *Chem. Soc. Rev.* **2009**, *38*, 3010.
[4] Constable, D. J. C.; Dunn, P. J.; Hayler, J. D.; Humphrey, G. R.; Leazer, Jr., J. L.; Linderman, R. J.; Lorenz, K.; Manley, J.; Pearlman, B. A..; Wells, A.; Zaks, A.; Zhang, T. Y. *Green Chem.* **2007**, *9*, 411.
[5] (a) Mitsunobu, O. *Synthesis* **1981**, 1. (b) But, T. Y. S.; Toy, P. H. *Chem. Asian J.* **2007**, *2*, 1340.

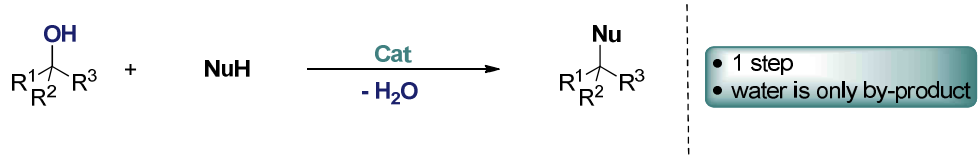
inefficient in terms of atom economy, producing mass-intensive stoichiometric by-products which are often difficult to separate from desired products, as well as employing explosive azodicarboxylate reagents (Scheme 1.2).



Scheme 1.2. *Drawbacks of alcohol substitution via Mitsunobu reaction.*

1.3 Direct dehydrative substitution of alcohols

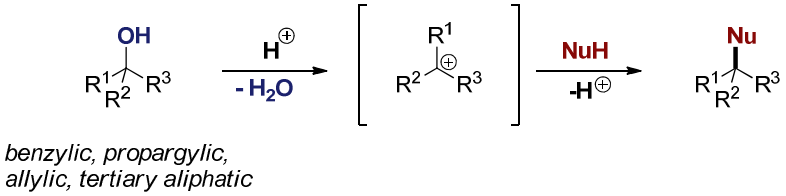
The preactivation of hydroxyl groups has historically dominated the field of alcohol substitution as a general method of making complex molecules from easily accessible starting materials. However, the growing demand for sustainable processes has forced chemists to introduce new synthetic methods that avoid preactivation. Thus, in such an ideal "green" reaction, the free alcohol is converted to the substitution products directly, without additional steps, reducing waste and increasing atom-economy of the overall process since water is the sole by-product (Scheme 1.3).



Scheme 1.3. *Direct dehydrative substitution of alcohols.*

1.3.1 S_N1 pathway and carbocationic intermediates

The direct substitution of free hydroxyl groups is conceivable through electrophilic activation by Lewis or Brønsted acids. In such a scenario, a range of benzylic, allylic, propargylic alcohols, herein collectively referred to as π-activated alcohols, and tertiary aliphatic alcohols react with nucleophiles through rate-limiting heterolytic cleavage of the C–O bond in what is called an S_N1 reaction pathway. The generation of a stabilized planar carbenium ion is generally followed by the addition of a nucleophile in a subsequent fast step to generate the final product (Scheme 1.4).



Scheme 1.4. *Carbocationic reaction pathway in direct dehydrative substitution of π-activated and tertiary aliphatic alcohols.*

1.3.2 **Carbocation stability/reactivity considerations**

Since different classes of alcohols undergo substitution reactions with different efficiency, one could conclude that the relative stability of the corresponding carbocations is an important factor when considering the success of S_N1 reactions. In this regard, understanding of the principles dictating stability, and therefore reactivity, of carbocations is of fundamental importance and will allow the design of and better control over the myriad of reactions which are associated with these ubiquitous intermediates.[6]

In this regard, the structure/stability relationship of different classes of carbocations has been the topic of chemists' attention for several decades. On a qualitative level, the stability of different classes of carbocations depends heavily on the electronics and sterics of the corresponding substituents on the ionized carbon. Thus, mesomeric stabilization from an adjacent π-system (aryl ring, alkene, alkyne or combination thereof) or positive inductive effects of three alkyl substituents adjacent to the former hydroxyl group-bearing carbon, is expected to increase the carbocation's lifetime, making it available for interception with nucleophiles in subsequent fast product-forming step (Figure 1.1).

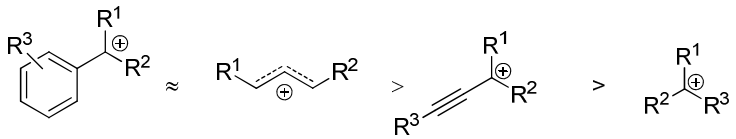


Figure 1.1. *Considerations in the relative stability of carbocations.*

[6] Olah, G. A.; Prakash, G. K. S. *Carbocation Chemistry*; John Wiley & Sons, Inc.: Hoboken, NJ, USA, **2004**.

On a quantitative level, drawing parallels between stability of distinct carbocations have been approached through the comparison of hydride affinities,[7] heats of ionization,[8] pKa values,[9] or solvolysis rate constants[10] (Figure 1.2). However, such approaches have been restricted to certain groups of compounds what did not allow the direct comparison of structurally different entities.

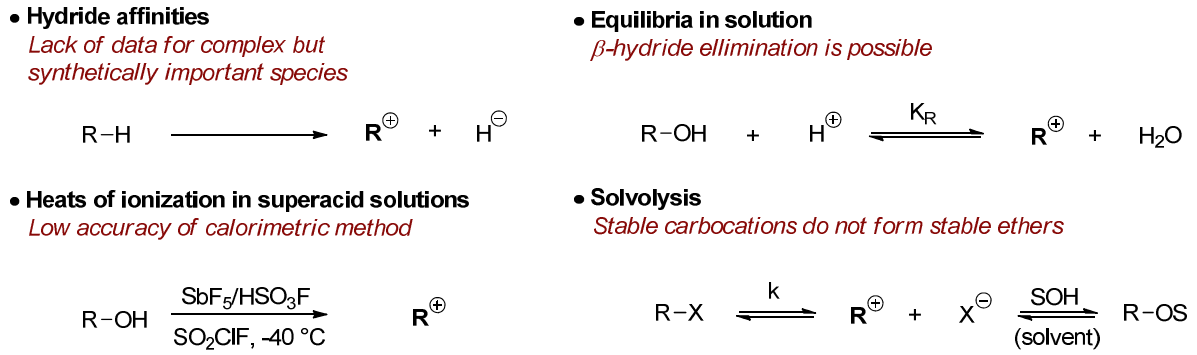


Figure 1.2. "*Stability scales" of carbocations and their limitations.*

A more practical way for the description of the relative stability of cationic intermediates in S_N1 reactions has been established by Mayr and co-workers.[11] In their approach, the reaction rates between given electrophile/nucleophile pairs have been selected as a reference point to characterize the reactivity of a range of benzylic carbenium ions and cationic metal π-complexes.[12] However, such an empirical comparison *a priori* requires that the nature of the nucleophile and of the solvent be taken into account. Although not allowing the direct comparison of structurally different classes of cationic electrophiles within the same set of reaction conditions, the corresponding electrophilicity and nucleophilicity parameters have been determined for an extensive range of reaction partners.[13] Based on these considerations, the Mayr group developed an equation for predicting the rate of a reaction between a given nucleophile/electrophile pair under a standard set of conditions:

$$log(k_{20°C}) = S_N(N + E),$$

[7] Lias, S. G.; Bartmess, J. E.; Liebman, J. F.; Holmes, J. L.; Levin, R. D.; Mallard. W. G. *J. Phys. Chem. Ref Data* **1988**, *17*, 1, Supplement 1.
[8] Arnett, E.; Hofelich, T. *J. Am. Chem. Soc.* **1983**, *80*, 2889.
[9] Deno, N. C.; Jaruzelski, J. J.; Schriesheim, A. *J. Am. Chem. Soc.* **1955**, *77*, 3044.
[10] Takeuchi, K.; Ohga, Y.; Ushino, T.; Takasuka, M. *J. Org. Chem.* **1997**, *62*, 4904.
[11] Mayr, H.; Ofial, A. R. *J. Phys. Org. Chem.* **2008**, *21*, 584.
[12] (a) Mayr, H.; Patz, M.; Gotta, M. F.; Ofial, A. R. *Pure Appl. Chem.* **1998**, *70*, 1993. (b) Mayr, H.; Bug, T.; Gotta, M. F.; Hering, N.; Irrgang, B.; Janker, B.; Kempf, B.; Loos, R.; Ofial, A. R.; Remennikov, G.; Schimmel, H. *J. Am. Chem. Soc.* **2001**, *123*, 9500. (c) Mayr, H.; Kempf, B.; Ofial, A. R. *Acc. Chem. Res.* **2003**, *36*, 66.
[13] The Mayr group website and database provides an excellent resource: "http://www.cup.uni-muenchen.de/oc/mayr/DBintro.html" accessed July 27th, 2015.

where E is electrophilicity parameter, N and S_N are solvent-dependent nucleophilicity and nucleophile-specific sensitivity parameters, respectively.[14]

Perhaps more significant to general practitioners of organic synthesis, the Mayr group has also established a rule-of-thumb for predicting whether a reaction between a given nucleophile/electrophile pair will occur within a realistic experimental timeframe ($E + N > -5$).[15] If the sum of the nucleophilicity parameter (N) and electrophilicity parameter (E) is greater than -5, a reaction can be expected at room temperature (Figure 1.3).

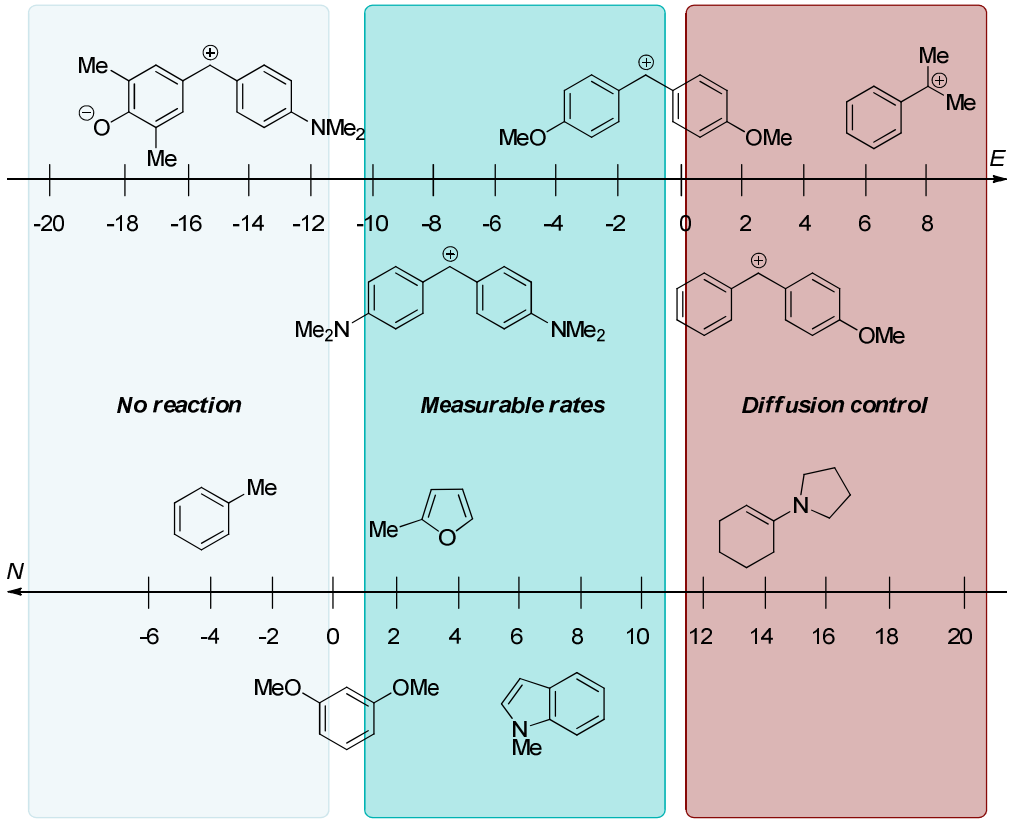


Figure 1.3. *Reactivity scale of nucleophiles and benzylic electrophiles according to Mayr and co-workers.*

Although an important empirical tool for the prediction of the "feasibility" of an S_N1 reaction between a given nucleophile/electrophile pair on a PhD thesis time scale, the three-parameter Mayr equation does not consider steric effects and, therefore, can only be used for semiquantitative predictions of rate constants. More importantly, electrophilicity parameters are only relevant for describing the reactivity of carbocations that are already preformed in

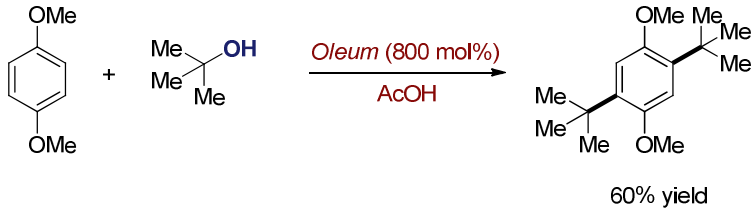
[14] Mayr, H.; Patz, M. *Angew. Chem. Int. Ed.* **1994**, *33*, 938.
[15] (a) Schindele, C.; Houk, K. N.; Mayr, H. *J. Am. Chem. Soc.* **2002**, *124*, 11208. (b) Mayr, H.; Ofial, A. R. *Pure Appl. Chem.* **2005**, *77*, 1807.

solution and cannot account for two other important aspects of catalytic alcohol S_N1 reactivity; the ease of carbocation formation and the interaction between catalyst and nucleophile. In a practical sense, the more electrophilic the nascent cation, the more difficult this species is to generate during the course of a dehydrative reaction.

1.3.3 **Direct nucleophilic substitution under stoichiometric activation**

The difficulties associated with the generation of carbocations from unfunctionalized C–O bond-bearing substrates have historically necessitated that strong Brønsted and Lewis acids be employed in stoichiometric quantities. Consequently, the need of performing reactions in strongly acidic media has strictly limited the substrate scope of these transformations to chemically robust alcohols, namely tertiary aliphatic alcohols, which are not prone to degradation in the presence of harsh acids. Although not being the focus of this thesis, this subsection aims to highlight the first examples of and representative conditions for such activation of hydroxyl groups.

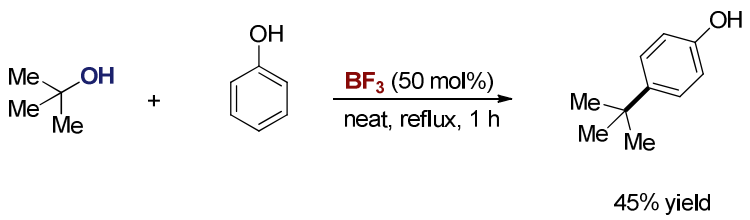
In pioneering work from 1942, the first Friedel-Crafts reaction of *tert*-butanol with electron rich 1,4-dimethoxybenzene was reported by Kharasch and co-workers.[16] Notably, superstoichiometric amounts of oleum (fuming sulfuric acid) and acetic acid were employed as both reaction promoter and solvent in order to accomplish the alkylation with robust tertiary aliphatic alcohol (Scheme 1.5).



Scheme 1.5. *Friedel-Crafts reaction of tert-butanol in the presence of superstoichiometric sulfuric acid.*

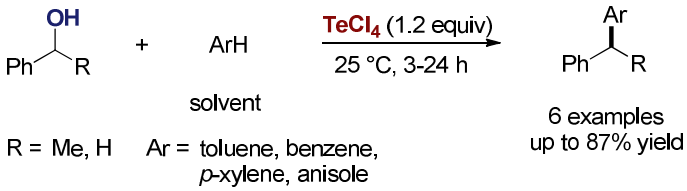
As an alternative to activation by superstoichiometric Brønsted acid, McKenna and Sowa[17] reported the use of 50 mol% of BF_3 for the activation of *tert*-butanol in the Friedel-Crafts alkylation of phenol (Scheme 1.6).

[16] Oesper, P. F.; Smyth, C. P.; Kharasch, M. S. *J. Am. Chem. Soc.* **1942**, *64*, 937.
[17] Mckenna, J. F.; Sowa, F. J. *J. Am. Chem. Soc.* **1938**, *60*, 124.



Scheme 1.6. *Lewis acid-promoted alkylation of phenol with tert-butanol.*

Similarly, even 50 years after the aforementioned initial discoveries, cationic Lewis acids were still typically employed in stoichiometric quantities also for the activation of benzylic alcohols. In a representative example from 1986,[18] despite the fact that benzylic alcohols are more readily ionizable substrates compare to tertiary aliphatic alcohols, stoichiometric $TeCl_4$ was used for the benzylation of aromatic compounds (Scheme 1.7).



Scheme 1.7. *Stoichiometric Lewis acid-promoted benzylation of arenes.*

1.3.4 Reactivity considerations in catalytic S_N1 reactions

Despite the initial employment of stoichiometric activating agents, decades of research in the field of alcohol activation and carbocation chemistry have resulted in a plethora of transformations that are now possible for a range of π-activated alcohols under substoichiometric loading of Lewis or Brønsted acid.[19] This explosion in the number of dehydrative transformations, although being beneficial for the collection of favorable reaction conditions, has made it difficult to compare the efficiency of different catalytic systems that vary drastically in terms of alcohols, nucleophiles, temperatures, solvents, catalysts and catalyst loadings.

[18] Yamauchi, T.; Hattori, K.; Mizutaki, S.; Tamaki, K.; Uemura, S. *Bull. Chem. Soc. Jpn*. **1986**, *59*, 3617.
[19] For reviews on alcohol activation, see: (a) Bandini, M.; Tragni, M. *Org. Biomol. Chem.* **2009**, *7*, 1501. (b) Rueping, M.; Nachtsheim, B. J. *Beilstein J. Org. Chem.* **2010**, *6*, 6. (c) Emer, E.; Sinisi, R.; Capdevila, M. G.; Petruzziello, D.; De Vincentiis, F.; Cozzi, P. G. *European J. Org. Chem.* **2011**, 647. (d) Sundararaju, B.; Achard, M.; Bruneau, C. *Chem. Soc. Rev.* **2012**, *41*, 4467. (e) Kumar, R.; Van der Eycken, E. V. *Chem. Soc. Rev.* **2013**, *42*, 1121. (f) Chen, L.; Yin, X.-P.; Wang, C.-H.; Zhou, J. *Org. Biomol. Chem.* **2014**, *12*, 6033.

A comprehensive effort aiming to benchmark representative alcohol substrates, nucleophiles, catalysts and conditions for direct alcohol substitution reactions was reported by Biswas and Samec in 2013.[20] In their study, prototypical alcohol substrates were ranked by their empirically observed reactivity with common *S*-, *C*-, *N*- and *O*-centered nucleophiles. A number of redox-active metals, Lewis acids and Brønsted acids were independently tested as catalysts under common sets of conditions. Highlighting the pronounced kinetic barrier for the heterolytic cleavage of the C–O bond, the authors determined that the reaction selectivity and conversion of the alcohols examined is "…governed by the ease of generating the corresponding carbocation rather than the electrophilicity of the generated cation" (Figure 1.4).

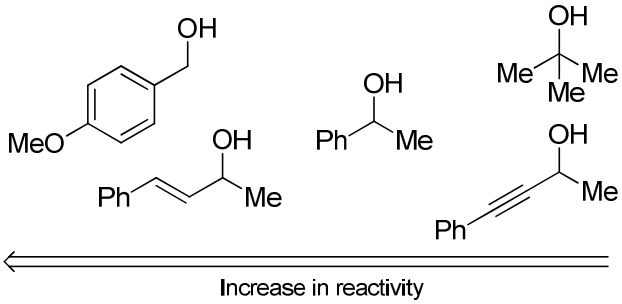
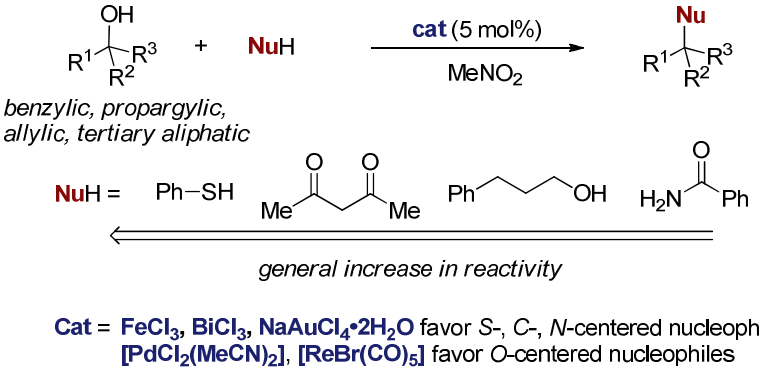


Figure 1.4. *Empirically observed order of reactivity in S_N1 reactions of representative alcohol substrates according to Samec and co-workers.*

Furthermore, the authors noticed that the efficiency of dehydrative substitution reactions depends significantly on the combination of nucleophile and catalyst employed, with Lewis acids better promoting the reactivity of *S*-, *C*- and *N*-centered nucleophiles, whilst redox metals, such as Pd, generally favor *O*-centered nucleophiles (Scheme 1.8). Although further systematic investigation is required in order to uncover the reasons behind such selectivity, these empirical observations reflect the importance of taking into account factors beyond the properties of the electrophile and nucleophile, such as catalyst/nucleophile compatibility, when considering the overall success of dehydrative alcohol substitution.

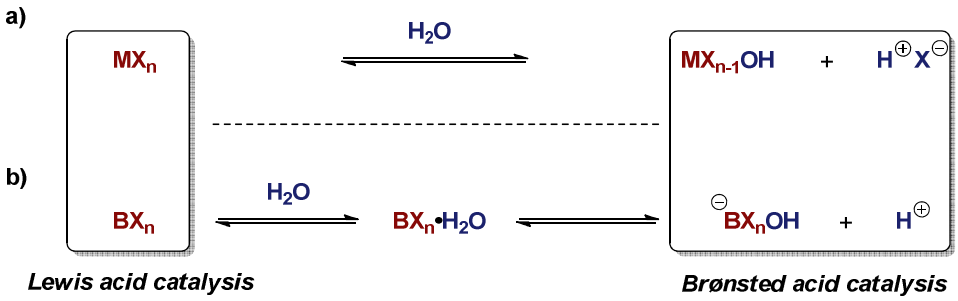
[20] Biswas, S.; Samec, J. S. M. *Chem. Asian J.* **2013**, *8*, 974.



Scheme 1.8. *Observed compatibility relationships provided by Samec's study.*

1.4 Lewis vs. hidden Brønsted acid catalysis

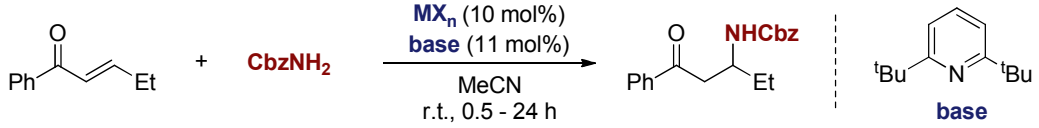
In addition to consideration of compatibility between catalyst, substrate and reagents, another important factor to keep in mind when developing dehydrative catalytic reaction is the tolerance of the catalyst towards water and protic functional groups. Although the simplicity of reaction conditions, such as the use of solvents that are not rigorously dried and of open-air reaction vessels, renders a synthetic methodology highly convenient and practical, such approaches often possess significant limitations which should not be ignored. In this regard, transformations that in principle could be catalyzed by variety of tunable Lewis acids, would need to compete with catalysis by protons due to the unavoidable hydrolysis of the corresponding Lewis acid if water is not excluded (Scheme 1.9, a). Alternatively, the formation of Lewis acid hydrates that are strong Brønsted acids could also readily take place in the presence of water (Scheme 1.9, b). Although this problem is rarely discussed in the literature on dehydrative transformations of alcohols, the following subsection aims to highlight representative examples of hidden Brønsted acid catalysis.



Scheme 1.9. *Lewis vs. Brønsted acid equilibrium in the presence of water: a) hydrolazible cationic Lewis acids; b) "non-hydrolazible" neutral Lewis acids.*

Spencer and co-workers[21] reported a comprehensive study which indicates that simple protons, rather than metal ions, serve as the active catalyst in Lewis acid "mediated" hetero-Michael reactions. In addition to a perfect correlation of catalytic activities with cation hydrolysis constants, a substoichiometric amount (11 mol%) of base, such as 2,6-di-*tert*-butylpyridine, completely inhibited the addition of nucleophiles to *α*, *β*-unsaturated ketones in the presence of 10 mol% of metal precatalyst (Table 1.1).

Table 1.1. *Inhibition of Lewis acid-catalyzed aza-Michael addition in the presence of weak non-coordinative base.*

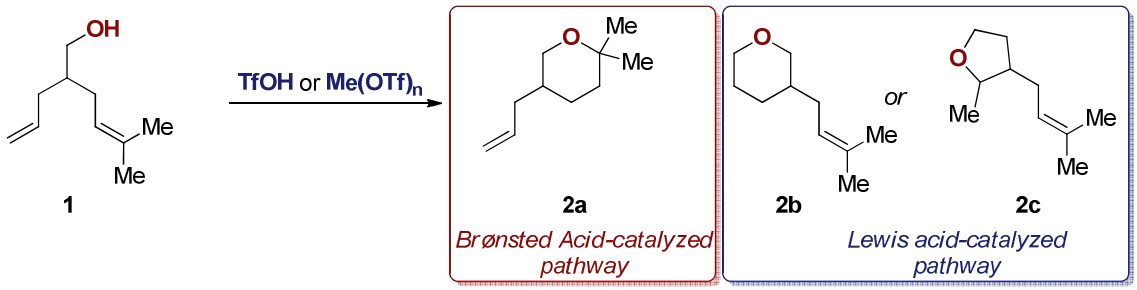


Entry	*Catalyst (MX_n)*	*Base added*	*Yield (%)*
1	$ReCl_5$	No	80
2	$ReCl_5$	Yes	-
3	$Cu(OTf)_2$	No	99
4	$Cu(OTf)_2$	Yes	-

In a closely related report, Hartwig and co-workers[22] studied the relationship between olefin hydroamination and hydroalkoxylation reactions catalyzed by substoichiometric triflic acid or by metal triflates. As a result of extensive experimentation, it has been noticed that the scope of these reactions is closely related, which allowed the qualitative comparison of the rates of the addition in the presence of triflic acid to those in the presence of metal triflates. Thus, it was shown that the rates of the reactions in the presence of 1 mol% of triflic acid were similar to the rates of metal triflates-catalyzed reactions. The close relationship between Brønsted and Lewis acid catalysis was further emphasized by the fact that the same set of byproducts is formed during the reaction of cyclooctene and cyclohexane with $TsNH_2$ in the presence of catalytic amounts of triflic acid or $(Ph_3P)AuOTf$. Based on this knowledge, the authors developed a protocol to distinguish between metal- and proton-catalyzed pathways based on intramolecular addition of O–H bond of alcohol **1** across two different olefins with distinct steric properties and ability to stabilize the carbocation (Scheme 1.10). Thus, catalysis by TfOH favors the protonation of the internal olefin and delivers **2a** through addition of the hydroxyl group to the stabilized carbocationic intermediate, whilst in case of

[21] Wabnitz, T. C.; Yu, J. Q.; Spencer, J. B. *Chem. Eur. J.* **2004**, *10*, 484.
[22] Rosenfeld, D. C.; Shekhar, S.; Takemiya, A.; Utsunomiya, M.; Hartwig, J. F. *Org. Lett.* **2006**, *8*, 4179.

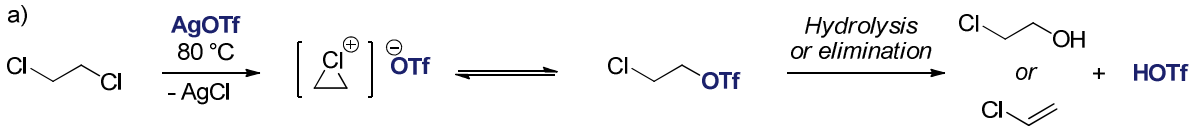
catalysis by metal triflates the sterics favor the activation of the terminal alkene to yield **2b** and **2c**.

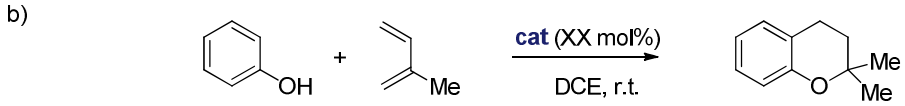


Scheme 1.10. *Hartwig's reaction system to distinguish between triflic acid and metal triflate-catalyzed pathways.*

In addition to the generation of Brønsted acid due to the hydrolysis of the corresponding metal salts, Hintermann and co-workers[23] reported the deliberate or controlled formation of TfOH in DCE caused by AgOTf reacting with the solvent (Table 1.2, a). Interestingly, such "hidden Brønsted acid catalysis" was shown to be advantageous in several cases, such as phenol addition to isoprene as a representative example (Table 1.2, b).

Table 1.2. *Hidden Brønsted acid catalysis: a) generation of triflic acid in DCE; b) comparison of catalyst efficiency*





Entry	*Catalyst (mol %)*	*Time, h*	*Yield (%)*
1	**AgOTf (5 mol%)**	48	65
2	**HOTf (5 mol%)**	2	21
3	**HOTf (0.5 mol%)**	2	63
4[a]	**AgOTf (1 mol%)**	0.3	79

[a]Catalyst prepared by refluxing AgOTf in DCE

[23] Dang, T. T.; Boeck, F.; Hintermann, L. *J. Org. Chem.* **2011**, *76*, 9353.

Thus, one must carefully consider whether such transformations catalyzed by cationic Lewis acids are true metal-catalyzed processes or if the metal simply generates a protic acid. These concerns become even more important in dehydrative transformations of alcohols, where water is generated as a stoichiometric by-product.

1.5 Recent advances in direct catalytic dehydrative substitution of π-activated alcohols

Since the early reports on alcohol substitutions in the presence of superstoichiometric amounts of harsh mineral acids, the field of alcohol activation has trended towards the development of low catalyst loading processes. The constructive analysis of the immense number of reports on the dehydrative transformations of alcohols that has appeared in the literature needs a fair degree of generalization which unavoidably leads to the simplification within arbitrary selected criteria. In contrast to existing reviews on the topic of alcohol activation,[19] the following introduction attempts to provide a broad picture of the state of the art, highlighting selected recent advances that have occurred up until August 2015. The main focus is placed on S_N1 reactivity of π-activated alcohols in direct intermolecular reactions using only substoichiometric homogeneous catalysts and without alcohol preactivation. The following sections are organized around transformations of representative substrates of each class (Figure 1.4) and therefore aim to provide a practical guide as to the compatibility between catalyst, alcohol and nucleophile. The more challenging activation of aliphatic alcohols, namely tertiary aliphatic alcohols, requires a somewhat different focus and will be discussed in depth in Chapter 3. Whenever possible, reactions of various nucleophiles with a particular alcohol have been placed in tables to facilitate direct comparison of catalysts and conditions. The selected nucleophiles (NuH) are indicative of the typical nucleophile class employed in each study.

1.5.1 Dehydrative catalytic substitution of benzylic alcohols

Benzylic alcohols are archetypal hydroxyl-bearing substrates on which to develop new catalytic substitution reactions. Table 1.3 highlights the nucleophilic substitution of *p*-methoxybenzyl alcohol as a representative primary benzylic alcohol. It is perhaps the most widely employed substrate owing to its easy ionization to generate a carbocation. Prior to 2012, standout methods for the catalytic activation of benzylic alcohols include Beller's

$FeCl_3$ catalyzed,[24] Rueping's $Bi(OTf)_3$ catalyzed,[25] McCubbin's $C_6F_5B(OH)_2$ boronic acid catalyzed[26] (entries 1-3) and Niggemann's $Ca(NTf_2)_2/Bu_4NPF_6$ catalyzed[27] (Table 1.4, entry 1) Friedel-Crafts systems. Amongst subsequent works, the aforementioned study by Samec provides interesting insight into the interplay between catalyst and nucleophile, as different catalysts are optimal for *C*-, *S*- or *O*-nucleophiles (entries 4-6).[20] However, a general approach for the rational selection of catalyst/nucleophile combination remains to be developed.

Since water has long been considered as an attractive solvent from both economic and environmental standpoints, catalytic systems have now been developed for alcohol substitution in this solvent. Building on previous work by Cozzi and co-workers on the catalyst-free substitution of secondary ferrocenyl alcohols "on water",[28] two research groups recently reported independent studies of catalytic activation of more challenging benzylic alcohols in water. Ji and co-workers reported the $In(OTf)_3$ catalyzed Friedel-Crafts reaction between benzylic alcohols and indoles in water (entry 7),[29] whilst Hikawa and co-workers reported a water-soluble gold catalytic system for the same reaction (entry 8).[30]

Typically, the direct use of free amines as nucleophiles poses a challenge due to potential catalyst deactivation by the basic nitrogen atom. Ghorai and co-workers have attacked this problem and disclosed an interesting Re_2O_7 catalyzed formal Friedel-Crafts arylation of benzylic alcohols using anilines (entry 9).[31] The authors proposed a two-step mechanism whereby nucleophilic addition initially occurs through the aniline nitrogen followed by a Hofmann-Martius rearrangement[32] to give the observed Friedel-Crafts products. In the same report, the authors also demonstrate this catalytic system to be equally applicable to the dehydrative substitution of allylic and propargylic alcohols. Similarly, the dehydrative amination of benzylic alcohols was also reported by Pamulaparthy and co-workers using TaF_5 as a catalyst (entry 10).[33]

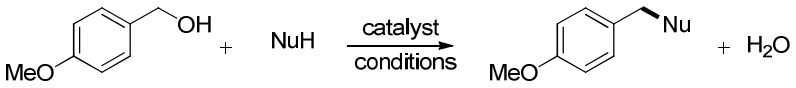
---

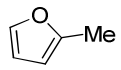
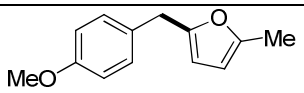
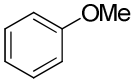
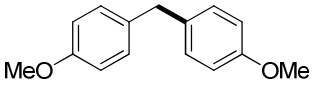
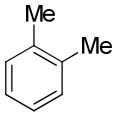
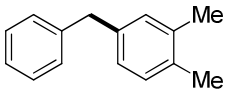
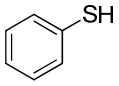
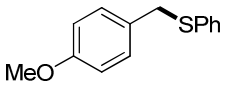
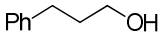
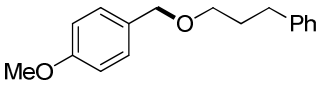
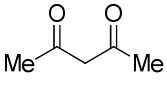
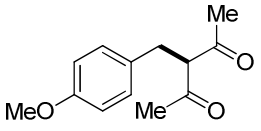
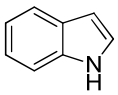
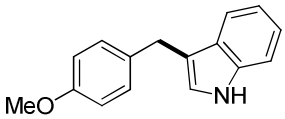
[24] Iovel, I.; Mertins, K.; Kischel, J.; Zapf, A.; Beller, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 3913.
[25] Rueping M.; Nachtsheim, B. J.; Ieawsuwan, W. *Adv. Synth. Catal.* **2006**, *348*, 1033.
[26] McCubbin, J. A.; Krokhin, O. V. *Tetrahedron Lett.* **2010**, *51*, 2447.
[27] Niggemann, M.; Meel, M. J. *Angew. Chem. Int. Ed.* **2010**, *49*, 3684.
[28] Cozzi, P. G.; Zoli, L. *Angew. Chem. Int. Ed.* **2008**, *47*, 4162.
[29] Wu, L.; Jiang, R.; Yang, J-M.; Wang, S-Y.; Ji, S-J. *RSC Adv*. **2013**, *3*, 5459.
[30] (a) Hikawa, H.; Suzuki, H.; Azumaya, I. *J. Org. Chem.* **2013**, *78*, 12128. (b) Hikawa, H.; Suzuki, H.; Yokoyama, Y.; Azumaya, I. *J. Org. Chem.* **2013**, *78*, 6714.
[31] Nallagonda, R.; Rehan, M.; Ghorai, P. *J. Org. Chem.* **2014**, *79*, 2934.
[32] (a) Hofmann, A. W. *Anilin. Ber. Dtsch. Chem. Ges.* **1871**, *4*, 742. (b) Magnus, P.; Turnbull, R. *Org. Lett.* **2006**, *8*, 3497.
[33] Gangaram, S.; Adimulam, C. S.; Akula, R. K.; Kengiri, R.; Pamulaparthy, S. R.; Madabhushi, S.; Banda, N. *Chem. Lett.* **2013**, *42*, 1522.

As a general trend, current emphasis in recent research with respect to benzylic alcohol activation is placed on improving the viability of catalytic methods by developing more active catalysts that allow for milder reaction conditions and improved chemoselectivity. In this regard, research groups have focused on the design of new, recyclable catalyst classes such as ionic liquids which can often be recovered by simple liquid-liquid extraction.[34] Thus, Ji and co-workers reported the ionic liquid catalyzed direct substitution of benzylic alcohols.[35] Anilines, benzothiazole derivatives and indoles all proved compatible nucleophiles for this catalytic system, furnishing the desired functionalized benzyl compounds in good yields (entry 11).

Quite recently, Moran and co-workers disclosed a highly active boronic ester catalyst formed *in situ* from pentafluorophenylboronic acid and oxalic acid, allowing remarkably fast room temperature Friedel-Crafts reactions of benzylic alcohols in nitromethane (entry 12).[36]

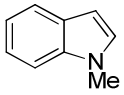
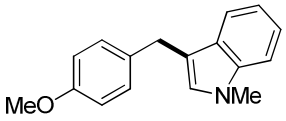
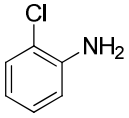
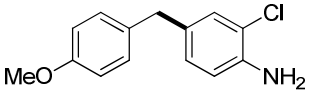
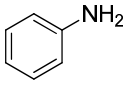
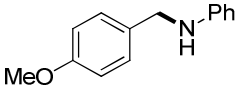
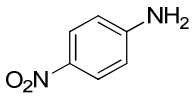
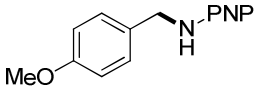
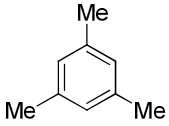
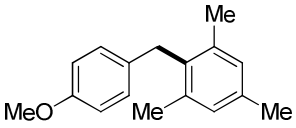
Table 1.3. *Recent advances in direct catalytic primary benzylic alcohol substitution.*



Entry	*NuH*	*Catalyst (loading)*	*Reaction Conditions*	*Product*	*Yield*
1		$C_6F_5B(OH)_2$ (10 mol%)	Toluene, reflux, 16 h		81%
2		$Bi(OTf)_3$ (1 mol%)	$MeNO_2$, 100 °C, 2 h		91%
3[†]		$FeCl_3$ (10 mol%)	*o*-Xylene, 80 °C, 24 h		99%
4		$BiBr_3$ (5 mol%)	$MeNO_2$, r.t., 10 h		99%
5		$[ReBr(CO)_5]$ (5 mol%)	$MeNO_2$, 60 °C, 6 h		78%
6		$FeCl_3$ (5 mol%)	$MeNO_2$, 60 °C, 10 h		99%
7		$In(OTf)_3$ (10 mol%)	H_2O, 100 °C, 4 h		83%

[34] Wu, B.; Liu, W.; Zhang, Y.; Wang, H. *Chem. Eur. J.* **2009**, *15*, 1804.
[35] Chu, X-Q.; Jiang, R.; Fang, Y.; Gu, Z-Y.; Meng, H.; Wang, S-Y.; Ji, S-J. *Tetrahedron*, **2013**, *69*, 1166.
[36] Wolf, E.; Richmond, E.; Moran, J. *Chem. Sci.* **2015**, *6*, 2501.

Table 1.3 (continued)

Entry	*NuH*	*Catalyst*	*Reaction Conditions*	*Product*	*Yield*
8		$NaAuCl_4 \bullet 2H_2O$ (2 mol%)/ TPPMS (2 mol%)	H_2O, 80 °C, 16 h		74%
9		Re_2O_7 (5 mol%)	MeCN, 100 °C, 10 h		65%
10		TaF_5 (10 mol%)	Toluene 110 °C, 2.5 h		90%
11		$[PMIm]HSO_4$ (10 mol%)	MeCN, 80 °C, 24 h		75%
12		$C_6F_5B(OH)_2$ (1 mol%)/ oxalic acid (2 mol%)	$MeNO_2$, r.t., 15 min		95%

[†]Reaction performed on benzyl alcohol.

Table 1.4 summarizes methods for the substitution of 1-phenylethanol, a representative secondary benzylic alcohol. In 2010, Niggemann and co-workers reported the $Ca(NTf_2)_2/Bu_4NPF_6$ catalyzed, room temperature Friedel-Crafts alkylation of electron-rich arenes (entry 1).[27] This catalyst system proved to be extremely broad, and in the same report the authors detail the use of benzylic, allylic and propargylic alcohols as alkylating agents in reaction with a range of arenes. In the following years, other cationic Lewis acids were also reported as catalysts for the azidation of secondary benzylic alcohols with $TMSN_3$ (entry 2-3),[37,38] as well as for carbamidation[39] and cyanation[40] using carbamates and TMS-CN as nucleophiles, respectively (entries 4-5).

Elaborate transition metal complexes have been also recently reported as potent catalysts for the activation of secondary benzylic alcohols. Thus, Nishayama reported a rhenium complex catalyzed C-C bond forming reaction using enolacetates (entry 6).[41] Bimetallic Ir-Sn complexes also proved to be effective in the dehydrative substitution of

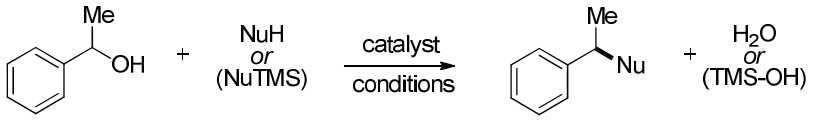
[37] Khedar, P.; Pericherla, K.; Kumar, A. *Synlett*, **2014**, *25*, 515.
[38] Sharma, G. V. M.; Kumar, K. S.; Kumar, B. S.; Reddy, S. V.; Prakasham, R. S.; Hugel, H. *Synth. Comm.* **2014**, *44*, 3156.
[39] Ohshima, T.; Ipposhi, J.; Nakahara, Y.; Shibuya, R.; Mashima, K. *Adv. Synth. Catal.* **2012**, *354*, 2447.
[40] Theerthagiri, P.; Lalitha, A. *Tetrahedron. Lett.* **2012**, *53*, 5535.
[41] Umeda, R.; Takahashi, Y.; Nishayama, Y. *Tetrahedron Lett.* **2014**, *55*, 6113.

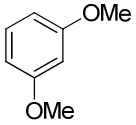
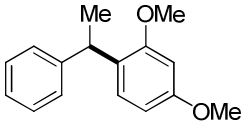
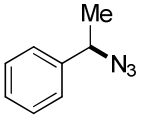
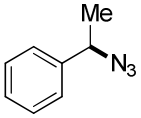
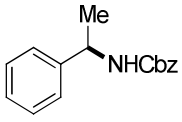
alcohols,[42] and recently were reported as highly active catalysts for the benzylation of 1,3-dicarbonyl compounds (entry 7).[43] Interestingly, a similar transformation is also catalyzed by a Lewis acidic zirconium complex in virtually the same efficiency (entry 8).[44]

On the other hand, simple Brønsted acids such as sulfuric acid[45] and triflimide[46] were employed as catalysts for substitution reactions with dicarbonyl compounds and styrene derivatives as nucleophiles, respectively (entry 9-10).

Cationic species such as pentafluorophenylammonium triflate are reported to catalyze a Ritter reaction and proved applicable for the transformation of a wide variety of alcohol substrates (entry 11).[47] Additionally, a highly active cationic iron porphyrin catalyst was developed by Matsubara and co-workers and was applied in the Friedel-Crafts arylation of benzylic and allylic alcohols (entry 12).[48] Importantly, the majority of the catalytic systems summarized above are also applicable to the catalytic substitution of diarylmethanols which could be considered as "overactivated" electrophiles.

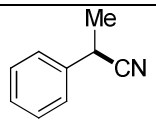
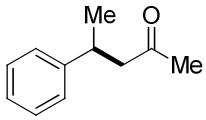
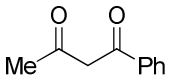
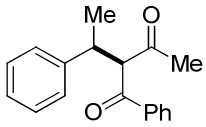
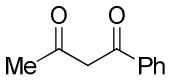
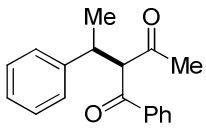
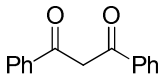
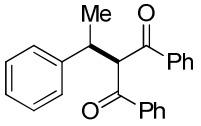
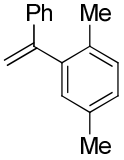
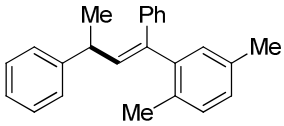
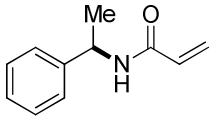
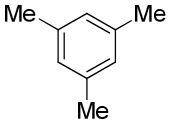
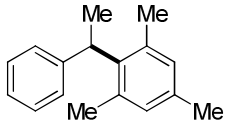
Table 1.4. *Recent advances in direct catalytic secondary benzylic alcohol substitution.*



Entry	*NuH*	*Catalyst*	*Reaction Conditions*	*Product*	*Yield*
1		$Ca(NTf_2)_2$ (5 mol%)/ Bu_4NPF_6 (5 mol%)	CH_2Cl_2, r.t., 1 h		85%
2	TMS-N_3	$Cu(OTf)_2$ (5 mol%)	CH_2Cl_2, r.t., 20 min		94%
3	TMS-N_3	$ZrCl_4$ (10 mol%)	MeCN, r.t., 30 min		87%
4	H_2N-Cbz	$Al(OTf)_3$ (5 mol%)	$MeNO_2$, 50 °C (MW), 10 min		97%

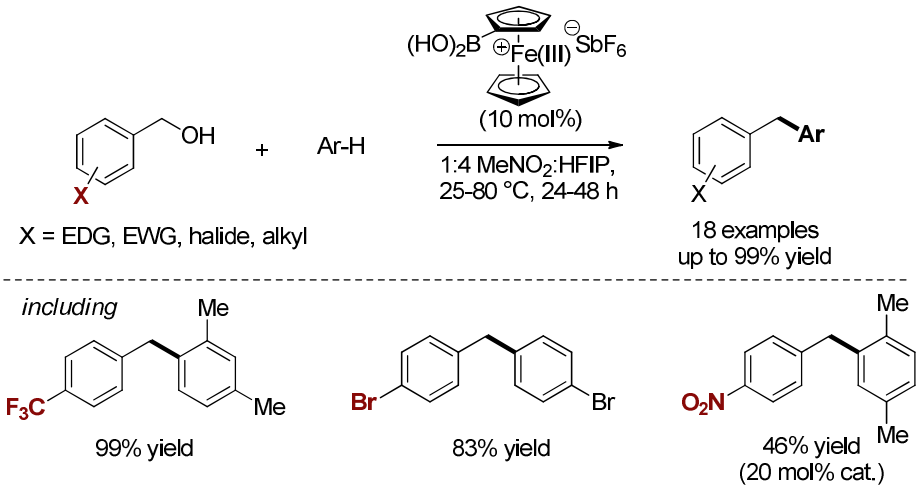
[42] Choudhury, J.; Podder, S.; Roy, S. *J. Am. Chem. Soc.* **2005**, *127*, 6162.
[43] Maity, A. K.; Chatterjee, P. N.; Roy, S. *Tetrahedron*, **2013**, *69*, 942.
[44] Zhang, X.; Qiu, R.; Zhou, C.; Yu, J.; Li, N.; Yin, S.; Xu, X. *Tetrahedron*, **2015**, *71*, 1011.
[45] Xia, F.; Zhao, Z. L.; Liu, P. N. *Tetrahedron Lett.* **2012**, *53*, 2828
[46] Li, H-H. *Chinese Chem. Lett.* **2015**, *26*, 320.
[47] Khaksar, S.; Fattahi, E.; Fattahi, E. *Tetrahedron Lett.* **2011**, *52*, 5943.
[48] Teranishi, S.; Kurahashi, T.; Matsubara, S. *Synlett*, **2013**, *24*, 2148.

Table 1.4 (continued)

Entry	*NuH*	*Catalyst*	*Reaction Conditions*	*Product*	*Yield*
5	TMS-CN	$Zn(OTf)_2$ (15 mol%)	$MeNO_2$, 100 °C, 8 h		43%
6		$ReBr(CO)_5$ (5 mol%)	DCE, 80 °C, 5 h		72%
7		Ir-Sn_3 complex (1 mol%)	DCE, r.t., 1 h		90%
8		Zr•H_2O complex (5 mol%)	CH_2Cl_2, 60 °C, 12 h		90%
9		H_2SO_4 (5 mol%)	$MeNO_2$, 101 °C, 5 min		98%
10		Tf_2NH (20 mol%)	$MeNO_2$, 60 °C, 7 h		63%
11		PFPAT (10 mol%)	neat, 90 °C, 2 h		95%
12		$[Fe(TPP)][SbF_6]$ (1 mol%)	DCE, 60 °C, 8 h		92%

Importantly, in 2015, Hall, McCubbin and co-workers disclosed a boronic acid catalyzed Friedel-Crafts reaction employing benzylic alcohols. This report is particularly impressive in that some benzylic alcohols bearing electron-withdrawing groups are tolerated under the catalytic conditions. Using a ferroceniumboronic acid with a non-coordinating hexafluoroantimonate counterion, the authors propose a mechanism that generates "…a more reactive carbocation paired with the non-coordinating hexafluoroantimonate counteranion." This enhanced reactivity allows the authors to access an extremely wide-range of diarylmethane products from electronically deactivated benzylic alcohols (Scheme 1.11).[49]

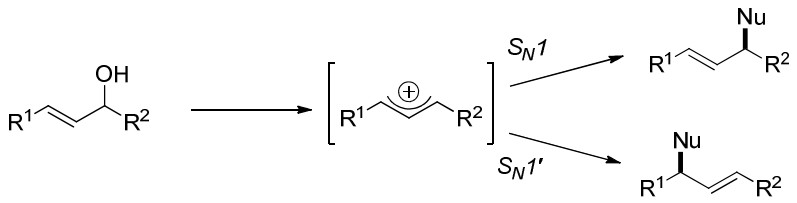
[49] Mo, X.; Yakiwchuk, J.; Danserau, J.; McCubbin, J. A.; Hall, D. G. *J. Am. Chem. Soc.* **2015**, *137*, 9694.



Scheme 1.11. *Friedel-Crafts reaction of electron-deficient benzylic alcohols catalyzed by a ferroceniumboronic acid.*

1.5.2 **Dehydrative catalytic substitution of allylic alcohols**

Alongside benzylic alcohols, allylic alcohols are commonly employed substrates in the development of new methods to enable the direct catalytic activation of alcohols. In the substitution reaction of pseudo-symmetrical allylic alcohols (Scheme 1.12, R^1=R^2), only one regioisomeric product can be formed. However regioselectivity concerns must be addressed in the case of non-symmetrical substrates (Scheme 1.12, $R^1 \neq R^2$).



Scheme 1.12. *Considerations in the catalytic activation of allylic alcohols.*

Early notable contributions to the field of direct catalytic S_N1-type allylic alcohol activation include Chan and co-workers' $AuCl_3$ catalyzed Friedel-Crafts reaction with electronically activated arenes[50] and Rueping's 2011 report of direct azidation catalyzed by AgOTf under mild reaction conditions (Table 1.5, entries 1-2).[51]

In the field of common Lewis acid catalysis, Prabhu and co-workers reported a highly efficient $Cu(ClO_4)_2$ catalyzed azidation of allylic alcohols (entry 3). In the same reaction

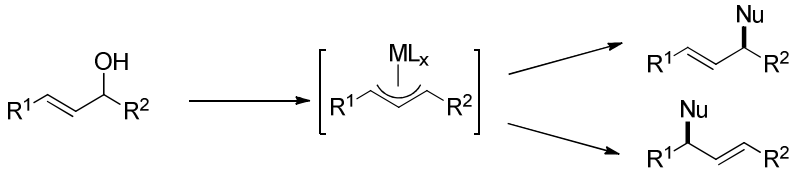
[50] Rao, W.; Chan, P. W. H. *Org. Biomol. Chem.* **2008**, *6*, 2426.
[51] Rueping, M.; Villa, C., Uria, U. *Org. Lett.* **2011**, *14*, 768.

vessel, the azides can be converted directly to allylic amides by *in situ* aqueous oxidation with DDQ and nitrogen gas extrusion.[52] Another related copper(II)-catalyzed transformation, the formal Friedel-Crafts reaction between allylic alcohols and anilines, has also been reported (entry 4).[53] The direct addition of nitrogen nucleophiles to allylic alcohols was reported in 2012 by Najera and co-workers under $FeCl_3$•$6H_2O$ catalysis[54] (entry 5) and by Ghorai and co-workers under Re_2O_7 catalysis (entry 6).[55]

The $Ca(NTf_2)_2/H_4NPF_6$ catalyzed addition of terminal acetylenes to allylic alcohols was reported by the Niggemann laboratory in 2015 to give the corresponding ketones after hydration of the cationic reaction intermediate (entry 7).[56] Interestingly, cyclopentanone is used as an additive in this study to stabilize the intermediate carbocations through a proposed Lewis basic electron pair donation. Another $Ca(NTf_2)_2$ catalyzed transformation was also reported in 2015 by the Gandon group, who disclosed the dehydrative addition of cinnamyl-type boronic acids to allylic alcohols under mild conditions (entry 8).[57]

Roy and colleagues further extended the utility of their aforementioned bimetallic Ir-Sn complexes to the activation of allylic alcohols in reaction with a variety of nucleophiles (entry 9).[58] The authors later employed their Re_2O_7 catalytic activation strategy as a key-step in the one-pot preparation of polysubstituted indoles[59] and quinolines.[60]

Although widely developed for the substitution reactions of pre-activated allylic alcohol derivatives such as allylic acetates and allylic carbonates,[61] the direct substitution of allylic alcohols via the formation of an intermediate metal π-allyl species has also been explored (Scheme 1.13).



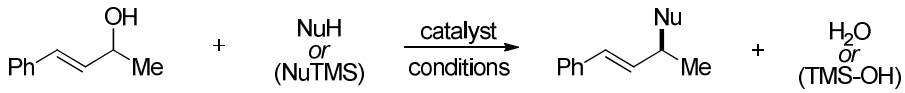
Scheme 1.13. *Dehydrative allylic alcohol activation by formation of a transition metal π-allyl intermediate.*

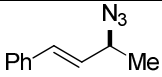
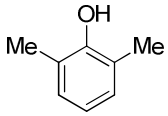
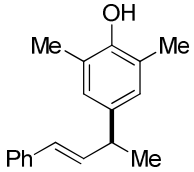
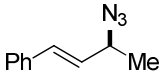
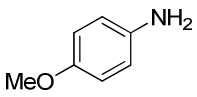
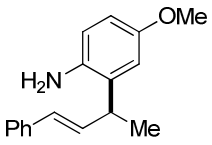
[52] Rokade, B. V.; Gadde, K.; Prabhu, K. R. *Eur. J. Org. Chem*. **2015**, 2706.
[53] Chen, K.; Chen, H. J.; Wong, J.; Yang, J.; Pullarkat, S. A. *ChemCatChem*, **2013**, *5*, 3882.
[54] Trillo, P.; Baeza, A.; Najera C. *Eur. J. Org. Chem.* **2012**, 2929.
[55] Das, B. G.; Nallagonda, R.; Ghorai, P. *J. Org. Chem.* **2012**, *77*, 5577.
[56] Stopka, T.; Niggemann, M. *Org. Lett.* **2015**, *17*, 1437.
[57] Leboeuf, D.; Presset, M.; Michelet, B.; Bour, C.; Bezzenine-Lafollee, S.; Gandon, V. *Chem. Eur. J.* **2015**, *21,* 11001.
[58] Chatterjee, P. N.; Roy, S. *Tetrahedron* **2012**, *68*, 3776.
[59] Nallagonda, R.; Rehan, M.; Ghorai, P. *Org. Lett.* **2014**, *16*, 4786.
[60] Rehan, M.; Hezra, G.; Ghorai, P. *Org. Lett.* **2015**, *17*, 1668.
[61] Trost, B. M.; Van Vranken D. L. *Chem. Rev.* **1996**, *96*, 395.

These approaches are attractive given a wide variety of strong, soft nucleophiles have been demonstrated as compatible with such systems, and often chemoselectivity of nucleophile addition can be controlled by judicious combination of transition metal and ligand. Approaches in the area to date have typically relied on the *in situ* stoichiometric activation of the allylic alcohol functionality to facilitate metal π-allyl formation. Recently, several palladium catalyzed systems, which are able to activate allylic alcohol directly, have been developed, including an elegant example from Huang and co-workers[62] (entry 11). Systems catalyzed by other transition metals (e.g. Ru, Ir) have also been reported and are well summarized in a recent review by Bruneau and co-workers.[63]

More recently, methods based on dual or bifunctional catalysis have proven particularly successful for the direct substitution of allylic alcohols via π-allyl intermediates. In 2014, the laboratories of Zhang and Ohshima developed catalytic methods for the direct addition of activated carbonyl derivatives to allylic alcohols under palladium[64] and platinum[65] catalyzed conditions, respectively (entries 12-13). Both groups employed a combination of transition metal catalyst, bisphosphine ligand and pyrrolidine as an organo-co-catalyst, generating the desired functionalized products in good yields and excellent regioselectivity.

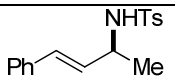
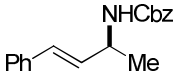
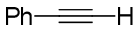
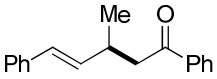
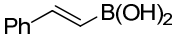
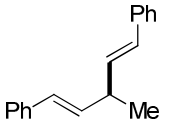
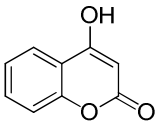
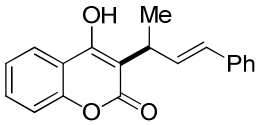
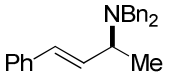
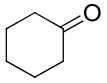
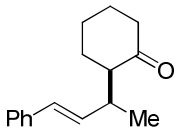
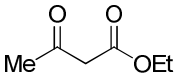
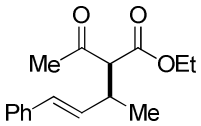
Table 1.5. *Recent advances in direct catalytic allylic alcohol substitution*



Entry	*NuH*	*Catalyst*	*Reaction Conditions*	*Product*	*Yield*
1	$TMS\text{-}N_3$	AgOTf (5 mol%)	toluene, r.t., 16 h		84%
2		$AuCl_3$ (5 mol%)	CH_2Cl_2, r.t., 2 h		97%
3	$TMS\text{-}N_3$	$Cu(ClO_4)_2 \cdot 6H_2O$ (5 mol%)	CH_2Cl_2, r.t., 30 min		79%
4		$Cu(OTf)_2$ (5 mol%)	DCE, 70 °C, 3 h		74%

[62] Wang, M.; Xie, Y.; Li, J.; Huang, H. *Synlett*, **2014**, *25*, 2781.
[63] Sundararaju, B.; Achard, M.; Bruneau, C. *Chem. Soc. Rev.* **2012**, *41*, 4467.
[64] Huo, X.; Yang, G.; Liu, D.; Liu, Y.; Gridnev, I.; Zhang, W. *Angew. Chem. Int. Ed.* **2014,** *53*, 6776.
[65] Shibuya, R.; Lin, L.; Nakahara, Y.; Mashima, K.; Ohshima, T. *Angew. Chem. Int. Ed.* **2014**, *53*, 4377.

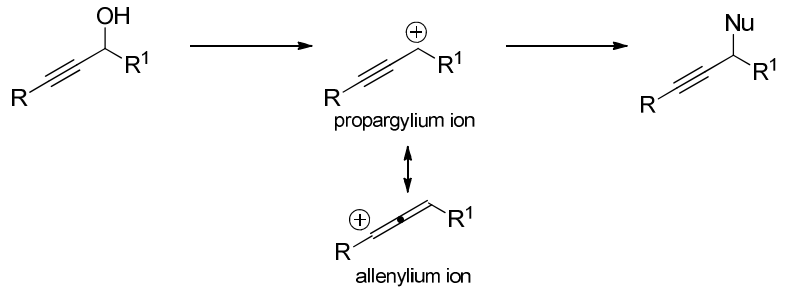
Table 1.5 (continued)

Entry	*NuH*	*Catalyst*	*Reaction Conditions*	*Product*	*Yield*
5	$TsNH_2$	$FeCl_3 \bullet 6H_2O$ (5 mol%)	1,4-dioxane, 50 °C, 24 h		90%
6	$CbzNH_2$	Re_2O_7 (1.5 mol%)	CH_2Cl_2, r.t., 3 h		99%
7		$Ca(NTf_2)_2$ (5 mol%)/ H_4NPF_6 (15 mol%)	DCE, r.t., 2.5 h		71%
8		$Ca(NTf_2)_2$ (5 mol%)	CH_2Cl_2, 10 °C, 10 min		63%
9		Ir-Sn_3 complex (1 mol%)	DCE, 80 °C, 1 h		80%
11	Bn_2NH	$Pd(xantphos)Cl_2$ (5 mol%)	*i*-PrOH, r.t., 12 h		51%
12		$[Pd(n^3\text{-allyl})Cl]_2$ (2.5 mol%)/ dppf (6 mol%)/ pyrrolidine (20 mol%)	MeOH, 20 °C, 24 h		82%
13		$[Pt(cod)Cl_2]$ (2 mol%)/ xantphos (2 mol%)/ pyrrolidine (50 mol%)/ $MeCO_2H$ (50 mol%)	DMF, 60 °C (MW), 5 h		80%

1.5.3 **Dehydrative catalytic substitution of propargylic alcohols**

The catalytic dehydration of propargylic alcohols yields an intermediate propargyl cation, for which two extreme resonance forms can be considered; the propargylium ion and the allenylium ion (Scheme 1.14). Although nucleophilic addition can theoretically occur at either carbon, such reactions typically proceed via a formal S_N1-process. However, a few examples of controllable distal nucleophilic substitution have been reported (*vide infra*). One of the major challenges that remains in the realm of direct propargylic alcohol activation is the generation and capture of unsubstituted propargylic cations (R^1 = H). Typically, the attempted activation of such compounds gives self-condensation and polymerization.

Consequently, the use of α-aryl or α-disubstituted propargylic alcohols is prevalent in the literature in order to enhance the stability and lifetime of such cationic intermediates.



Scheme 1.14. *Considerations in the catalytic activation of propargylic alcohols.*

Table 1.6 provides a summary of recently developed dehydrative, catalytic transformations employing 1,3-diphenylprop-2-yn-1-ol as a prototypical substrate and aligns the catalytic system with a representative nucleophile from each report. Early studies by Hidai, Uemura and Nishibayashi in the area of catalytic propargylic alcohol activation established a cationic methanethiolate-bridged diruthenium complex (*vide infra*) as a highly active catalyst for Friedel-Crafts propargylations (entry 1),[66] while Toste reported activation by a Re(V)-oxo complex for catalytic substitution of propargylic alcohols with allylsilanes[67] and electron rich arenes (entry 2). [68]

Recent advances in the field have been largely based on the use of cationic Lewis acids as catalyst for the propargylation of variety of *C*-, *N*-, *O*- and *S*-centered nucleophiles. Thus, Friedel-Crafts reactions catalyzed by $Ce(OTf)_3$[69] (entry 3) and $Al(OTf)_3$ (entry 4)[70] or by $Cu(OTf)_2$[71] have been recently reported. Similar transformations were also reported by Campagne and co-workers who developed a Au(III) catalyzed system for the direct allylation and arylation of propargylic alcohols (entry 5).[72] The propargylation of a range of electron rich arenes, heteroarenes and 1,3-dicarbonyl compounds, as well as sulfonamides,

[66] (a) Nishibayashi, Y.; Yoshikawa, M.; Inada, Y.; Hidai, M.; Uemura, S. *J. Am. Chem. Soc.* **2002**, *124*, 11846. (b) Nishibayashi, Y.; Inada, Y.; Yoshikawa, M.; Hidai, M.; Uemura, S. *Angew. Chem. Int. Ed.* **2003**, *42*, 1495. (c) Inada, Y.; Yoshikawa, M.; Milton, M. D.; Nishibayashi, Y.; Uemura, S. *Eur. J. Org. Chem.* **2006,** 881.
[67] Luzung, M. R.; Toste, F. D. *J. Am. Chem. Soc.* **2003**, *125*, 15760.
[68] Kennedy-Smith, J. J.; Young, L. A.; Toste, F. D. *Org. Lett.* **2004**, *6*, 1325.
[69] Silveira, C. C.; Mendes, S. R.; Martins, G. M. *Tetrahedron Lett.* **2012**, *53*, 1567.
[70] Gohain, M.; Marais, C.; Bezuidenhoudt, B. C. B. *Tetrahedron Lett.* **2012**, *53*, 4704.
[71] Zhang, L.; Zhu, Y.; Yin, G.; Lu, P.; Wang, Y. *J. Org. Chem.* **2012,** *77*, 9510.
[72] Georgy, M.; Boucard, V.; Campagne, J-M. *J. Am. Chem. Soc.* **2005**, *127*, 14180.

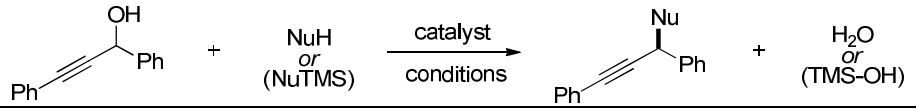
carbamates, and carboxamides has been catalyzed by weakly Lewis acidic $SnCl_2$ as well (entry 6).[73]

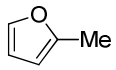
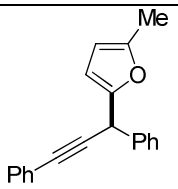
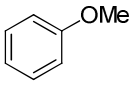
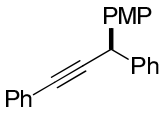
Notably, in 2014, Zheng and co-workers developed a $AgSbF_6$ catalyzed one-pot synthesis of substituted pyrroles, using propargylic alcohols as starting materials (entry 7). Initial $AgSbF_6$ catalyzed dehydrative addition of 1,3-dicarbonyl compounds was followed by treatment with anilines to provide a range of penta-substituted pyrroles in good to excellent yield over two steps.[74]

Pan, Zhang and co-workers report the $Cu(OTf)_2$ catalyzed dehydrative addition of styrene derivatives to propargylic alcohols,[75] advancing earlier work by Wang and co-workers who reported the same system using $FeCl_3$ as a catalyst, but were limited to the more potent 1,1-diarylalkenes as nucleophiles in this ene-type reaction (entries 8-9).[76] In another report, Bezuidenhoudt and co-workers extended their $Al(OTf)_3$ catalyzed activation of propargylic alcohols with the use of 4-hydroxycoumarins as nucleophiles (entry 10).[77]

Alternatively to Lewis acid-type catalysis, Savarimuthu and co-workers reported the *p*-nitrobenzenesulfonic acid catalyzed dehydrative activation of propargylic alcohols (entry 11). This catalyst was shown to be active at room temperature and compatible with *O*-, *N*- and *C*-nucleophiles.[78]

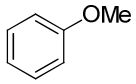
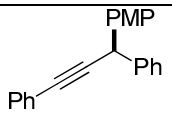
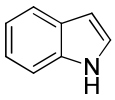
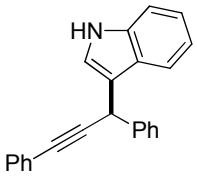
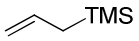
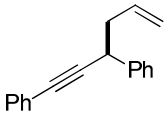
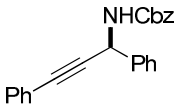
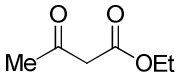
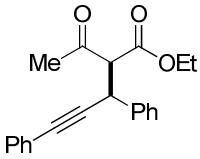
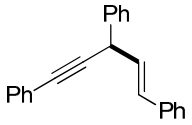
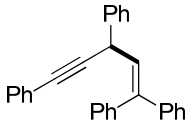
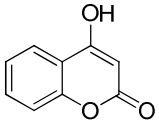
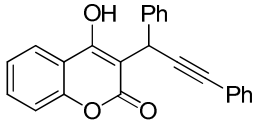
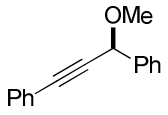
Table 1.6. *Recent advances in direct catalytic propargylic alcohol substitution.*



Entry	*NuH*	*Catalyst*	*Reaction Conditions*	*Product*	*Yield*
1		Ru(thiolate)dimer (5 mol%)	DCE, 60 °C, 1 h		88%
2		$(dppm)Re(O)Cl_3$ (5 mol%)/ KPF_6 (5 mol%)	$MeNO_2$, 65 °C, 5 h		80%

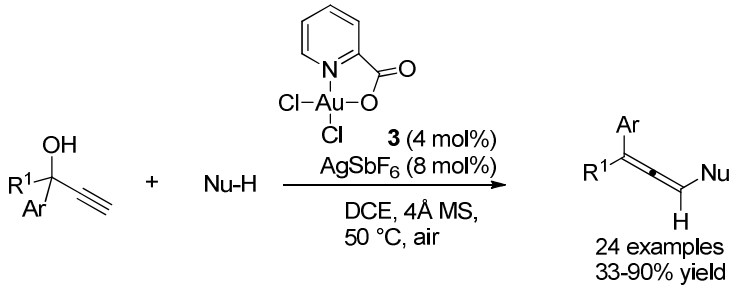
[73] Masuyama, Y.; Hayashi, M.; Suzuki, N. *Euro. J. Org. Chem.* **2013**, 2914.
[74] Gujarathi, S.; Liu, X; Song, L.; Hendrickson, H.; Zheng, G. *Tetrahedron*, **2014**, *70*, 5267.
[75] Huang, G-B.; Wang, X.; Pan, Y-M.; Wang, H. S.; Yao, G-Y. *J. Org. Chem.* **2013**, *78*, 2742.
[76] Peng, S.; Wang, L.; Wang, J. *Org. Biomol. Chem*, **2012**, *10*, 225.
[77] Ponra, S.; Gohain, M.; van Tonder, J. H.; Bezuidenhoudt, B. C. B. *Synlett*, **2015**, 745.
[78] Savarimuthu, S. A.; Prakash, D. G. L.; Thomas, S. A. *Tetrahedron Lett.* **2014**, *55*, 3213.

Table 1.6 (continued)

Entry	*NuH*	*Catalyst*	*Reaction Conditions*	*Product*	*Yield*
3		$Ce(OTf)_3$ (30 mol%)	$MeNO_2$, 40 °C, 30 sec		95%
4		$Al(OTf)_3$ (2 mol%)	MeCN, 85 °C, 2 h		88%
5		$NaAuCl_4•2H_2O$ (5 mol%)	CH_2Cl_2, r.t., 2 h		97%
6	$CbzNH_2$	$SnCl_2$ (10 mol%)	$MeNO_2$, 80 °C, 3 h		83%
7		$AgSbF_6$ (5 mol%)	Toluene, 60 °C, 30 min		82%
8		$Cu(OTf)_2$ (10 mol%)	DCE, reflux, 10 min		90%
9		$FeCl_3•6H_2O$ (10 mol%)	MeCN, 80 °C, 30 min		81%
10		$Al(OTf)_3$ (10 mol%)	MeCN, reflux, 5 h		91%
11	MeOH	*p*-NBSA (5 mol%)	MeCN, r.t., 30 min		89%

An interesting study, different to the aforementioned systems, was reported by Li and co-workers, who opted to investigate the gold catalyzed dehydrative substitution of propargylic alcohols (Scheme 1.15). Using Au(III)-precatalyst **3** and $AgSbF_6$ as a co-catalyst, nucleophilic addition of a range of typical arenes was found to occur at the distal C3-position to generate a series of tri-substituted allenes. Interestingly, when anisole or trimethoxybenzene were employed as nucleophiles, exclusive C1-substitution was observed to yield diarylacetylene derivatives. The authors ascribe this selectivity switch to the

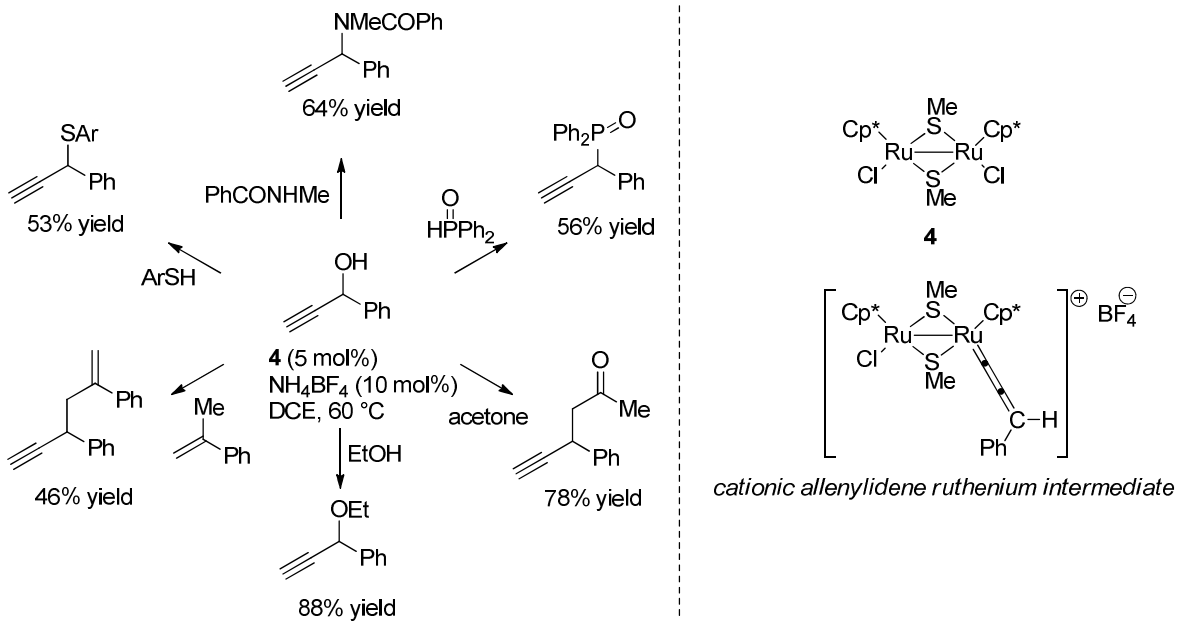
coordination of the anisole oxygen residues to the gold catalyst thereby preferentially delivering the arene to the proximal C1-position.[79]



Scheme 1.15. *Au/Ag catalyzed dehydrative arylation reaction generating trisubstituted allenes.*

The catalytic activation of terminal propargylic alcohols with diruthenium thiolate-bridged complexes has proved a fruitful area of research. In a comprehensive series of reports, Nishibayashi, Uemura, Hidai and co-workers developed ruthenium thiolate complexes of the type **4** capable of catalytically activating terminal propargylic alcohols under mild reaction conditions.[80] The key intermediate in such transformations is reported as an allenylidene ruthenium complex that can be intercepted by a range of nucleophilic species to furnish an array of functionalized products (Scheme 1.16). A 2014 report has also demonstrated the ability of preformed cationic allenylidene mono-ruthenium complexes to function as catalysts for the dehydrative etherification of terminal propargylic alcohols.[81] Haak and co-workers have also demonstrated the use of cyclopentadienone ruthenium complexes as catalysts in related dehydrative transformations of terminal propargylic alcohols, proposing similar key allenylidene intermediates in such processes.[82]

[79] Xu, C-F.; Xu, M.; Yang, L-Q.; Li, C-Y. *J. Org. Chem.* **2012**, *77*, 3010.
[80] (a) Nishibayashi, Y.; Wakiji, I.; Hidai, M. *J. Am. Chem. Soc.* **2000**, *122*, 11019. (b) Nishibayashi, Y.; Wakiji, I.; Ishii, Y.; Uemura, S.; Hidai, M. *J. Am. Chem. Soc.* **2001**, *123*, 3393. (c) Nishibayashi, Y.; Inada, Y.; Hidai, M.; Uemura, S. *J. Am. Chem. Soc.* **2003**, *125*, 6060. (d) Nishibayashi, Y.; Yoshikawa, M.; Inada, Y.; Hidai, M.; Uemura, S. *J. Org. Chem.* **2004**, *69*, 3408.
[81] Alkhaleeli, D. F.; Baum, K. J.; Rabus, J. M.; Bauer, E. B. *Catal. Commun.* **2014**, *47*, 45.
[82] (a) Thies, N.; Hrib, C. G.; Haak, E. *Chem. Eur. J.* **2012**, *18*, 6302. (b) Thies, N.; Haak, E. *Angew. Chem. Int. Ed.* **2015**, *54*, 4097.



Scheme 1.16. *Transformations of terminal propargylic alcohols catalyzed by a thiolate-bridged diruthenium complex.*

1.6 Critical summary and aim of the thesis

The continued efforts of synthetic chemists over the last decades have now made the previously elusive direct catalytic dehydrative transformations of π-activated alcohols a reality for organic synthesis. Nowadays, a variety of π-activated alcohols can be successfully coupled with a range of carbon-carbon and carbon-heteroatom bond-forming nucleophiles under catalytic loading of Brønsted or Lewis acids. Although good synthetic yields have been achieved with certain catalysts, the scope of transformations performed by a given catalyst remains largely limited to certain classes of alcohols and nucleophiles. Furthermore, with catalyst systems prevalent in many of the described transformations, cleavage of sensitive functional groups such as silyl groups or Boc groups is commonplace. Thus, the field overall lacks a general set of mild conditions for substitution reactions of various classes of activated and non-activated alcohols with weak and strong nucleophiles. In our eyes, an ideal catalyst system should comply with the following criteria:

- Catalyze direct reaction of unactivated alcohols
- Afford general reactivity for various hydroxyl group-bearing substrates
- Display high functional group compatibility
- Provide compatibility with wide range of *C*-, *N*-, *S*-, *O*-centered nucleophiles
- No dry solvent or inert atmosphere required

- Low catalyst loadings
- Short reaction time
- Room temperature reactivity
- Catalyst being cheap to make or ideally commercially available

Therefore, our search for such an ideal catalytic system will be detailed in this thesis.

In this context, in Chapter 2 we will attack the problem of the compromise between reactivity and chemoselectivity in dehydrative transformations of π-activated alcohols. Specifically, we will perform a systematic survey of common Lewis and Brønsted acid catalysts in order to uncover a powerful yet mild catalyst for the nucleophilic substitution of a broad range of π-activated alcohols with variety of common *C*-, *N*-, *S*-, *O*-centered nucleophiles.

In Chapter 3, with a powerful catalyst in hand we will handle the problem of the challenging substitution of a non-activated class of substrates, namely tertiary aliphatic alcohols. Our previously discovered catalytic system will be tested on Friedel-Crafts and thiodehydration reactions of tertiary aliphatic alcohols and the tolerance to acid sensitive functionalities will be verified under the new set of reaction conditions.

Chapter 4 will focus on mechanistic experiments designed to understand why dehydroazidation of tertiary aliphatic alcohols with $TMSN_3$ is much faster than with other nucleophiles and to further probe the observation that nitro compounds act as co-catalysts in these transformations.

In Chapter 5, application of our catalytic system will be extended beyond alcohol activation and applied to the cleavage of the strongest carbon-heteroatom bond, the C–F bond, in corresponding defluorinative Friedel-Crafts reactions of tertiary aliphatic fluorides.

Finally, Chapter 6 will summarize the conclusions of the thesis and provide perspectives for the future directions of the research developed herein.

CHAPTER 2[83]

Reactivity *vs*. Chemoselectivity in the Catalytic Dehydrative Substitution of π-Activated Alcohols

[83] Portions of this chapter have been published: Hellal, M.; Falk, F. C.; Wolf, E.; Dryzhakov, M.; Moran, J. *Org. Biomol. Chem.* **2014**, *12*, 5990.

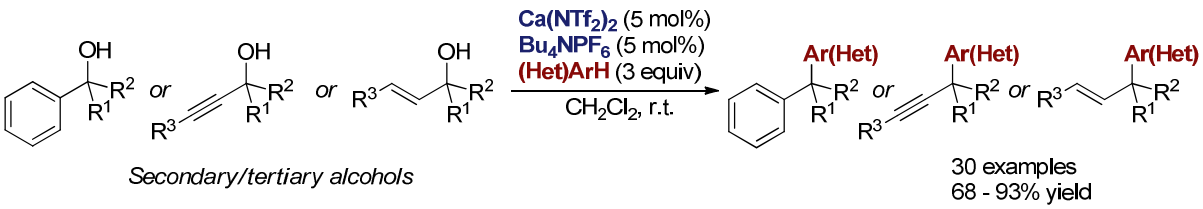
2.1 Introduction to dichotomy between reactivity and chemoselectivity in dehydrative S_N1 reactions

The usefulness of a catalytic system for a given chemical transformation is understood in terms of its catalytic activity and selectivity. Catalytic activity refers to the extent of the rate increase of a specific chemical reaction caused by a catalyst. This rate increase may be represented by direct metrics such as turnover frequency, as well as by indirect metrics such as the substrate scope, the energy input and time required to obtain a synthetically useful yield of a desired product. On the other hand, catalytic selectivity refers to the relative rates of two or more competing reactions enabled by the same catalyst system.[84] Catalytic selectivity may be embodied in many different forms including regioselectivity, stereoselectivity or chemoselectivity. Although catalysts of high structural complexity, such as enzymes, often display high catalytic activity and high selectivity of all flavors at the same time due to the exceptional level of molecular recognition between catalyst and substrate, the inferior substrate recognition characteristic of structurally simple man-made catalysts often leads to an undesirable dichotomy between catalytic activity and selectivity. An illustrative example of this problem is the dichotomy between catalytic activity and chemoselectivity in the catalytic dehydrative S_N1 reaction of π-activated alcohols, whose synthetic limitations will be detailed in the following section.

2.1.1 Catalytic activity vs. chemoselectivity in dehydrative substitution of π-activated alcohols

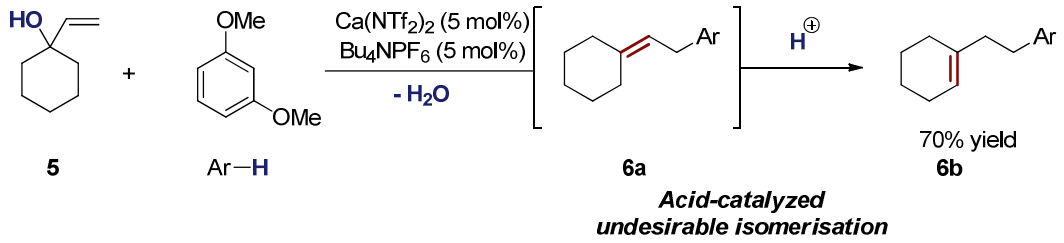
In a notable contribution from Niggemann and Meel,[27] a substoichiometric $Ca(NTf_2)_2/Bu_4NPF_6$ bicomponent system for the activation of a range of secondary and tertiary benzylic, allylic and propargylic alcohols in Friedel-Crafts alkylation of arenes and heteroarenes was reported (Scheme 2.1).

[84] McNaught, A. D.; Wilkinson, A. *Compendium of Chemical Terminology*, 2nd ed. Blackwell Scientific Publications, Oxford, **1997**.



Scheme 2.1. *$Ca(NTf_2)_2/Bu_4NPF_6$-catalyzed Friedel-Crafts alkylation with secondary and tertiary π-activated alcohols.*

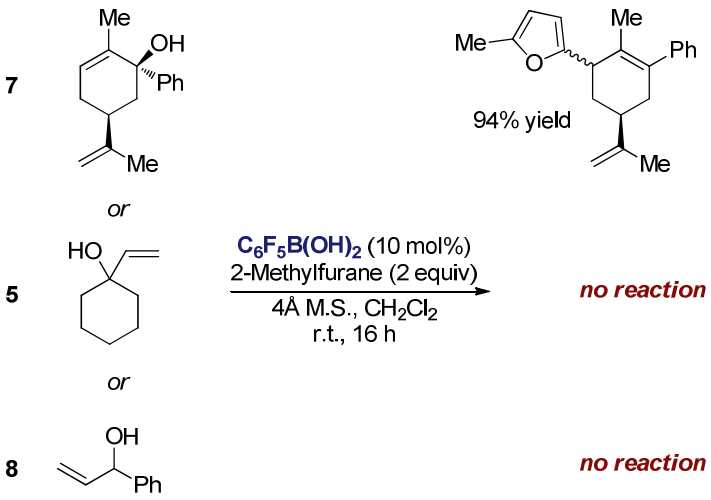
In a representative example from the aforementioned report, the $Ca(NTf_2)_2/Bu_4NPF_6$ system was able to catalyze the intermolecular alkylation of 1,3-dimethoxybenzene by allylic alcohol **5** in 70% isolated yield (Scheme 2.2). However, as has been noted by the authors, the initially formed exocyclic alkene **6a** undergoes an additional Brønsted acid-catalyzed isomerization to the thermodynamically favored endocyclic regioisomer **6b**. The presence of Brønsted acid in the reaction mixture is unavoidable due to hydrolysis of the strong Lewis acid by stoichiometric water by-product or even due to reaction between the catalyst and the alcohol itself. A similar outcome is expected to be commonplace in the majority of Lewis acid-catalyzed dehydrative transformations, thus emphasizing the chemoselectivity limitations in this otherwise powerful synthetic methodology.



Scheme 2.2. *Brønsted acid catalyzed isomerization of acid-sensitive alkenes upon hydrolysis of Niggemann's Friedel-Crafts alkylation catalyst.*

On the other hand, recent research towards chemoselective catalytic systems for direct alcohol activation has resulted in the development of mild boron-based catalysts that are tolerated by acid sensitive functionalities. However, this valuable advantage has typically been achieved at the cost of a reduced catalytic activity resulting in a limited alcohol scope for the reaction. McCubbin and co-workers originally reported pentafluorophenylboronic acid as a catalyst for the Friedel-Crafts reaction of electron rich arenes and heteroarenes with

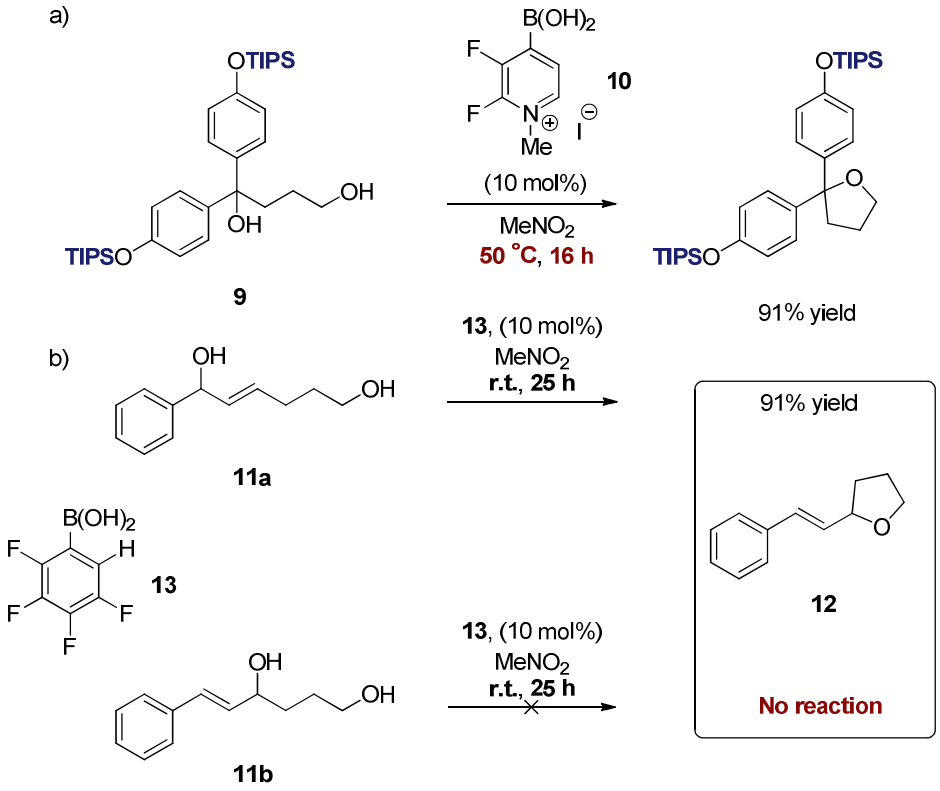
benzylic,[26] allylic,[85a] and propargylic[85b] alcohols. Although the catalyst was able to promote the reactivity of selected allylic alcohols, such as **7**, with no observable acid-catalyzed alkene isomerization, substrate **5** from Niggemann's study showed no conversion under standard reaction conditions (Scheme 2.3). Likewise, acyclic allylic alcohol **8**, a precursor to a highly stabilized carbocation due to the presence of additional phenyl group adjacent to the hydroxyl-bearing carbon atom, does not react under these milder conditions.



Scheme 2.3. *Limited but chemoselective pentafluorophenylboronic acid-catalyzed dehydrative Friedel-Crafts reactions of allylic alcohols.*

In notable work by Hall and co-workers, the reactivity of a series of electron-poor boronic acids was evaluated in the 1,3-transposition of allylic alcohols, the Meyer-Schuster rearrangement of propargylic alcohols,[86a] and in the carbo- and heterocyclization of allylic alcohols.[86b] In representative examples from the latter report, bis-benzylic alcohol **9** bearing TIPS protected phenol was cyclized in 91% yield. However, prolonged reaction time and elevated temperature were necessary to achieve the reactivity using a catalyst **10** that was not commercially available (Scheme 2.4, a). Although effective in dehydrative cyclisation of doubly-activated alcohol **11a** to deliver **12**, electron-poor boronic acid **13** failed to promote the cyclization of the isomeric allylic alcohol **11b** at room temperature (Scheme 2.4, b). Once again, the mild, chemoselective nature of these catalysts comes at the cost of reduced catalytic activity and substrate scope.

[85] (a) McCubbin, J. A.; Hosseini, H.; Krokhin, O. V. *J. Org. Chem.* **2010**, *75*, 959. (b) McCubbin, J.; Nassar, C.; Krokhin, O. *Synthesis* **2011**, 3152.
[86] (a) Zheng, H.; Lejkowski, M.; Hall, D. G. *Chem. Sci.* **2011**, *2*, 1305. (b) Zheng, H.; Ghanbari, S.; Nakamura, S.; Hall, D. G. *Angew. Chem. Int. Ed.* **2012**, *51*, 6187.



Scheme 2.4. *Electron-poor boronic acid catalysis for a) chemoselective but sluggish cyclisation b) cyclisation of regioisomers **11a** and **11b**.*

2.1.2. General conclusion and aim of the chapter

Although powerful catalytic systems have been identified for the transformations of π-activated alcohols, the challenge of activating hydroxyl groups selectively and without undesirable cleavage or isomerization of acid-sensitive functional groups remains unanswered. Thus, to consider the alcohol activation as a "solved problem", further investigations are necessary in order to identify catalytic systems that provide an ideal balance between catalytic activity and chemoselectivity. Our search for such an "ideal dichotomous" catalyst for the direct dehydrative transformation of π-activated alcohols will be detailed in the following section.

2.2 Discussion

The identification of an optimal catalyst system requires extensive screening but also the judicious selection of the substrate to be studied so as to allow easy examination of the

catalyst's performance. Complex studies which must address the effects of the catalyst and solvent on the catalysis are discussed below.

2.2.1 **Choice of model system and catalyst screen**

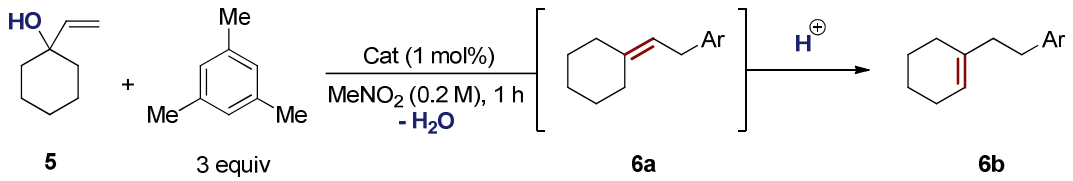
We began our initial investigation by undertaking a catalyst screen on the relatively challenging intermolecular Friedel-Crafts reaction of allylic alcohol **5** with "electron-neutral" mesitylene as a nucleophile. This reaction initially forms the exocyclic alkene product **6a** which tends to isomerize to thermodynamically favorable endocyclic alkene **6b** in the presence of strong Brønsted acid, which is potentially generated upon hydrolysis of the catalyst by the stoichiometric water by-product or by the alcohol itself. The ratio of **6a/6b** regioisomers, alongside the total yield of substitution products, could therefore serve as a probe of reactivity/chemoselectivity behavior for a range of acid catalysts. Although room temperature is usually sufficient, an additional comparison of the reaction outcomes at room and elevated temperature provides further valuable information.

After a brief optimization of the reaction conditions, a survey of common Brønsted and Lewis acids was undertaken at 1 mol% catalyst loading in nitromethane (Table 2.1). The presence of the catalyst proved to be essential to the reactivity (entry 1). Strong Brønsted acids (entries 2-5) are all able to catalyze the dehydrative transformation in 1 h at 80 °C accompanied by high degree of olefin isomerization. Chemoselectivity could be significantly increased with the decrease in acid strength such as in the case of weaker trifluoroacetic acid (entry 6), however not without slowing down the desired reactivity, even at 80 °C. Cationic Lewis acids (entries 6-12), including Niggemann's $Ca(NTf_2)_2/Bu_4NPF_6$ system[27] (entry 7) and "water-stable" $Yb(OTf)_3$,[87] furnished appreciable amounts of the product, but all induce alkene isomerization. Brief investigation of "neutral" Lewis acid catalysts (entries 13-15) revealed either extensive olefin isomerization (entry 13) or the absence of reactivity as in the case of electron-poor pentafluorophenyl boronic acid (entry 14) or triphenylborane (entry 15). Among all the catalysts surveyed, tris(pentafluorophenyl)borane hydrate showed the highest conversion, but with a remarkable degree of chemoselectivity even at elevated temperature (entry 16). With only 1 mol% of this easily weighable solid catalyst, 77% isolated yield of pure **6a** could be obtained at room temperature after the simple extension of the reaction time to 4 h. In contrast, strong Brønsted acids (entries 19-20) induce olefin isomerization even at

[87] Kobayashi, S.; Nagayama, S.; Busujima, T. *J. Am. Chem. Soc.* **1998**, *120*, 8287.

room temperature with an overall slower rate of substitution reaction. Notably, weaker Brønsted acids were ineffective at the same catalyst loading (entry 21).

Table 2.1. *Screen of catalysts for chemoselective activation of alcohol* ***5****.*



5 3 equiv **6a** **6b**

Entry	*Catalyst*	*T, (°C)*	*Yield[a] 6a + 6b, (%)*	*Ratio 6a/6b*
1	None	80	<5	N/A
2	TfOH	80	77	1:10
3	HBF_4	80	88	1:9
4	H_2SO_4	80	78	1:5
5	*p*-TsOH	80	74	4:1
6	TFA	80	68	>20:1
7	$Ca(NTf_2)_2/Bu_4NPF_6$	80	74	1:9
8	$Bi(OTf)_3$	80	83	1:12
9	$Sc(OTf)_3$	80	83	1:9
10	$Yb(OTf)_3$	80	62	4:1
11	$FeCl_3$	80	82	1:3
12	$AuCl_3$	80	85	6:1
13	BF_3•THF	80	82	1:10
14	$B(C_6F_5)(OH)_2$	80	<5	N/A
15	BPh_3	80	<5	N/A
16	$B(C_6F_5)_3$•H_2O	80	92	>20:1
17	$B(C_6F_5)_3$•H_2O	22	60	>20:1
18[b]	$B(C_6F_5)_3$•H_2O	22	77	>20:1
19	TfOH	22	47	2:1
20	*p*-TsOH	22	32	>20:1
21	TFA	22	<5	N/A

[a]Isolated yield. [b]Reaction time extended to 4 h.

2.2.2 **Physicochemical properties of tris(pentafluorophenyl)borane hydrate**

The aforementioned superior balance in reactivity and chemoselectivity of tris(pentafluorophenyl)borane in catalytic Friedel-Crafts reaction of allylic alcohol **5** is potentially associated with specific physicochemical properties of the catalyst. Although considered as a strong Lewis acid in its anhydrous form,[88] commercial

[88] For reviews on use of tris(pentafluorophenyl)borane, most notably as a co-catalyst for olefin polymerization, see: (a) Piers, W. E.; Chivers, T. *Chem. Soc. Rev.* **1997**, *26*, 345. (b) Chen, E. Y. X.; Marks, T. J. *Chem. Rev.*

tris(pentafluorophenyl)borane purchased from *SigmaAldrich*™ or *Alfa Aesar*™ is known to rapidly hydrate to $B(C_6F_5)_3 \bullet H_2O$ if moisture or air is not rigorously excluded.[89] Upon slow evaporation of a $B(C_6F_5)_3$ solution in wet $CHCl_3$, crystals of $B(C_6F_5)_3 \bullet H_2O$[90] and $[B(C_6F_5)_3 \bullet H_2O] \bullet 2H_2O$[91] have been both isolated and fully characterized. Crystallographic analysis of the latter revealed that one molecule of water is coordinated to the boron directly, whilst the two remaining water molecules accept hydrogen bonds from each of two coordinated waters' hydrogen atoms (Figure 2.1).

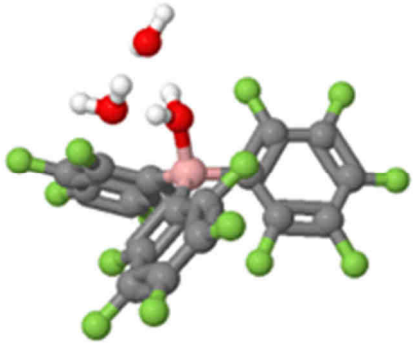


Figure 2.1. *CSD crystal structure of $[B(C_6F_5)_3 \bullet H_2O] \bullet 2H_2O$ showing one innersphere water molecule bonded directly to boron and two outsphere hydrogen-bonded water molecules (H-white, C-grey, O-red, F-green, B-pink).*

In fact, in a solution of wet solvent, 1 equivalent of water bonds quantitatively to $B(C_6F_5)_3$ with the subsequent hydrates being in dynamic equilibrium with each other (Scheme 2.5).[92] The formation of hydrated species happens in a stepwise manner upon the addition of stoichiometric water, and this hydration could be monitored by ^{19}F and ^{1}H NMR. Thus, it is already known that under our standard open-air reaction conditions, commercial tris(pentafluorophenyl)borane indeed undergoes rapid hydration with the major component $B(C_6F_5)_3 \bullet H_2O$ being present in the solution at room temperature.

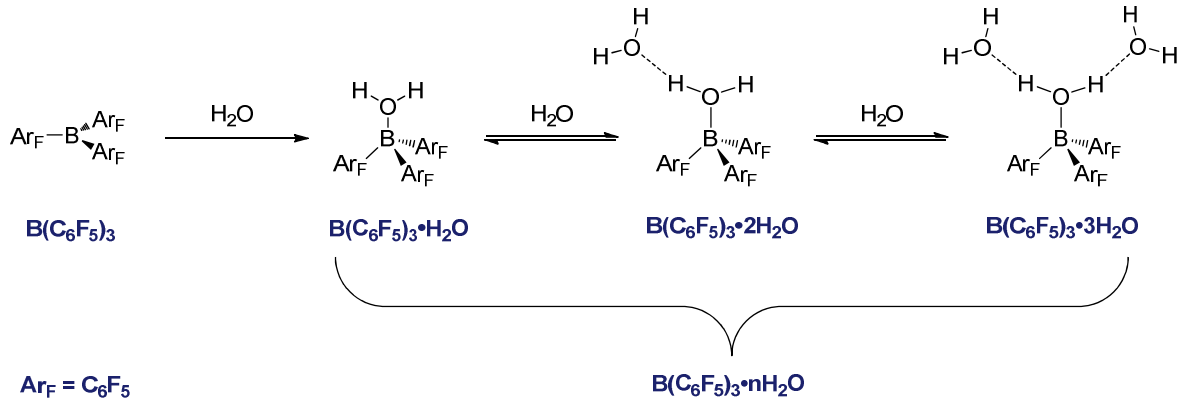
2000, *100*, 1391. (c) Piers, W. E. *Adv. Organomet. Chem.* **2004**, *52*, 1. (d) Kargbo, R. B. *Synlett* **2004**, 1118. (e) Erker, G. *Dalt. Trans.* **2005**, 1883.

[89] Bergquist, C.; Bridgewater, B. M.; Harlan, C. J.; Norton, J. R.; Friesner, R. A.; Parkin, G. *J. Am. Chem. Soc.* **2000**, *122*, 10581.

[90] Doerrer, L. H.; Green, M. L. H. *J. Chem. Soc., Dalt. Trans.* **1999**, 4325.

[91] Danopoulos, A. A.; Galsworthy, J. R.; Green, M. L. H.; Cafferkey, S.; Doerrer, L. H.; Hursthouse, M. B. *Chem. Commun.* **1998**, 2529.

[92] Beringhelli, T.; Maggioni, D.; D'Alfonso, G. *Organometallics* **2001**, *20*, 4927.



Scheme 2.5. *Dynamic equilibrium of tris(pentafluorophenyl)borane hydrates.*

The Brønsted acidity of $B(C_6F_5)_3$•H_2O has also been extensively studied. NMR titration experiments and DFT calculations allowed Bergquist and Parkin to estimate its pKa as 8.4 in acetonitrile and to predict a hypothetical pKa value in water of less than 0.9.[89] This pKa is roughly comparable to that of HCl. In this regard, $B(C_6F_5)_3$•H_2O has been reported to protonate a range of metallocenes[90] and a synthetic analog of a zinc-bearing enzyme.[93]

Although not being discussed in the literature as Brønsted acid catalyst for alcohol substitution,[94] we hypothesized that such non-conventional properties of $B(C_6F_5)_3$•H_2O could be at the origin of its superior efficiency in acid-catalyzed alcohol activation. In fact, the observed high degree of both reactivity and chemoselectivity in our Friedel-Crafts reaction must imply the superior degree of molecular recognition between substrate and active catalyst compare to the simple proton or common Lewis acid catalysts (Figure 2.2). In principle, such an approach could be expected to facilitate alcohol ionization and allow the better control over the actual product-forming step.

[93] Bergquist, C.; Parkin, G. *J. Am. Chem. Soc.* **1999**, *121*, 6322.

[94] Several reports on the use of $B(C_6F_5)_3$ as Lewis acid in nucleophilic substitution of π-activated alcohols and acetates have been reported,: (a) Rubin, M.; Gevorgyan, V. *Org. Lett.* **2001**, *3*, 2705. (b) Reddy, C. R.; Rajesh, G.; Balaji, S. V.; Chethan, N. *Tetrahedron Lett.* **2008**, *49*, 970. (c) Rajagopal, G.; Kim, S. S. *Tetrahedron* **2009**, *65*, 4351. (d) Reddy, C.; Vijaykumar, J.; Grée, R. *Synthesis* **2010**, *21*, 3715.

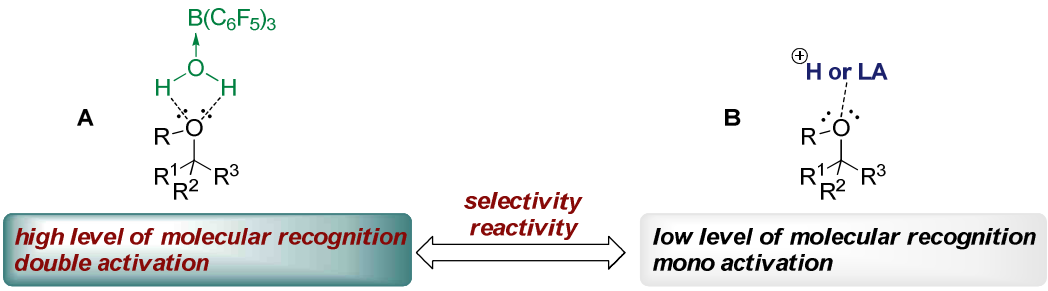
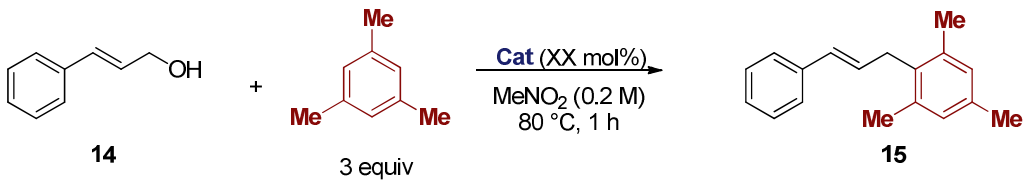


***Figure 2.2**. Virtual comparison in efficiency of $B(C_6F_5)_3 \bullet H_2O$ (A) and common Lewis acids (B) in alcohol activation.*

2.2.3. Comparison of $B(C_6F_5)_3 \bullet H_2O$ with other boron catalysts

The unusual reactivity profile of $B(C_6F_5)_3 \bullet H_2O$ raised an opportunity to compare this catalyst with related boron-based catalysts. For this goal we chose to study the intermolecular Friedel-Crafts reaction of mesitylene with cinnamyl alcohol **14** to produce **15** (Table 2.2). No product formation was observed in the absence of catalyst (entry 1) after 1 h at 80 °C. However, the desired **15** could be obtained in 65% isolated yield with 10 mol% of $B(C_6F_5)_3 \bullet H_2O$ (entry 2). This reactivity proved to be superior to other boranes, boronic, borinic, and boric acids (entry 3-8), regardless of the fact that penta- and tetrafluorophenylboronic acids (entry 2-3) were reported as effective catalysts for the dehydrative transformations of π-activated alcohols.[85,86] Surprisingly, at reduced catalyst loading the yield of the desired product increased to 86% (entry 9), while other boron compounds became ineffective in this reaction (entry 10-11). Finally, $BF_3 \bullet THF$ displayed inferior reactivity in this reaction (entry 12).

Table 2.2. *Comparison of $B(C_6F_5)_3 \bullet H_2O$ with other boron-based catalysts.*



Entry	*Catalyst*	*Loading, (mol%)*	*Yield,[a] (%)*
1	None	n/a	<5
2	$B(C_6F_5)_3 \bullet H_2O$	10	65
3	$C_6F_5B(OH)_2$	10	22
4	$C_6HF_4B(OH)_2$	10	13
5	Ph_3B	10	31
6	Ph_2BOH	10	17

Table 2.2 Continued

Entry	***Catalyst***	***Loading, (mol%)***	***Yield,[a] (%)***
7	$PhB(OH)_2$	10	<5
8	$B(OH)_3$	10	12
9	$B(C_6F_5)_3•H_2O$	1	86
10	$C_6F_5B(OH)_2$	1	<5
11	$C_6HF_4B(OH)_2$	1	<5
12	BF_3•THF	1	68

[a]Isolated yield.

2.2.4. **Effect of nitromethane**

The ability of the solvent to drastically influence the progress of the reaction by altering the dielectric properties, donicity and hydrogen-bonding capability of the medium is well documented in the literature.[95] Our curiosity to uncover the physicochemical factors responsible for the origin of the mild and chemoselective reactivity of $B(C_6F_5)_3•H_2O$ in dehydrative transformations of alcohols led us to evaluate the effect of solvent in this reaction more deeply. The compatibility of a range of common polar and nonpolar organic solvents was tested for the Friedel-Crafts reaction of cinnamyl alcohol **14** (Figure 2.3). Surprisingly, nitromethane was the only solvent to promote the desired reactivity in contrast to the frequently used DCE or mesitylene in the Friedel-Crafts-type transformations with mesitylene nucleophile. Although the dielectric constant of the solvent does not necessarily take into account all important properties of the medium, the intermediate value of such for nitromethane highlights the unusual behavior of this solvent. This effect will be explored further in the following chapters of this thesis.

[95] Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*, 3rd updated and enlarged ed.; Wiley-VCH: Weinheim, **2003**.

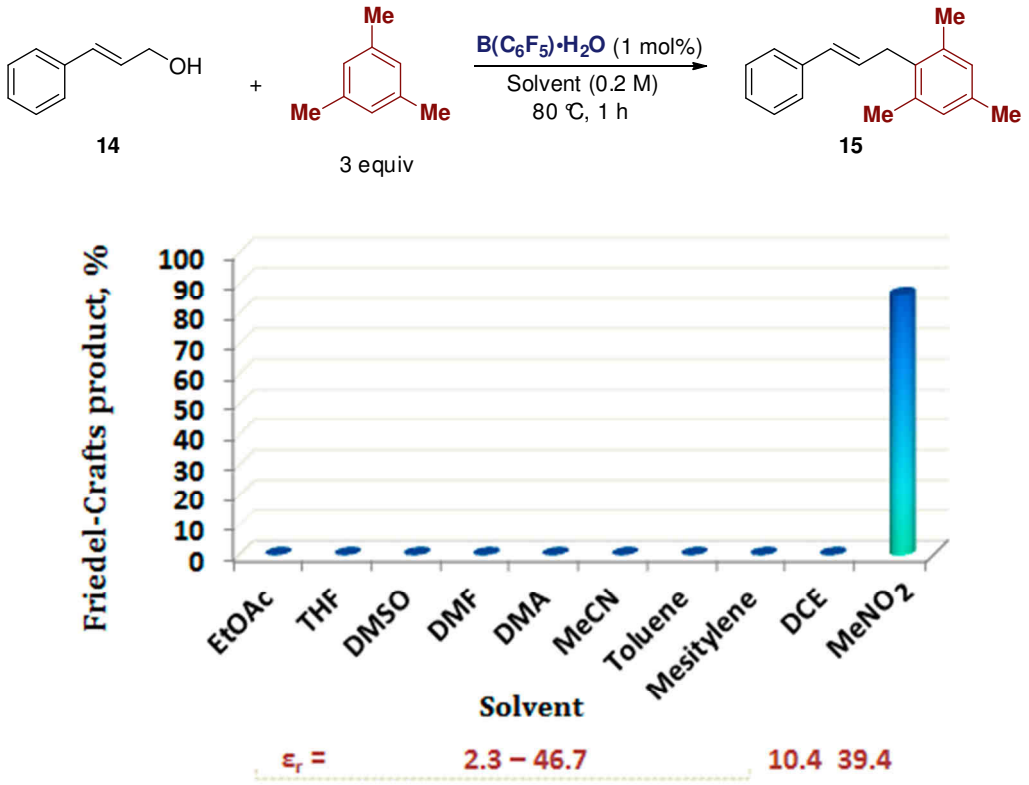


Figure 2.3. *Solvent screen for the Friedel-Crafts reaction of cinnamyl alcohol **14** with mesitylene (NMR yield).*

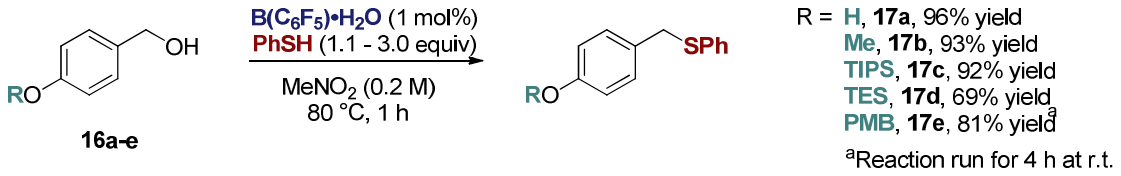
2.2.5 **Chemoselective alcohol substitution in the presence of silyl ether functionalities**

Silyl ethers are commonly employed as protecting groups for alcohols in organic synthesis.[96] The selective installation and cleavage of silyl ethers is commonplace throughout complex molecule synthesis and the latter typically relies on the use of protic reagents with a finely tuned acidity. Therefore, the use of acid-catalyzed functionalization reactions for substrates bearing a silyl-ether group represents a difficult challenge for chemoselectivity and is typically avoided in synthesis.

To test the viability of silyl ether functionalities under our reaction conditions, we examined the intermolecular coupling of protected 4-hydroxybenzyl alcohols **16a-e** with thiophenol at 1 mol% loading of $B(C_6F_5)_3$•H_2O at 80 °C in nitromethane (Scheme 2.6), although room temperature was also sufficient for reactivity (for comparison with other catalysts, please see chapter 3). As with free phenol **17a** and methyl ether **17b**, TIPS-protected product **17c** is formed smoothly in 92% yield after 1 h and no cleavage of the silyl ether is observed. To test the limits of compatibility, TES-protected product **17d** (≈10^3 times

[96] Wuts, P. G. M.; Greene, T. W. *Greene's protective groups in organic synthesis*, Fourth Edition.; John Wiley & Sons, Inc., Hoboken, New Jersey, **2007**.

more labile) is isolated intact in a lower 69% yield. The more facile activation of alcohols compared to ethers can be exploited to achieve selectivity when benzylic ethers and benzylic alcohols are both present on the same substrate. Although not stable at 80 °C, benzylic alcohol **16e** converts to **17e** in 81% yield without cleavage of the PMB-protected phenol simply by carrying out the reaction at room temperature over 4 h.

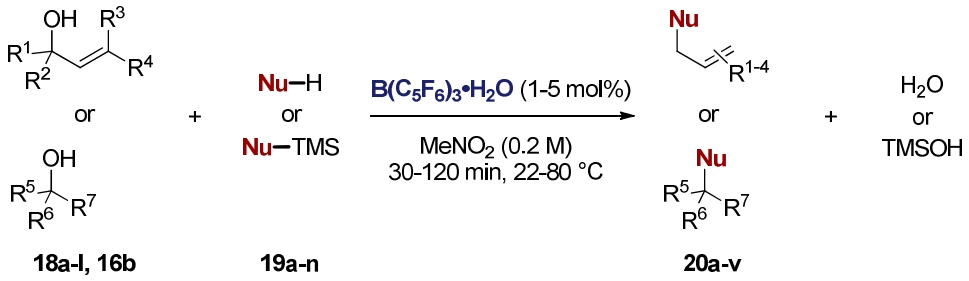


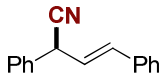
Scheme 2.6. *$B(C_6F_5)_3$•H_2O-catalyzed chemoselective benzylic alcohol activation in the presence of silyl ethers functionalities.*

2.2.6 **Substrate scope for chemoselective alcohol substitution**

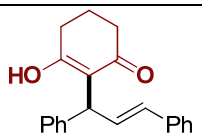
With the superior chemoselectivity profile of $B(C_6F_5)_3$•H_2O in hand, we directed our attention towards the scope of catalytic dehydrative or deoxygenative intermolecular transformations of allylic, benzylic, and propargylic alcohols with representative *C*-, *N*-, *S*- and *O*-nucleophiles (Table 2.3). Thus, cyanation of benzylic alcohols was accomplished with trimethylsilyl cyanide **19a** to give nitrile **20a**. Direct alkylation of 1,3-cyclohexanedione **18b** occurs in high yield to give **20b**. Allylation of primary benzylic or allylic alcohols with allyltrimethylsilane **19c** occurs smoothly under the standard conditions to give compounds **20c**-**20e**. Dehydrative Friedel-Crafts alkylation occurs with electronically diverse arenes such as 2-methylfuran **19d**, indole **19e**, and mesitylene **19f** to give products **20f**-**20i**. Benzene **19g**, a challenging Friedel-Crafts nucleophile, gives diarylmethane **20j** as a single compound in 96% yield. Mildly basic heteroatomic nucleophiles are also well tolerated. For example, nitrogen nucleophiles including carbamates **19h** and **19i**, benzenesulfonamide **19j** and trimethylsilyl azide **19k** react to give *N*-alkyl carbamates, sulfonamides and azides **20k**-**20q**. The *N*-Boc carbamate **19h** and the resulting *N*-Boc protected amine **20k** survive under these conditions. Finally, reactions of oxygen and sulfur nucleophiles occur under the standard conditions. Primary aliphatic alcohol **19l** undergoes nucleophilic addition to secondary benzylic alcohol **18k** without observable elimination to give ether **20r**. Thiophenol **19m** and thioacetic acid **19n** react with allylic and benzylic alcohols to give thioethers **20s**-**20u** and thioester **20v**, respectively.

Table 2.3. *Representative nucleophile and alcohol scope*[a,b]

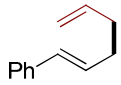




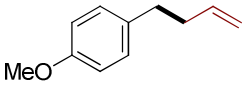
91% yield,[c] 22 °C
18b + 19a = 20a



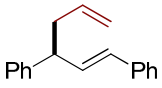
96% yield,[c] 22 °C
18b + 19b = 20b



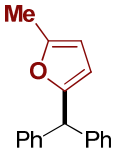
99% yield,[e] 80 °C
18a + 19c = 20c



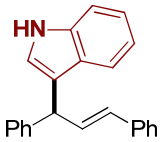
97% yield,[c] 80 °C
16b + 19c = 20d



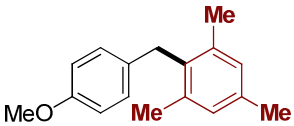
99% yield,[e] 22 °C
18b + 19c = 20e



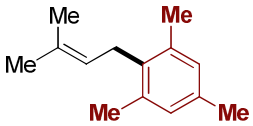
99% yield,[c] 80 °C
18h + 19d = 20f



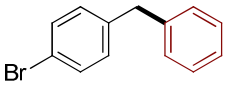
96% yield,[d] 22 °C
18b + 19e = 20g



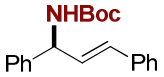
99% yield,[c] 80 °C
16b + 19f = 20h



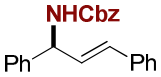
69% yield,[c] 80 °C
18g + 19f = 20i



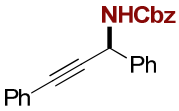
96% yield,[e] 100 °C
18j + 19g = 20j



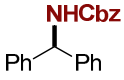
94% yield,[d] 22 °C
18b + 19h = 20k



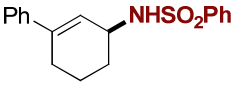
99% yield,[d] 22 °C
18b + 19i = 20l



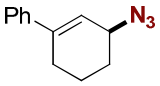
98% yield,[d] 80 °C
18l + 19i = 20m



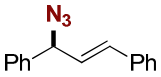
88% yield,[e] 80 °C
18h + 19i = 20n



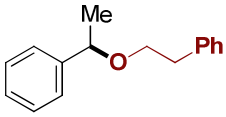
81% yield,[d] 22 °C
18e + 19j = 20o



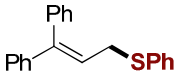
90% yield,[f] 22 °C
18e + 19k = 20p



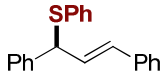
95% yield,[f] 22 °C
18b + 19k = 20q



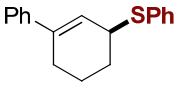
96% yield,[c] 80 °C
18k + 19l = 20r



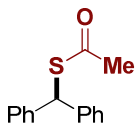
99% yield,[c] 80 °C
18d + 19m = 20s



99% yield,[c] 22 °C
18b + 19m = 20t

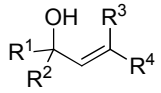
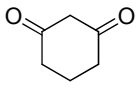
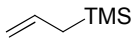
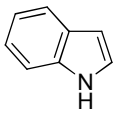
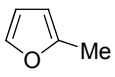


90% yield,[c] 22 °C
18e + 19m = 20u



85% yield,[d] 80 °C
18h + 19n = 20v

Table 2.3 (continued)

Alcohols		Nucleophiles	
		**19a**, TMSCN	
		19f, Mesitylene	
		19g, PhH	
		19h, NH_2Boc	**19b**
		19i, NH_2Cbz	
		19j, NH_2SO_2Ph	
		19k, $TMSN_3$	**19c**
		19l, $Ph(CH_2)_2OH$	
		19m, PhSH	
		19n, AcSH	
18a, R^1, R^2, R^3 = H; R^4 = Ph	**18h**, R^5, R^6 = Ph; R^7 = H		**19e**
18b, R^1 = Ph; R^2, R^3 = H; R^4 = Ph	**18i**, R^5 = Ph; R^6, R^7 = H	**19d**	
18c, R^1 = Ph; R^2, R^3, R^4 = H	**18j**, R^5 = 4-Br(C_6H_4); R^6, R^7 = H		
18d, R^1, R^2 = Ph; R^3, R^4 = H	**18k**, R^5 = Ph; R^6 = Me; R^7 = H		
18e, R^1 = Ph; R^2, R^4 = C_3H_6; R^3 = H	**18l**, R^5 = CCPh; R^6 = Ph; R^7 = H		
18f, R^1, R^2 = C_5H_{10}; R^3, R^4 = H	**16b**, R^5 = 4-MeO(C_6H_4); R^6, R^7 = H		
18g, R^1, R^2 = Me; R^3, R^4 = H			

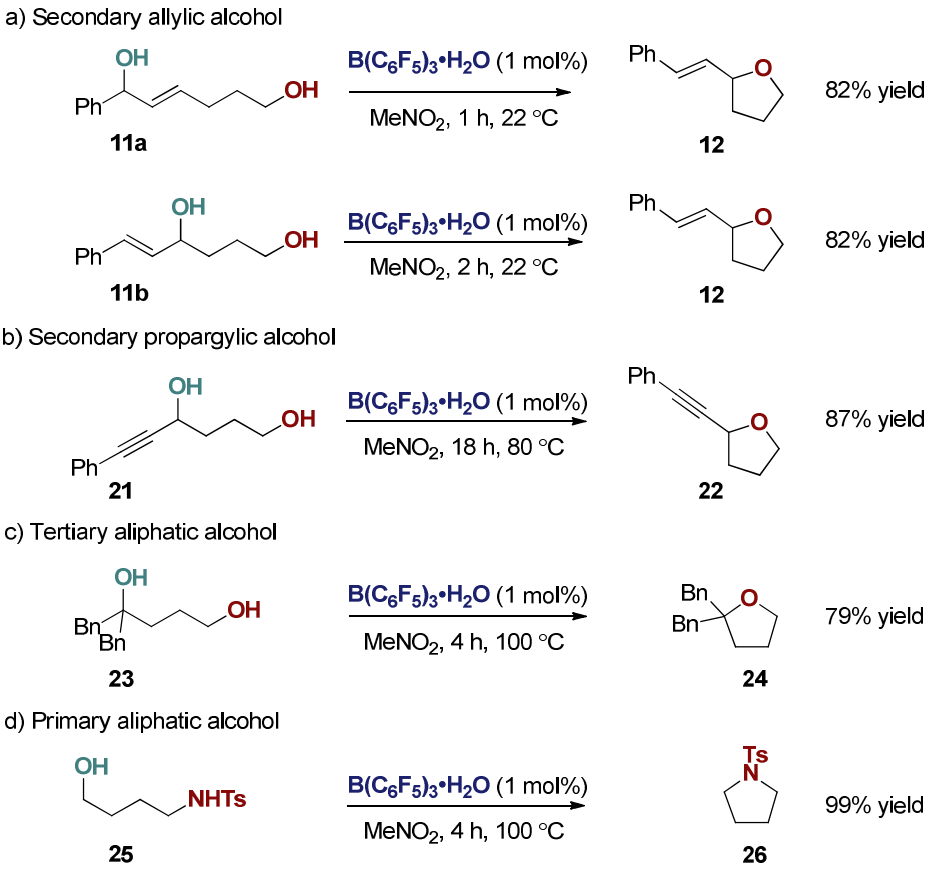
[a]Conditions: 1 equiv alcohol (0.2 M in $MeNO_2$), 1.1 – 3.0 equiv nucleophile. [b]Yields of isolated product purified by column chromatography on silica gel. [c]1 mol% catalyst. [d]2 mol% catalyst. [e]3 mol% catalyst. [f]5 mol% catalyst.

2.2.7 **Scope for $B(C_6F_5)_3$•H_2O-catalyzed dehydrative cyclizations**

Catalytic cyclodehydration is another transformation that allows direct comparison of the catalytic activity of $B(C_6F_5)_3$•H_2O in nitromethane with Hall's reported boronic acid cyclodehydration catalysts (Scheme 2.7).[86b] Compared to $(C_6HF_4)B(OH)_2$ **13**, $B(C_6F_5)_3$•H_2O converts **11a** to **12** in identical yield using 1/10th the catalyst loading in 1/25th the time under otherwise identical conditions. Remarkably, though 10 mol% of $(C_6HF_4)B(OH)_2$ **13** was reportedly unable to cyclize isomer **11b**, this transformation is accomplished readily at room temperature with 1 mol% $B(C_6F_5)_3$•H_2O in just 2 h. Secondary propargylic alcohol **21** is cyclized to 2-alkynyl tetrahydrofuran **22** in 87% yield without an additional pre-activation step.[97] Cyclizations of challenging aliphatic alcohols are facile at 100 °C. Tertiary aliphatic alcohol **23** forms 2,2-dialkyltetrahydrofuran **24** in 79% yield after 4 h, a ten-fold reduction in catalyst loading and four-fold reduction in time compared to 2,3-difluoro-4-methylpyridiniumboronic acid catalyst **10** under otherwise identical conditions.[86b] Even primary aliphatic alcohols, which are typically activated by superacids, undergo intramolecular dehydrative coupling under these conditions. Hydroxytosylamide **25** cyclizes

[97] Daniels, D. S. B.; Thompson, A. L.; Anderson, E. A. *Angew. Chem. Int. Ed.* **2011**, *50*, 11506.

to pyrrolidine **26** in nearly quantitative yield, a reaction previously accomplished only by stoichiometric preactivation.[98]



Scheme 2.7. *Challenging dehydrative cyclizations catalyzed by $B(C_6F_5)_3$•H_2O.*

2.3 Conclusion to Chapter 2

A systematic survey of Brønsted and Lewis acid catalysts revealed $B(C_6F_5)_3$•H_2O as a potent yet mild catalyst for the dehydrative coupling of a range of π-activated alcohols with a variety of *C*-, *N*-, *S*-, and *O*-nucleophiles. Amongst others, silyl ether protecting groups and acid sensitive alkenes proved to be tolerant to these standard reaction conditions. Direct comparison with competing state of the art catalytic systems highlights the superior reactivity of $B(C_6F_5)_3$•H_2O, which is achieved without compromising compatibility with acid-labile functional groups. The ability to tolerate acid-sensitive functional groups increases the potential synthetic utility of direct dehydrative transformations of π-activated alcohols by

[98] (a) Henry, J. R.; Marcin, L. R.; McIntosh, M. C.; Scola, P. M.; Davis Harris, G.; Weinreb, S. M. *Tetrahedron Lett.* **1989**, *30*, 5709. (b) Aikawa, H.; Tago, S.; Umetsu, K.; Haginiwa, N.; Asao, N. *Tetrahedron* **2009**, *65*, 1774.

offering an optimal compromise between reactivity and chemoselectivity. A drastic solvent effect favoring nitromethane in these transformations was noted, an observation that would prove crucial in future investigations. In order to explore the limits of reactivity, we next decided to apply our reaction conditions to the challenging intermolecular substitution of non-activated aliphatic alcohols, which will be discussed in the next chapter.

CHAPTER 3

Catalytic Dehydrative Transformations of Tertiary Aliphatic Alcohols

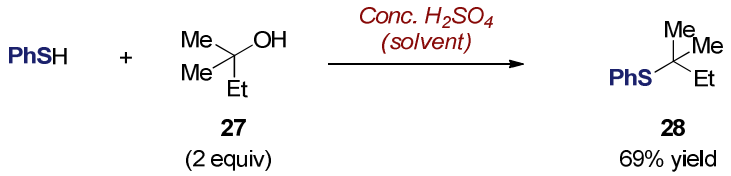
3.1 Introduction

In the previous chapter we described the case of mild and selective $B(C_6F_5)_3 \bullet H_2O$ catalysis in nitromethane, highlighting that a wide range of π–activated alcohols could easily be substituted under convenient reaction conditions and with a wide functional group compatibility. However, the utility of this catalytic system still remained to be demonstrated on intermolecular reactivity of unactivated substrates such as simple aliphatic alcohols. In addition to the higher kinetic barrier of aliphatic alcohols towards ionization, the reduced lifetime of the nascent carbocation due to its high propensity for competitive elimination poses a substantial challenge towards the development of a well-controlled substitution process. Thus, in sharp contrast to π-activated alcohols, the activation of aliphatic alcohols remains an unsolved problem for catalysis and typically requires the use of superstoichiometric amounts of Brønsted or Lewis acids. A SciFinder search on the topic of tertiary aliphatic alcohol activation reveals over one thousand examples of direct S_N1 substitution promoted by superstoichiometric Brønsted or Lewis acids as well as by heterogeneous acid catalysts, but truly catalytic examples remain rare. Rather than discuss every instance of reported conditions, the following introductory section aims to highlight the pioneering results in the field alongside recent substoichiometric examples of the activation of tertiary aliphatic alcohols.

3.1.1 Activation of tertiary aliphatic alcohols with superstoichiometric Brønsted acid

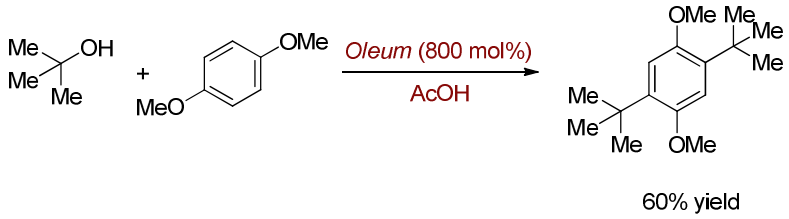
In a seminal report from 1938 by Ipatieff and co-workers,[99] *tert*-amyl alcohol **27** has been shown to undergo thiodehydration with thiophenol. Although the corresponding sulfide **28** was obtained in 69% yield, the challenging activation of the requisite aliphatic alcohol required superstoichiometric concentrated sulfuric acid, which effectively serves as both reaction promoter and solvent in this transformation (Scheme 3.1).

[99] Ipatieff, V. N.; Pines, H.; Friedman, B. S. *J. Am. Chem. Soc.* **1938**, *60*, 2731.



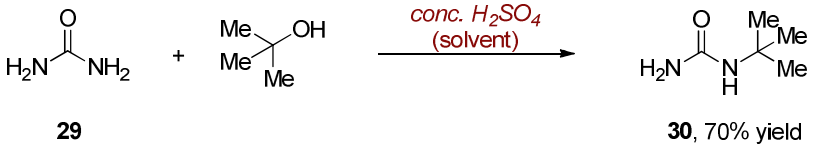
Scheme 3.1. *Thiodehydration reaction of tert-amyl alcohol **27** in the presence of superstoichiometric sulfuric acid.*

A few years later, the first Friedel-Crafts reaction of *tert*-butyl alcohol with electron rich 1,4-dimethoxybenzene was reported by Kharasch and co-workers.[16] However, superstoichiometric amounts of oleum (fuming sulfuric acid) and acetic acid were employed as both reaction promoter and solvent in order to accomplish the alkylation with unactivated *tert*-butanol (Scheme 3.2).



Scheme 3.2. *Superstoichiometric H_2SO_4-promoted Friedel-Crafts reaction of tert-butanol.*

In 1938, perhaps inspired by the industrial potential of direct alkylation reactions with unactivated alcohols, a methodology for the alkylation of urea **29** was patented by Harvey and Caplan.[100] Although allowing the formation of simple mono-(tertiary)alkyl ureas, the transformation still required the presence of 2 equiv of concentrated sulfuric acid. Remarkably, when the amount of acid was reduced, this resulted in lower yields of the mono-alkylated product **30** (Scheme 3.3).



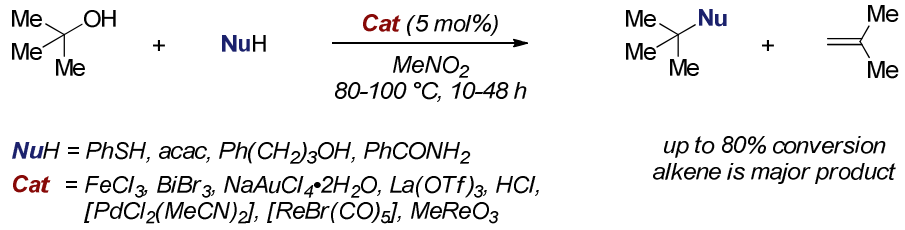
Scheme 3.3. *Alkylation of urea **29** with tert-butyl alcohol in the presence of superstoichiometric sulfuric acid.*

[100] Harvey, M. T.; Caplan, S. Patent US 2247495, **1938**.

Since these early reports, numerous alcohol activation systems have been developed, but nearly all require stoichiometric quantities of strong acid or heterogeneous catalysis at high temperatures. Examples of homogeneous catalytic substitution of tertiary aliphatic alcohols with catalytic turnover are uncommon, while examples with secondary or primary aliphatic alcohols are still limited.

3.1.2 **Catalytic activation of aliphatic alcohols**

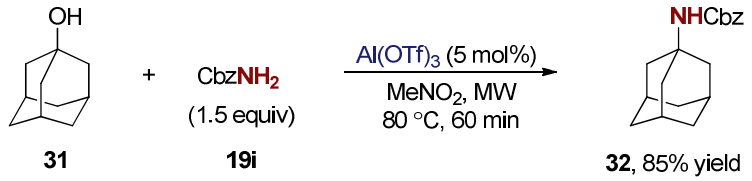
As illustrated in Samec's recent study,[20] attempts to achieve truly catalytic nucleophilic substitution of *tert*-butyl alcohol was plagued by low efficiency. In all cases, elevated temperatures of 80–100 °C were required for reactions with *C*-, *N*-, *S*- and *O*-centered nucleophiles in the presence of a broad selection of catalysts. In addition, isobutylene was typically formed as the major product (Scheme 3.4). These results highlight the relative difficulty in activating aliphatic alcohols compared to π-activated alcohols, but also the challenges associated with the efficient capture of the generated carbocation prior to elimination.



Scheme 3.4. *Catalytic activation of tert-butanol in reaction with representative S-, C-, O- and N-centered nucleophiles.*

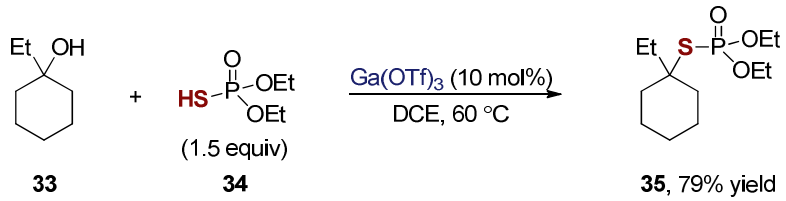
Although not a global solution to the problem of efficient aliphatic alcohol activation, catalytic substitution of tertiary aliphatic substrates could be performed effectively in the case of alcohols that cannot undergo competitive elimination. Thus, Ohshima, Mashima and co-workers[101] showed that 1-adamantol **31** can be successfully reacted with weakly nucleophilic benzyl carbamate **19i** under microwave-assisted conditions in the presence of 5 mol% of $Al(OTf)_3$ catalyst to deliver **32** (Scheme 3.5).

[101] Ohshima, T.; Ipposhi, J.; Nakahara, Y.; Shibuya, R.; Mashima, K. *Adv. Synth. Catal.* **2012**, *354*, 2447.



Scheme 3.5. *Al(OTf)$_3$-catalyzed activation of 1-adamantol **31**.*

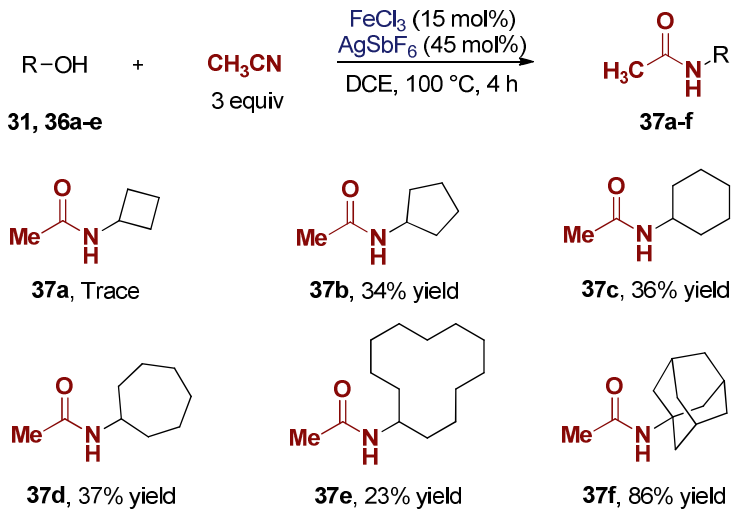
Judicious combination of strong nucleophiles with a Lewis acid that minimizes catalyst poisoning can allow for the substitution of tertiary aliphatic alcohols in synthetically useful yields. In a rare example from Han and Wu,[102] 10 mol% of Ga(OTf)$_3$ catalyzed the dehydrative reaction between 1-ethylcyclohexanol **33** and phosphorothioic acid **34**, a strong *S*-nucleophile which, due to its bidentate nature, is able to coordinate to the metal center with a possible release of triflic acid (Scheme 3.6).



Scheme 3.6. *Ga(OTf)$_3$-catalyzed thiodehydration reaction with phosphorothioic acid.*

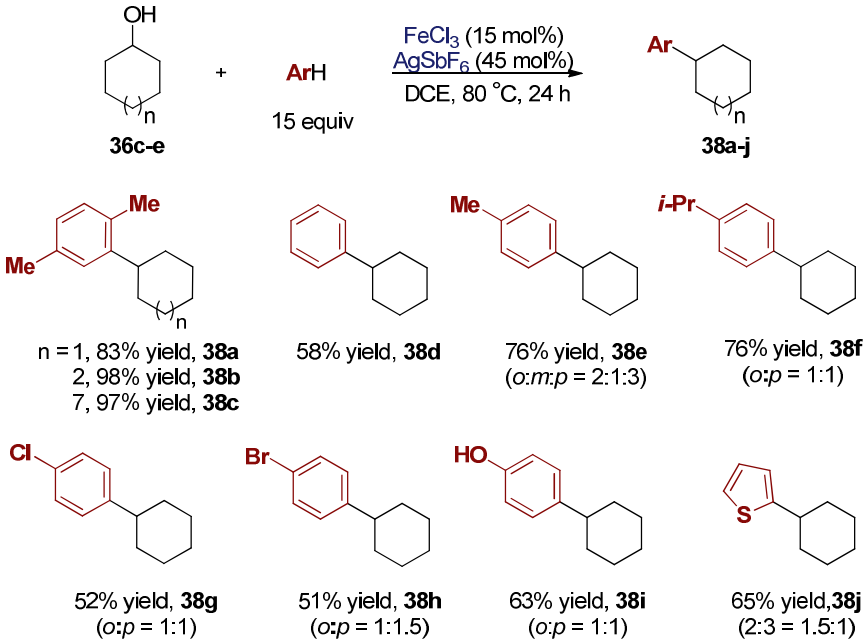
During the course of this thesis, progress in the field of catalytic alcohol activation has been marked by an important contribution from Cook and Jefferies,[103] who reported an effective set of conditions for the Ritter reaction of secondary aliphatic alcohols **36a-e** and 1-adamantol **31**. Although, the corresponding amide products **37a-f** could be obtained in modest yields by employing a catalytic system consisting of $FeCl_3$ (15 mol%) and $AgSbF_6$ (45 mol%), the actual mode of alcohol activation (Lewis acid *vs.* Brønsted acid) is highly debatable, as the *in situ* formation of 45 mol% of the superacid $HSbF_6$ is highly likely under the reaction conditions (Scheme 3.7).

[102] Han, X.; Wu, J. *Org. Lett.* **2010**, *12*, 5780.
[103] Jefferies, L. R.; Cook, S. P. *Tetrahedron* **2014**, *70*, 4204.



Scheme 3.7. *Ritter reaction of secondary aliphatic alcohols and 1-adamantol catalyzed by a $FeCl_3/AgSbF_6$ system.*

As was stated above, the Friedel-Crafts reaction is an important transformation that traditionally has been accomplished with superstoichiometric acid if alcohols are used as alkylating agents. However, Cook and Jefferies have recently shown[104] that an $FeCl_3/AgSbF_6$ catalyst system could be also effective with a limited range of cyclic secondary aliphatic alcohols **36c-e** in challenging Friedel-Crafts transformations (Scheme 3.8).



Scheme 3.8. *Friedel-Crafts reaction of secondary aliphatic alcohols **36c-e** catalyzed by $FeCl_3/AgSbF_6$ system.*

[104] Jefferies, L. R.; Cook, S. P. *Org. Lett.* **2014**, *16*, 2026.

3.1.3 **Critical conclusion and aim of the chapter**

Despite recent progress in the catalytic dehydrative substitution of alcohols, the direct intermolecular replacement of unfunctionalized hydroxyl groups in simple aliphatic alcohols remains a major challenge. The large kinetic barrier for the ionization of aliphatic alcohols has rendered true catalysis difficult to achieve and the use of superstoichiometric quantities of acids remains commonplace. Existing methods are applicable only to a narrow selection of nucleophiles and to chemically robust alcohols that are not prone to competitive degradation or elimination. Presumably because of these reasons, the question of functional group compatibility has not been addressed in existing studies. Finally, Cook's catalytic system has recently allowed the catalytic Friedel-Crafts reaction of cyclic secondary aliphatic alcohols to take place, however $HSbF_6$ is almost certainly released upon the hydrolysis of the Lewis acid catalyst by stoichiometric water by-product.

Based on the abovementioned precedents and our laboratory experience in dehydrative transformations of π–activated alcohols, we decided to probe the utility of our substoichiometric $B(C_6F_5)_3$•H_2O/nitromethane system toward the activation of simple tertiary aliphatic alcohols. As the reference point in the field, we selected Friedel-Crafts and thiodehydration reactions to highlight the potential advantages and limitations of our catalyst system.

3.2 **Discussion**

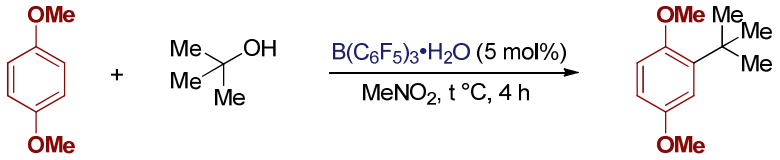
In attempting to extend the reaction scope beyond π–activated alcohols, we quickly learned that a catalytic amount of $B(C_6F_5)_3$•H_2O in nitromethane is able to promote the Friedel-Crafts alkylation of electron-rich arenes by *tert*-butanol at elevated temperatures. However, in order to obtain reasonable yields of mono-alkylated products, the optimization of the reaction conditions was necessary.

3.2.1 **Screening of reaction conditions**

A brief screen of reaction conditions eventually resulted in the reaction being performed at 90 °C in nitromethane with 5 mol% loading of $B(C_6F_5)_3$•H_2O catalyst (Table 3.1, entry 1). Raising or lowering the reaction temperature hampered the outcome (entries 2-4). The reaction was shown to be less efficient at lower concentrations, where

capture of the resulting carbocation does not compete effectively with elimination (entries 5-6). Increasing the substrate concentration from 2 M to 6.7 M, at which point only ≈3 equiv of nitromethane are present with respect to the alcohol, did not have any significant impact on reaction efficiency (entry 7). However, a neat reaction was unsuccessful (entry 8), demonstrating the critical role of nitromethane. Finally, simply extending the reaction time to 6 h allowed the mono-*tert*-butylation product **39** to be isolated in good yields after column chromatography (entries 9-10).

Table 3.1. *Optimization of an intermolecular Friedel-Crafts reaction.*[a]



39

Entry	*Temperature, °C*	*[tert-BuOH], M*[b]	*Yield,*[c] *%*
1	90	2.0	83
2	70	2.0	<5
3	80	2.0	47
4	120	2.0	61
5	90	0.2	63
6	90	1.0	77
7	90	6.7	79
8[d]	90	N/A	<5
9[e,f]	**90**	**2.0**	**91**
10[e,f]	90	6.7	86

[a]Conditions: 1 equiv **1,4-dimethoxybenzene**, 3 equiv **tert-BuOH**. [b]**[tert-BuOH]** with respect to volume of $MeNO_2$. [c]Yields determined by ^1H NMR using DMSO as an internal standard. [d]Reaction carried out without solvent [e]Reaction time extended to 6 h. [f]Yield of isolated product after silica gel chromatography.

3.2.2 **Effect of nitromethane**

The drastic effect of nitromethane on the reactivity of π–activated alcohols made us wonder whether such dependence is also taking place for the Friedel-Crafts reaction of tertiary aliphatic alcohols. Thus, a selection of typical polar and apolar organic solvents was tested for the alkylation reaction of 1,4-dimethoxybenzene with *tert*-butanol (Figure 3.1). A variety of common solvents did not lead to any observable reactivity, however a small amount of monoadduct was detected in DCE. This unique reactivity in nitromethane, despite the broad range of dielectric properties of the medium in the case of all other solvents tested,

constitutes a valuable seminal discovery, and was critical to our musings on the important role of nitromethane in later studies (please, see chapter 4).

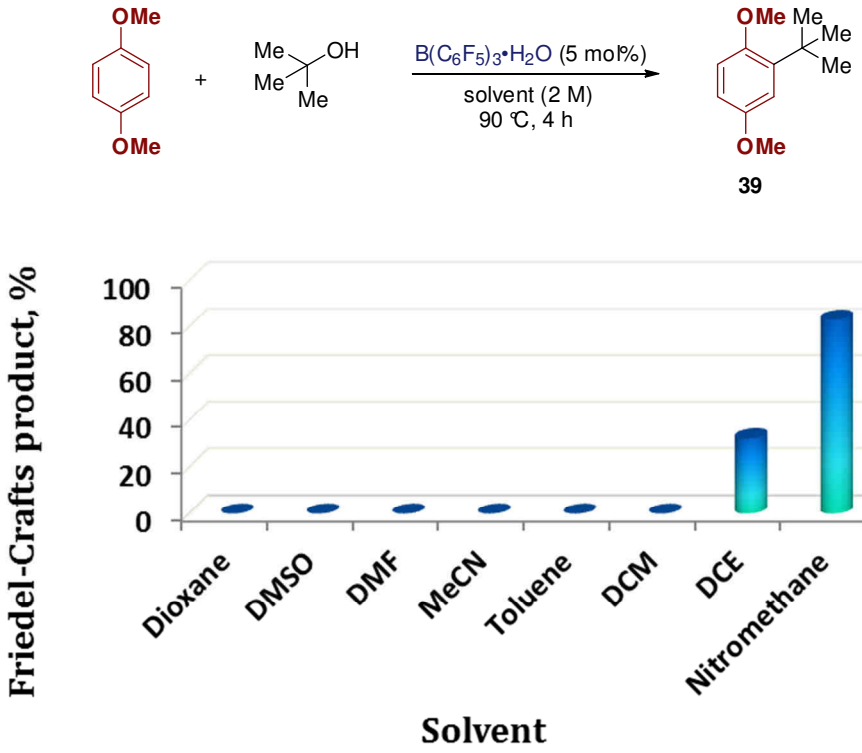
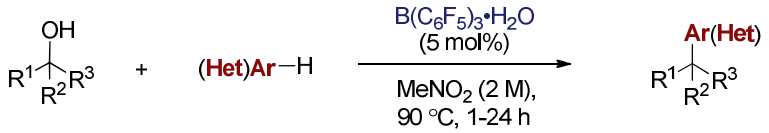


Figure 3.1. *Solvent screen for Friedel-Crafts alkylation with tert-butanol (NMR yield)*

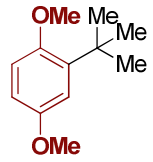
3.2.3 **Scope of Friedel-Crafts reaction**

The scope of the Friedel-Crafts transformation was then investigated (Table 3.2). In general, most electron-rich nucleophiles react under our previously optimized conditions provided they are not sufficiently basic to quench the catalyst. Amongst others, anisole reacts efficiently with *tert*-butanol in completely *para*-selective fashion to give **40a** in 82% yield. Electron-rich nitrogen-containing heterocycle *N*-methylindole was compatible and gave 94:6 selectivity for the 3-position of **40b** in 85% yield. The free phenolic OH groups of 2,6-dimethylphenol were tolerated and gave complete *C*-selectivity for **40f**. Remarkably, *β*-aryl substituted alcohols did not lead to intramolecular indane formation but to intermolecular adduct **40g**. Cyclic tertiary aliphatic alcohols react smoothly to furnish adducts **40h**, **40i** and **40j**. If needed, bis-substitution can also be accomplished deliberately by inverting the relative stoichiometry of the reagents which resulted in 57% isolated yield of **40k**.

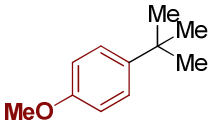
Table 3.2. *Scope of Friedel-Crafts alkylation with tertiary aliphatic alcohols.*[a,b]



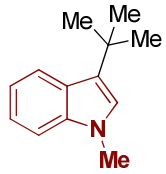
39, **40a-k**



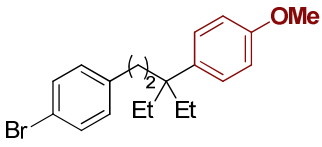
39, 91% yield



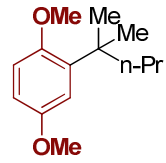
40a, 82% yield



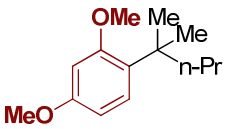
40b, 85% yield[c,d,h]



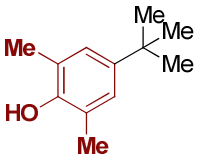
40c, 10% yield[e]



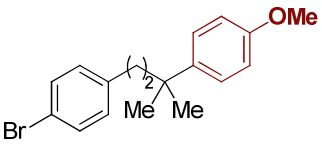
40d, 89% yield



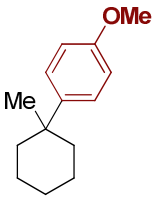
40e, 60% yield



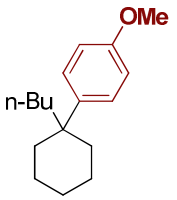
40f, 94% yield[c,d]



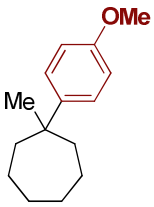
40g, 74% yield[e]



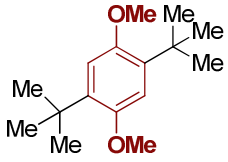
40h, 70% yield[e]



40i, 54% yield[e]



40j, 67% yield[e]



40k, 57% yield[d]

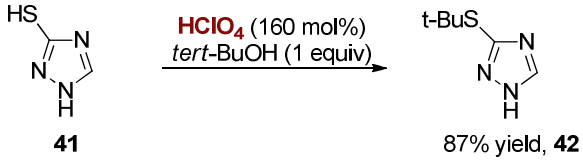
[a]1 equiv alcohol (2 M in $MeNO_2$), 2-3 equiv nucleophile, 6 h. [b]Yields of isolated products after silica gel chromatography. [c]24 h reaction time. [d]2 equiv alcohol, 1 equiv nucleophile. [e]6.7 M concentration with respect to alcohol. [h]Regioselectivity of *C*-3 vs *C*-2 alkylation is 94:6.

3.2.4 Thiodehydration reaction of tertiary aliphatic alcohols

Given the success of the aforementioned Friedel-crafts reaction, we wondered if our catalytic conditions would be suitable for the dehydrative coupling of tertiary aliphatic alcohols with other nucleophiles. As a representative case we selected the thiodehydration reaction to give the corresponding tertiary aliphatic thioethers, the prototypical sulfur(II) compounds which have versatile applications in synthetic, biological and medicinal chemistry.[105] Despite the utility of such substrates, methods for the synthesis of tertiary thioethers are rather limited compared to other substitution patterns,[106] and typically rely

[105] Cremlyn, R. J. *An Introduction to Organosulfur Chemistry*; Wiley: Chichester, **1996**.
[106] Clayden, J.; MacLellan, P. *Beilstein J. Org. Chem.* **2011**, *7*, 582.

either on the use of stoichiometric quantities of harsh acids[99,107] (Scheme 3.9, ref 107b) or on low yielding modified Mitsunobu conditions.[108]

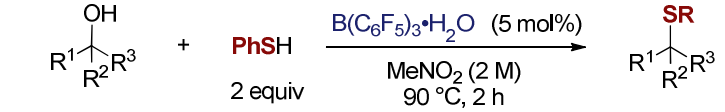


Scheme 3.9. *Representative alkylation of 3-mercaptotriazole **41** under stoichiometric Brønsted acid catalysis.*

3.2.4.1 **Scope of tertiary aliphatic alcohols for thiodehydration reaction**

Under our conditions developed for the Friedel-Crafts reaction, the scope of thiodehydration with tertiary aliphatic alcohols proved to be extremely broad with respect to both electrophile and nucleophile. Typically, all reactions were accomplished in 2 h in nitromethane, furnishing the desired products in high isolated yields. The scope of electrophiles in dehydrative transformation with thiophenol **19m**, a standard *S*-nucleophile, was examined first (Table 3.3). Both acyclic (entry 1-5) and cyclic (entry 6-8) long- and short-chain substrates react well. The presence of a ketone functionality was tolerated under the reaction conditions, although the reactivity was slowed down and the target product (entry 9) was obtained in 62% isolated yield. A range of functionalized arene substrates (entry 10-14) react quickly in an intermolecular fashion with no intramolecular indane-forming carbocation capture being observed.

Table 3.3. *Scope of tertiary aliphatic alcohols for thiodehydration reaction.*



Entry	*Alcohol*	*Product*	*R^1*	*R^2/R^3*	*Yield (%)[a]*
1	***tert*-BuOH**	**44**	Me	Me/Me	89
2	**43a**	**45a**	Me	Me/*n*-Pr	79
3	**43b**	**45b**	Me	Me/$(CH_2)_7$Me	99

[107] For the use of Brønsted acids, see: (a) Cain, M. E.; Evans, M. B.; Lee, D. F. *J. Chem. Soc*. **1962**, 1694. (b) Voitekhovich, S. V.; Lyakhov, A. S.; Ivashkevich, L. S.; Matulis, V. E.; Grigoriev, Y. V.; Gaponik, P. N.; Ivashkevich, O. A. *Tetrahedron* **2012**, *68*, 4962; for the use of Lewis acids, see: Firouzabadi, H.; Iranpoor, N.; Jafarpour, M. *Tetrahedron Lett.* **2006**, *47*, 93.

[108] (a) Kuroda, K.; Maruyama, Y.; Hayahi, Y.; Mukaiyama, T. *Chem. Lett.* **2008**, *37*, 836. (b) Kuroda, K.; Maruyama, Y.; Hayashi, Y.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **2009**, *82*, 381. (c) Mukaiyama, T.; Kuroda, K.; Maruyama, Y.; *Heterocycles*, **2010**, *80*, 63.

Table 3.3 (continued)

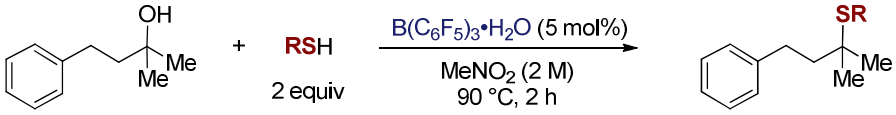
Entry	*Alcohol*	*Product*	R^1	R^2/R^3	*Yield (%)*[a]
4	**43c**	**45c**	Me	Et/*n*-Bu	92
5	**43d**	**45d**	Me	*n*-Bu/*n*-Bu	94
6	**43e**	**45e**	Me	$(CH_2)_6$	99
7	**43f**	**45f**	Me	$(CH_2)_5$	96
8	**43g**	**45g**	*n*-Bu	$(CH_2)_5$	99
9	**43h**	**45h**	Me	Me/CH_2COMe	62[b]
10	**43i**	**45i**	Me	Me/$(CH_2)_2Ph$	97
11	**43j**	**45j**	Me	Me/$(CH_2)_2$(4-Br-C_6H_5)	99
12	**43k**	**45k**	Me	Me/$(CH_2)_2$(4-Cl-C_6H_5)	97
13	**43l**	**45l**	Me	Me/$(CH_2)_2$(4-OMe-C_6H_5)	96
14	**43m**	**45m**	Et	Et/$(CH_2)_2$(4-Br-C_6H_5)	97

[a]Isolated yield after column chromatography on silica gel. [b]15h reaction time.

3.2.4.2 **Scope of *S*-nucleophiles**

Next, the scope of suitable arene (Table 3.4, entry 1-3) and alkyl (Table 3.4, entry 4-8) thiol coupling partners was examined in the direct reaction with **43i**. In agreement with the generally strong nucleophilicity of thiols, all desired products were obtained in high yields after routine chromatographic purification.

Table 3.4. *Scope of S-nucleophiles for thiodehydration reaction.*



43i **46a-h** **47a-h**

Entry	*Thiol*	*Product*	*R*	*Yield (%)*[a]
1	**46a**	**47a**	4-OMe-C_6H_5	89
2	**46b**	**47b**	4-Br-C_6H_5	94
3	**46c**	**47c**	4-Cl-C_6H_5	98
4	**46d**	**47d**	Et	86
5	**46e**	**47e**	*n*-Bu	98
6	**46f**	**47f**	Bn	99
7	**46g**	**47g**	*i*-Pr	97
8	**46h**	**47h**	Cyclopentyl	99

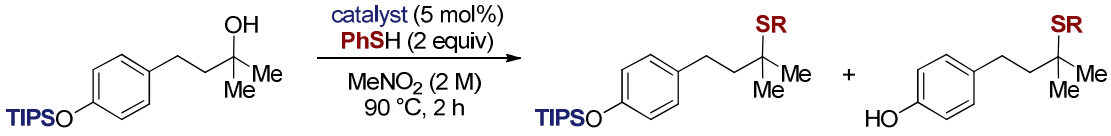
[a]Isolated yield after column chromatography on silica gel.

3.2.4.3 **Chemoselectivity**

As has been shown in the previous chapter, the chemoselectivity of acid catalyzed dehydration reactions must be properly addressed if the acid-labile functionalities are present

in the structure of the corresponding molecular scaffold. To assess the mildness of $B(C_6F_5)_3$•H_2O catalysis in nitromethane, tertiary aliphatic alcohol **48** bearing TIPS-protected phenol motif was prepared and subjected to the standard reaction conditions (Table 3.5). Gratifyingly, the corresponding uncleaved thioether **49** was obtained in 77% isolated yield. Furthermore, the efficiency of $B(C_6F_5)_3$•H_2O proved to be superior to standard Brønsted and Lewis acids, once again emphasizing the mild nature of $B(C_6F_5)_3$•H_2O catalysis in nitromethane.

Table 3.5. *Comparison of $B(C_6F_5)_3$•H_2O with other catalysts for chemoselective thiodehydration in nitromethane.*



48 **49** **50**

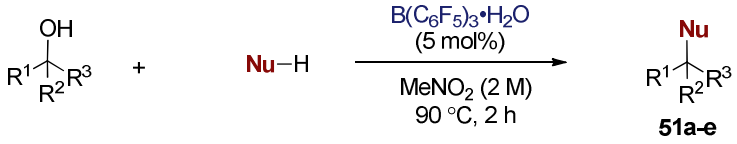
Entry	*Catalyst*	*GC Yield 49 (%)*	*GC Yield 50 (%)*
1	**$B(C_6F_5)_3$•H_2O**	92 (77)[a]	<5
2	**TfOH**	35	59
3	**H_2SO_4**	58	32
4	**TsOH**	58	7
5	**TFA**	49	<5
6	**$FeCl_3$**	65	23
7	**$AuCl_3$**	<5	<5
8	**$Sc(OTf)_3$**	39	54
9	**$Bi(OTf)_3$**	13	24
10	**$Ca(NTf)_2$/Bu_4NPF_6**	20	77
11	**$B(C_6F_5)(OH)_2$**	<5	<5

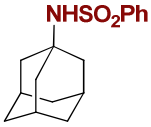
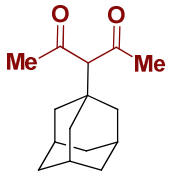
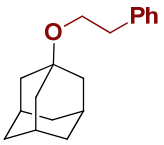
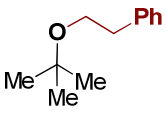
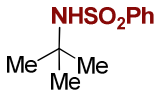
[a]Isolated yield after column chromatography on silica gel.

3.2.5 **Dehydrative substitutions with other nucleophiles**

The successful cases of Friedel-Crafts and thiodehydration reactions described previously in this chapter raised the question of whether the formation of other carbon–heteroatom bonds is possible under the same reaction conditions. Of particular interest are C–N or C–O bond forming dehydrative transformations, given the challenge associated with enhanced basicity and sluggish nucleophilicity of typical *N*- and *O*-centered nucleophiles. However, a brief preliminary survey of common nucleophiles provided a "proof of principle" for the general feasibility and efficiency of dehydrative transformations of tertiary aliphatic alcohols catalyzed by $B(C_6F_5)_3$•H_2O in nitromethane (Table 3.6).

Table 3.6. *Selection of other nucleophiles.*[a]



				
51a, 93% yield	**51b,** 96% yield	**51c,** 91% yield	**51d,** 52% yield[b]	**51e,** 84% yield[b]

[a]Yield of isolated product after column chromatography on silica gel. [b]6 h reaction time.

3.5 Conclusion to Chapter 3

In contrast to the well-developed catalytic dehydrative transformations of π-activated alcohols, the direct activation of unprotected aliphatic substrates has proven to be rather difficult and typically has been accomplished in the presence of superstoichiometric Brønsted or Lewis acids. However, the application of $B(C_6F_5)_3•H_2O$ catalysis in nitromethane was surprisingly efficient for the dehydrative transformation of tertiary aliphatic alcohols. Thus, a broad variety of tertiary aliphatic alcohols was successfully activated in Friedel-Crafts alkylation and thiodehydration reactions with a range of electron-rich arenes and thiols, respectively. Moreover, the described catalysis has been additionally highlighted by its mild nature and selectivity as acid-sensitive silyl ether functionalities are well tolerated under the standard reaction conditions. More importantly, similarly to the previous case involving dehydrative substitution of π-activated alcohols, nitromethane has shown again a high propensity to enhance the substitution of unactivated hydroxyl group under acid catalysis. As we will see in the next chapter, this interesting phenomenon turned out to be even more pronounced and essential in the case of the azidodehydration of tertiary aliphatic alcohols.

CHAPTER 4[109]

Nitro Assisted Brønsted Acid Catalysis: Application to a Challenging Catalytic Azidation

[109] Portions of this chapter have been published: Dryzhakov, M.; Hellal, M.; Wolf, E.; Falk, F. C.; Moran, J. *J. Am. Chem. Soc.* **2015**, *137*, 9555.

4.1 Introduction

Over 150 years since their discovery by Peter Grieß in 1864,[110] organic azides have gained tremendous significance in synthetic organic chemistry,[111] material science,[112] biology[113] and medicine.[114] A SciFinder search indicates approximately one thousand reports per year for the last decade have been published on the topic of azides. However, despite the high demand for azides, economic and environmentally friendly routes for their preparation are still lacking. This is particularly pronounced in the case of the direct dehydrative azidation of aliphatic alcohols to give alkyl azide products – the "green" and highly desirable transformation that has typically relied on the use of stoichiometric Brønsted and Lewis acids. The following introductory section aims to give an overview of the field of alkyl azide preparation with a focus on the synthetic methodologies allowing the synthesis of tertiary aliphatic azides directly from the corresponding alcohols.

4.1.1 Safety considerations when handling azides

Perhaps as a result of the extensive practical experimentation with azide molecules, chemists quickly noticed that azides explosively decompose with the release of nitrogen if subjected to external stimulus such as heat, pressure or mechanical impact. Thereby, sodium azide is applied in airbags while heavy-metal azides are used in shotfiring to detonate target explosive assemblies.

In order for organic azides to be non-explosive, a rule of thumb has been derived by Smith such that $N_C \geq N_N$ and $(N_C + N_O)/N_N \geq 3$, where N is the number of atoms in the molecule of interest.[115] Among others, trimethylsilyl azide is considered as a toxic[116] but stable compound if stored in the fridge at 2 – 8 °C. Nevertheless, safety measures must be respected at all times when manipulating even seemingly stable organic azides on larger scales, as they are occasionally known to detonate unexpectedly.

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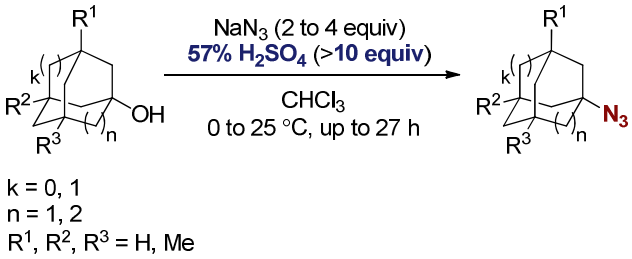
[110] Grieß, P. *Philos. Trans. R. Soc. London* **1864**, *13*, 377.
[111] (a) Bräse, S.; Gil, C.; Knepper, K.; Zimmermann, V. *Angew. Chem. Int. Ed.* **2005**, *44*, 5188. (b) Scriven, E. F. V; Turnbull, K. *Chem. Rev.* **1988**, *88*, 297.
[112] Li, N.; Binder, W. H. *J. Mater. Chem.* **2011**, *21*, 16717.
[113] Mamidyala, S. K.; Finn, M. G. *Chem. Soc. Rev.* **2010**, *39*, 1252.
[114] Tron, G. C.; Pirali, T.; Billington, R. A.; Canonico, P. L.; Sorba, G.; Genazzani, A. A. *Med. Res. Rev.* **2007**, *28*, 278.
[115] (a) Smith, P. A. S. *Open-Chain Nitrogen Compounds, vol. 2*, Benjamin, New York, **1966**, 211. (b) Boyer, J. H.; Moriarty, R.; de Darwent, B.; Smith, P. A. S. *Chem. Eng. News* **1964**, *42*, 6.
[116] TerBeek, K. J. *Chem. Eng. News* **1998**, *76*, 6.

4.1.2 **Dehydrative azidation of aliphatic alcohols with stoichiometric Brønsted acid**

Difficulties associated with the direct ionization of unactivated C–O bonds as well as with the relatively low stability of the associated carbocation historically necessitated the use of stoichiometric Brønsted acid activators for the preparation of tertiary aliphatic azides from alcohol starting materials.

In the pioneering report of Sasaki and co-workers,[117] 1-azidoadamantane and related bridgehead azides were synthesized from the corresponding 1-adamantol derivatives. However, from 2 to 4 equiv of NaN_3 and approximately 10 equiv of H_2SO_4 were used in the standard reaction procedure in order to assure reactivity, despite generating large amounts of explosive and toxic HN_3 and making the reaction conditions far too harsh for selective modification of any acid labile substrate (Scheme 4.1). In a closely related study from Timberlake and co-workers,[118] the same conditions were applied for the azidation of tertiary aliphatic alcohols beyond the adamantane family.



Scheme 4.1. *Synthesis of bridgehead azides with superstoichiometric sulfuric acid.*

In addition to the above-mentioned systems, Bottaro and co-workers[119] reported a mole-scale synthesis of *tert*-butyl azide from *tert*-butanol using 50 wt% aqueous sulfuric acid.

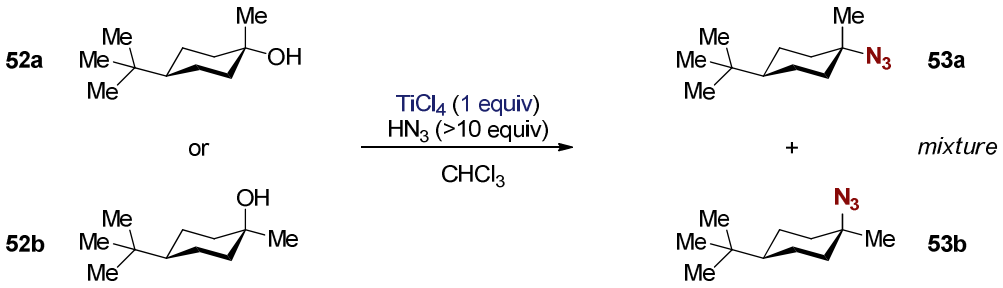
4.1.3 **Dehydrative azidation of aliphatic alcohols with stoichiometric Lewis acid**

The azidation of aliphatic alcohols with Lewis acid has long been used as an alternative to the abovementioned transformation with Brønsted acid. However, practice

[117] Sasaki, T.; Eguchi, S.; Katada, T.; Hiroaki, O. *J. Org. Chem.* **1977**, *42*, 3741.
[118] Timberlake, J. W.; Alender, J.; Garner, A. W.; Hodges, M. L.; Ozmeral, C.; Jacobus, J. O. *J. Org. Chem.* **1981**, *46*, 2082.
[119] Bottaro, J. C.; Penwell, P. E.; Schmitt, R. J. *Synth. Commun.* **1997**, *27*, 1465.

shows that such an approach does not preclude the use of stoichiometric quantities of Lewis acid promoters as well as dangerous azidation reagents.

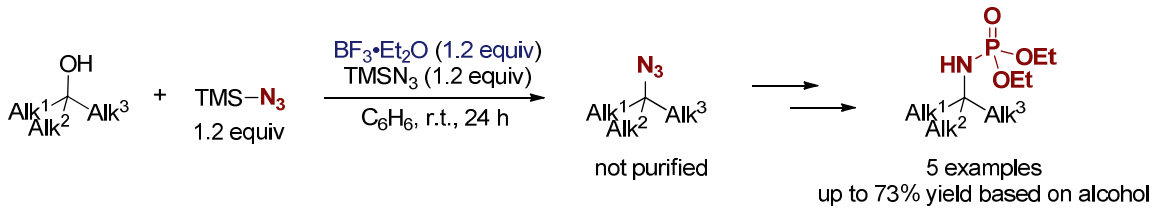
In pioneering work from Hassner and co-workers,[120] a few selected tertiary aliphatic azides were isolated after the treatment of the corresponding alcohols with stoichiometric $TiCl_4$ and hydrazoic acid. A mixture of *cis* and *trans* l-azido-4-*tert*-butyl-l-methylcyclohexanes **53a,b** was obtained from the preceding alcohols **52a,b** with the conformationally locked hydroxyl group in either equatorial **52a** or axial **52b** orientation, strongly suggesting the intermediacy of a carbocation (Scheme 4.2). As was shown by the authors, the required azide products could also be formed from the corresponding alkenes under similar reaction conditions or even in the absence of Lewis acid activator, this emphasizing the potential chemoselectivity issues if alkene and alcohol functionalities are both present in the reacting substrate. Notably, primary alcohols were shown to be unaffected by this transformation, reflecting the major challenge associated with the ionization of these substrates even under harsh acidic conditions.



Scheme 4.2. *Racemization experiment in the presence of stoichiometric $TiCl_4$.*

Introducing trimethylsilyl azide as an azidation reagent, Koziara and Zwierzak[121] described the preparation of tertiary aliphatic azides and their subsequent conversion to the corresponding amines via Staudinger reaction. This approach allowed users to circumvent certain practical limitation in azide synthesis, such as the use of poisonous and explosive hydrazoic acid or sodium azide. However, a stoichiometric quantity of boron trifluoride etherate was still required for this transformation to take place and only a narrow substrate scope was presented (Scheme 4.3).

[120] Hassner, A.; Fibiger, R.; Andisik, D. *J. Org. Chem.* **1984**, *49*, 4237.
[121] (a) Koziara, A.; Zwierzak, A. *Tetrahedron Lett.* **1987**, *28*, 6513. (b) Zwierzak, A. *Phosphorus. Sulfur. Silicon Relat. Elem.* **1993**, *75*, 51.

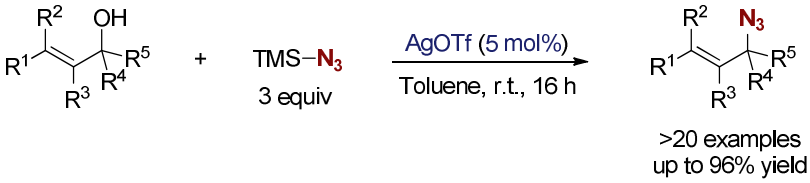


Scheme 4.3. *Azidation of tertiary aliphatic alcohols with $TMSN_3$ and stoichiometric BF_3•Et_2O.*

4.1.4 Catalytic azidation of π-activated alcohols and silyl ethers

While dehydrative azidation of aliphatic alcohols with trimethylsilyl azide has been shown to proceed under stoichiometric loading of BF_3•Et_2O,[121] this transformation could be rendered catalytic if π-activated alcohols are employed as substrates.

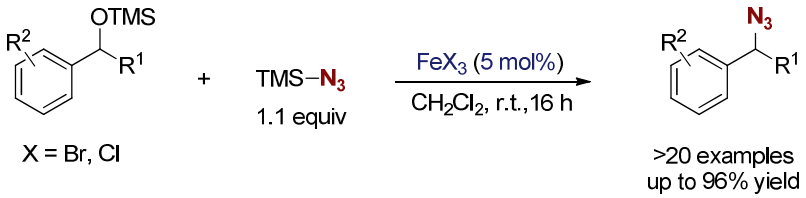
Thus, Rueping and co-workers[122] reported the direct azidation of primary, secondary and tertiary allylic alcohols using 5 mol% of AgOTf as a catalyst. High yields of the desired products were obtained at room temperature in toluene (Scheme 4.4). Interestingly, when triflic acid was employed instead of silver triflate, the formation of the product was also observed suggesting that Brønsted acid catalysis is taking place in the open-air reaction system.



Scheme 4.4. *Direct azidation of allyl alcohols with $TMSN_3$ and AgOTf catalyst.*

In another study from Sawama, Sajiki and co-workers,[123] a series of secondary and tertiary benzylic silyl ethers was converted into the corresponding azides products by treatment with $TMSN_3$ in the presence of 5 mol% of iron catalyst (Scheme 4.5). Notably, the reaction demonstrates tolerance to the presence of alkyl chloride, aldehyde and *α*, *β*-unsaturated ester functionalities, although primary benzylic ethers do not react under the reported conditions.

[122] Rueping, M.; Vila, C.; Uria, U. *Org. Lett.* **2012**, *14*, 768.
[123] Sawama, Y.; Nagata, S.; Yabe, Y.; Morita, K.; Monguchi, Y.; Sajiki, H. *Chem. Eur. J.* **2012**, *18*, 16608.



Scheme 4.5. *Azidation with $TMSN_3$ of silyl benzyl ethers catalyzed by iron trihalide.*

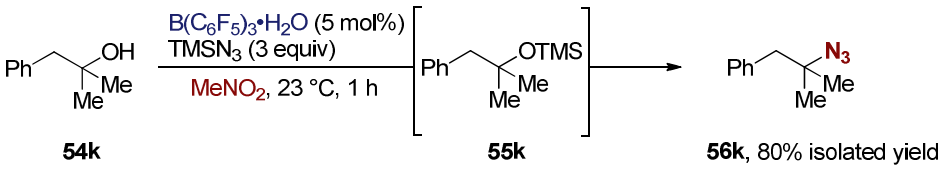
4.1.5 Critical summary

Contrasting sharply with the catalytic conditions employed for the azidation of π-activated alcohols, the substitution of unactivated aliphatic alcohols remains underdeveloped and relies heavily on the usage of superstoichiometric harsh mineral acids or stoichiometric quantities of Lewis acids. Though perhaps sufficient for the preparation of exceptionally robust substrates derived from simple unfunctionalized aliphatic alcohols, these reaction conditions are too harsh for the synthesis of more delicate molecules. The goal of transforming unactivated tertiary aliphatic alcohols into azides directly and chemoselectively employing mild catalysis will be developed in the following section.

4.2 Discussion: part 1. Catalytic azidation of tertiary aliphatic alcohols

4.2.1 Reaction discovery and general considerations

Building on previous experience in the laboratory while working with tertiary aliphatic alcohols, our particular interest in azidation reactions was enhanced by the observation that, in contrast to thiodehydration and Friedel-Crafts alkylation at 90 °C, **54k** reacted with $TMSN_3$ at room temperature in nitromethane in the presence of 5 mol% of $B(C_6F_5)_3$•H_2O catalyst (Scheme 4.6). Furthermore, GCMS analysis indicated that the alcohol was nearly immediately converted into the corresponding silyl ether intermediate **55k**, which was in turn transformed into azide product **56k** in less than 60 min at room temperature. Importantly, direct submission of silyl ether **55k** to the reaction conditions also yielded **56k** with similar efficiency, indicating that the silyl ether is likely an intermediate in the reaction.



Scheme 4.6. *Room temperature catalytic azidation in nitromethane.*

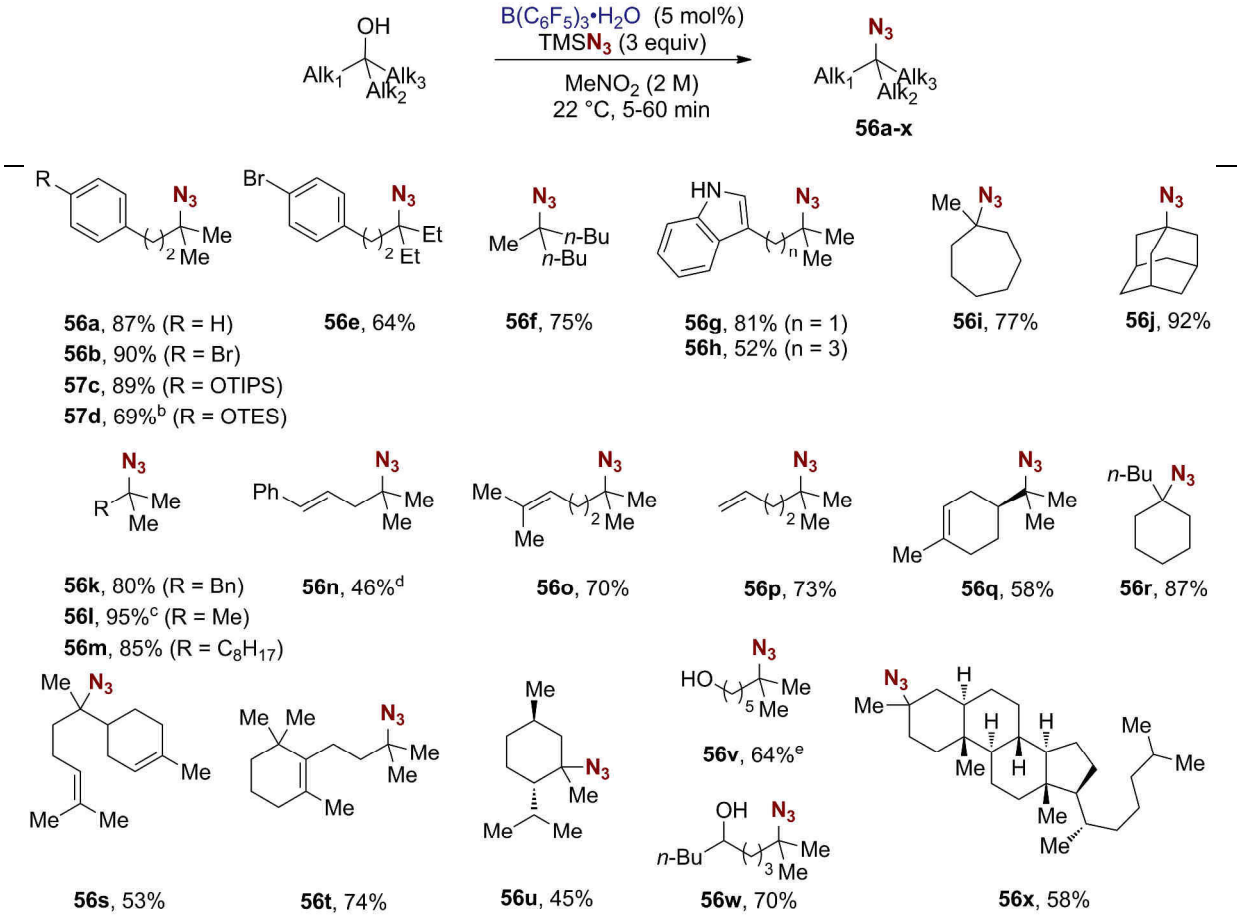
4.2.2 **Scope for azidation**

The substrate scope was next examined in order to probe the generality of the method. A wide variety of tertiary aliphatic alcohols proved compatible with the developed methodology, furnishing the desired products in good to high yields under standard reaction conditions (Table 4.1, please see next page). Quite remarkably, acid-sensitive functionalities such as OTES **56d** and OTIPS **56c** are well tolerated with the method. Indole-bearing azides **56q,h** could be obtained from the corresponding alcohols in good yields. Among others, alkene-bearing products **56n-q,s,t** are isolated with no observation of competitive bis-azidation occurring at room temperature. Diols undergo azidation selectively at the tertiary position furnishing the corresponding mono-azidation products **56v,w**.

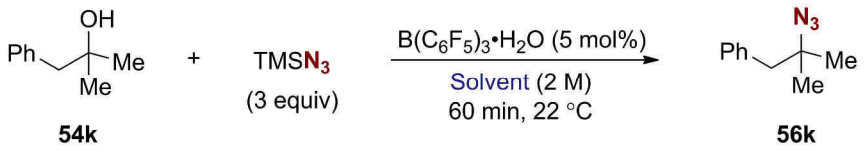
4.2.3 **Effect of nitro solvent**

The unusually broad and rapid room temperature reactivity of unactivated aliphatic alcohols raised a burning question as to the possible mechanism of the transformation. The effect of the solvent on the reaction outcome was evaluated first (Figure 4.1). With a selection of 11 common polar and apolar organic solvents typically used in chemical laboratories (from benzene to $MeNO_2$ on the plot below), we quickly observed superior azidation reactivity in nitromethane. Although a detectable amount of azide **56k** (<10%) was noticed in DCM and DCE, all other solvents either did not result in any reaction or furnished the silyl ether as the sole product. Furthermore, a further curious aspect of the solvent trend became apparent when it was observed that all five solvents assayed that contained a nitro group all resulted in high conversion to the azide product, despite the fact that in some cases their dielectric constants were much lower than that of nitromethane. Typically, the dielectric constant of a solvent is an important factor in a nucleophilic substitution. These results hinted at a potential role of the nitro functionality on the catalysis in this system, presumably being a key factor that allows the reaction to take place at room temperature.

Table 4.1. *Substrate scope for catalytic azidation of tertiary aliphatic alcohols.*[a]



[a]Isolated yield. [b]1 mol% $B(C_6F_5)_3•H_2O$. [c]Yield estimated by ^1H NMR using 1.0 equiv of anisole as internal standard. [d]Reaction performed at 0 °C. [e]Reaction performed at 90 °C.



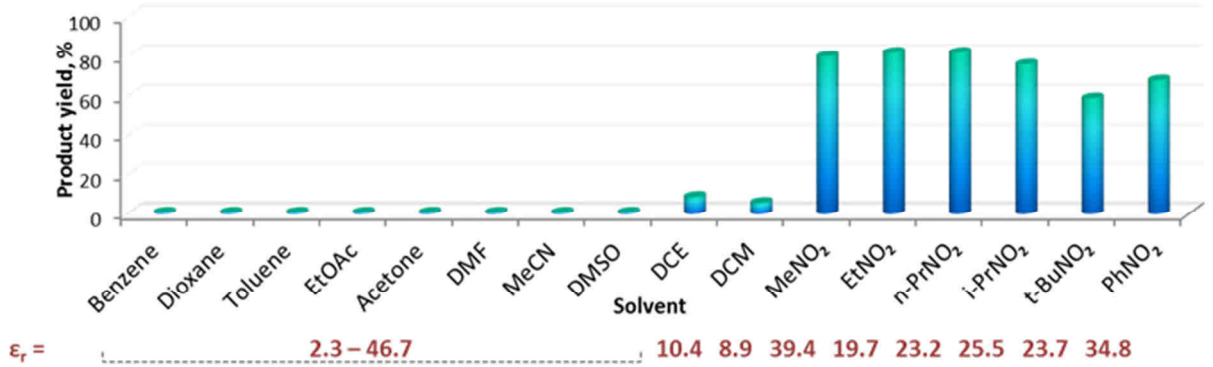


Figure 4.1. *Solvent screen for azidation reaction (NMR yield).*

4.2.4 **Rate dependence on the electronics of the nitro compounds**

Such a drastic effect of solvent on the reaction outcome raised the question of whether the nitro-compound is able to promote the reactivity if present in co-catalytic amount and how the electronic nature of the corresponding nitro functionality influences the reaction rate. In order to verify this hypothesis, the conversion of silyl ether **55a** to azide **56a** was monitored in the presence of 100 mol% of nitro compound. After reoptimization of the reaction conditions, with benzene being chosen as an "unreactive" solvent, the corresponding profile was obtained (Figure 4.2).

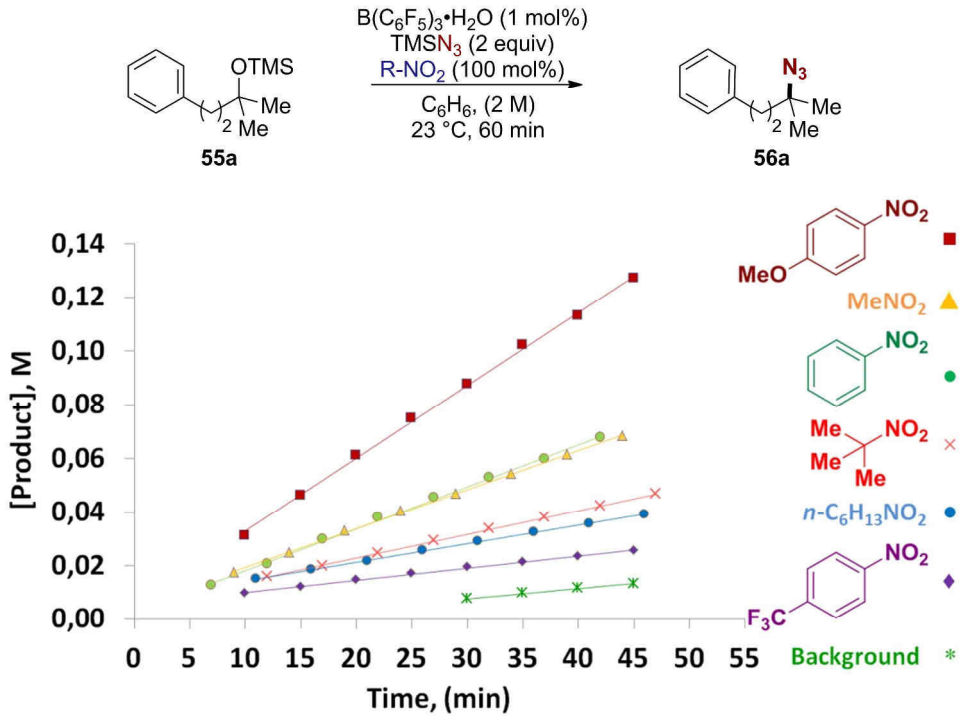


Figure 4.2. *Initial rate dependence on the electronics of the nitro compounds.*

As could be deduced from the plot above, electron-rich nitro compounds (4-nitroanisole, 100 mol%) have significantly larger promoting effect compare to their electron-poor analogs (nitrobenzene and 4-nitrobenzotrifluoride). Since 4-nitroanisole (ε = 27.5) is less polar than nitrobenzene (ε = 36.1), one might come to the logical assumption that changes in the dielectric constants of the medium due to the additive are not responsible

for the rate acceleration in this reaction.[124] With this somewhat surprising result, we decided to probe the reaction system further through additional kinetic experiments.

4.2.5 **Kinetic study**

Mechanistic investigations are essential to understanding unexpected catalytic phenomenon.[125] Thus, in order to explain the origin of the unusual nitro effect and to understand the role of the catalytically relevant species in our azidation reaction, the chemical kinetics were carefully investigated.

The method of initial rates was employed to determine the order of the individual components for the reaction in benzene (Figure 4.3). Keeping the amount of reaction ingredients being constant, the amount of examined component has been independently varied and the initial reaction progress was monitored at the region below 30 % of the overall conversion. Concentration effect was evaluated for each reaction component and the corresponding plots were built in the appropriate coordinates according to the equation $log(rate) = x(log([C_a]) + const$, where *rate* is the reaction rate, $[C_a]$ is the concentration of the appropriate reagent, x is the order in the appropriate reagent. Thus, the slow background reaction that occurs in the absence of nitro additives is first order in acid (0.98 ± 0.02). In contrast, co-catalyzed reactions in benzene in the presence of nitromethane reveal a second-order (1.96 ± 0.04) rate dependence on the concentration of nitro compound, an approximately second-order (1.8 ± 0.1) rate dependence on the concentration of acid, an approximately first-order (0.83 ± 0.02) rate dependence on the concentration of silyl ether **55a**, and a zero-order (−0.025 ±0.002) rate dependence on the concentration of $TMSN_3$, demonstrating that the nitro compound is in fact a co-catalyst and induces a change in the concentration dependence of the Brønsted acid.

[124] Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*, 3rd updated and enlarged ed.; Wiley-VCH: Weinheim, **2003**.
[125] Anslyn, E. V.; Dougherty, D. A. *Modern physical organic chemistry*, University Science Books, Sausalito, California, **2006**.

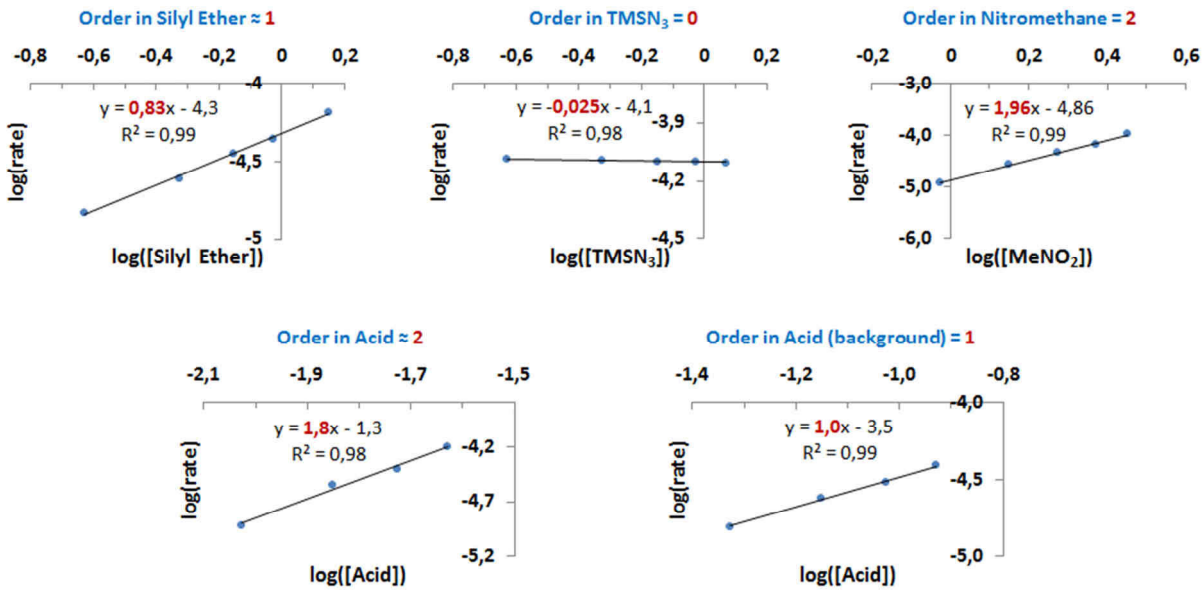


Figure 4.3. *Kinetic study of concentration dependence.*

The atypical observation of higher order rate dependence in Brønsted acid and nitro compound led us to consider whether the nitro functionality might increase the effective acidity, and hence the catalytic ability, of the Brønsted acid. In this regard, the plausible formation of higher order aggregates of acid and nitro compounds was hypothesized as a key factor to allow the otherwise challenging azidation of aliphatic alcohols to take place. The following section of this chapter gives an overview of the state of the art of aggregation-enhanced acid or hydrogen bond catalysis in solution.

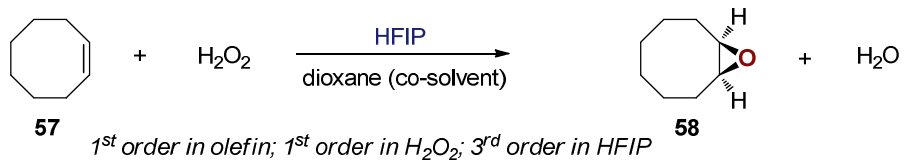
4.3 Introduction to hydrogen bond-assisted catalysis in solution

The power of hydrogen bond catalysis and Brønsted acid catalysis has been widely explored in organic synthesis and biochemistry.[126] The activity of molecular catalysts can be dramatically enhanced by favoring their interaction with suitable H-bond donors.[127] This approach is well known to increase reaction rates and to lead to impressive selectivity within enzymes and their mimics.[128] Rather than discussing H-bond assisted catalysis within enzyme-like supramolecular pockets, this section details acid or rather strong H-bond donor catalysis, which is accelerated or better controlled *via* catalyst aggregation in solution.

[126] Eigen, M. *Angew. Chem. Int. Ed.* **1964**, *3*, 1.
[127] Pihko, P. M. *Hydrogen Bonding in Organic Synthesis*. Wiley, Weinheim, **2009**.
[128] (a) Raynal, M.; Ballester, P.; Vidal-Ferran, A.; van Leeuwen, P. W. N. M. *Chem. Soc. Rev.* **2014**, *43*, 1660. (b) Raynal, M.; Ballester, P.; Vidal-Ferran, A.; van Leeuwen, P. W. N. M. *Chem. Soc. Rev.* **2014**, *43*, 1734.

4.3.1 **Hydrogen-bonded aggregates as catalysts for accelerated reactivity**

The cooperative enhancement of hydrogen bond donating ability of a single molecule catalyst through intermolecular H-bond networking represents a fundamental approach to accelerate reaction kinetics. The group of Berkessel reported a complete study on the epoxidation of olefins by hydrogen peroxide, which is accelerated up to 10^5 fold if HFIP is used as a solvent (Scheme 4.7).[129] Kinetic and theoretical investigation revealed that the reaction follows first-order rate dependence on the concentration of olefin **57**, first-order rate dependence on the concentration of oxidant, and approximately third-order rate dependence on the concentration on HFIP, resulting in fifth-order reaction rate dependence overall and indicating that the higher order hydrogen bonded aggregates of HFIP are responsible for the dramatic rate acceleration.



Scheme 4.7. *Epoxidation of (Z)-cyclooctane **57** by H_2O_2 in the presence of HFIP.*

4.3.2 **Hydrogen-bonded aggregates as catalysts for enhanced stereocontrol**

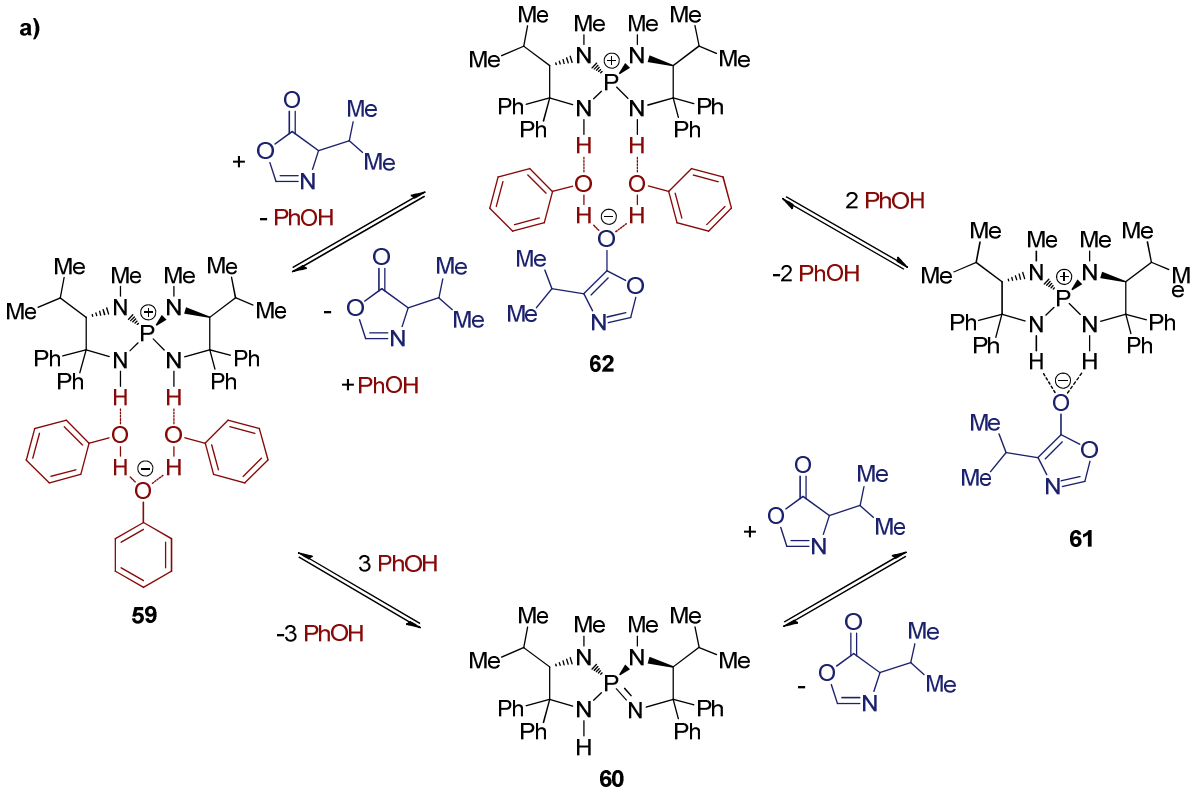
In contrast to the abovementioned situation, where the kinetically competent H-bond catalyst is effectively also the solvent, the fine-tuning of hydrogen bond networks can also be achieved at low concentrations. In a series of reports, Ooi and co-workers described a chiral ion pair catalyst **59** that assembles through a hydrogen bonding network between chiral P-spiro-triaminoiminophosphorane **60**-derived cation, two phenols and a phenoxide anion (Table 4.2).[130] Notably, X-ray analysis of the corresponding crystal of **59** revealed that in the solid state the catalyst components are aligned through a 10-membered cyclic network of intermolecular hydrogen-bonding interactions. Under dynamic equilibration with an acyl anion to produce **62** (Table 4.2, a), the chiral supramolecular architecture **59** was shown to catalyze the conjugate addition of azlactone **63** to α, β–unsaturated ester equivalent **64**

[129] (a) Berkessel, A.; Adrio, J. A.; Hüttenhain, D.; Neudörfl, J. M. *J.Am Chem. Soc.* **2006**, *128*, 8421. (b) Berkessel, A.; Adrio, J. *J. Am. Chem. Soc.* **2006**, *128*, 13412. (c) Berkessel, A.; Krämer, J.; Mummy, F.; Neudörfl, J.-M.; Haag, R. *Angew. Chem. Int. Ed.* **2013**, *52*, 739.
[130] (a) Uraguchi, D.; Ueki, Y.; Ooi, T. *Science* **2009**, *326*, 120. (b) Uraguchi, D.; Ueki, Y.; Ooi, T. *Angew. Chem. Int. Ed.* **2011**, *50*, 3681. (c) Uraguchi, D.; Ueki, Y.; Ooi, T. *Chem. Sci.* **2012**, *3*, 842.

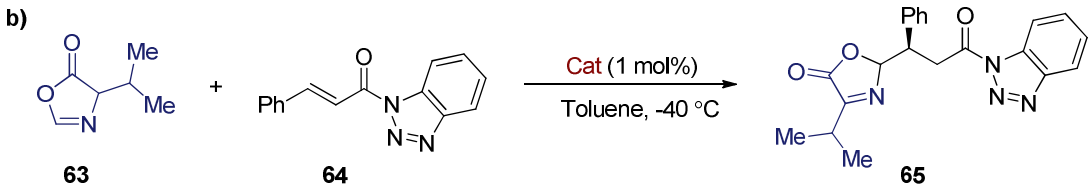
(Table 4.2, b). Importantly, in the presence of an H-bond donating phenol additive the reaction proceeded with superior enantiocontrol compared to the faster but less selective reaction if **60** was employed as a catalyst with no phenol added.

Table 4.2. *Chiral ion pair catalyst assembled through a hydrogen-bonding network: a) modes of assembly; b) comparison of catalytic activity.*

a)



b)

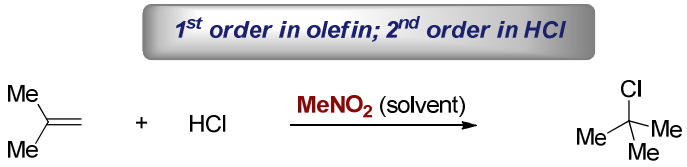


Entry	*Catalyst*	*Time, (h)*	*Yield, (%)*	*ee, (%)*
1	**59**	2	99	34
2	**60**	6	99	60

4.3.3 **Rate acceleration and cooperation effects in nitromethane**

Some acid-catalyzed reactions in nitromethane have already been noted for their higher order rate dependence on the concentration of Brønsted acid, though a role for the

nitro compound in inducing H-bond aggregation was never considered. Pocker and co-workers documented that the hydrochlorination of olefins displays first-order rate dependence on the concentration of isobutylene and second-order rate dependence on the concentration of HCl, specifically when carried out in nitromethane (Scheme 4.8).[131] Based on a series of kinetic experiments, the authors concluded that cooperative effects between two molecules of HCl were responsible for the observed concentration dependence with the overall rate of addition being described as $rate = k(olefin)(HCl)^2$. Although nitromethane was chosen on the basis of its low nucleophilicity and good propensity to sustain carbocation intermediates, no efforts were made to uncover any mechanistic involvement of nitromethane in this reaction.



Scheme 4.8. *Kinetic study of olefin hydrochlorination in nitromethane.*

In relation to the abovementioned works, nitromethane has been also shown to drastically affect the kinetics of proton transfer in zeolites, microporous acid catalysts widely used in industry.[132] Thus, several small scale reactions and commercial catalytic processes, such as isopropanol dehydration, methanol to gasoline conversion, and acetone conversion to acetic acid/hydrocarbons, have been studied with a model zeolite catalyst in nitromethane and *n*-pentane, demonstrating much higher conversion and reduced temperatures in the cases when nitromethane was used as a solvent.

4.4.4 Nitro functionality as H-bond acceptor

The spectroscopic observation of intermolecular hydrogen bonding of nitro compounds has been well documented in the literature.[133] On a practical level, nitro compounds have been recognized more recently in catalysis as weak H-bond acceptors. As an

[131] (a) Pocker, Y. *J. Chem. Soc.* **1960**, 1292. (b) Pocker, Y.; Stevens, K. D.; Champoux, J. J. *J. Am. Chem. Soc.* **1969**, *91*, 4199. (c) Pocker, Y.; Stevens, K. D. *J. Am. Chem. Soc.* **1969**, *91*, 4205.
[132] Haw, J. F.; Xu, T.; Nicholas, J. B.; Goguen, P. W. *Nature* **1997**, *389*, 832.
[133] (a) Baitinger, W. F.; Schleyer, P.; Murty, T. S. S. R.; Robinson, L. *Tetrahedron* **1964**, *20*, 1635. (b) Ungnade, H. E.; Roberts, E. M.; Kissinger, L. W. *J. Phys. Chem.* **1964**, *68*, 3225. (c) Etter, M. C.; Urbañczyk-Lipkowska, Z.; Zia-Ebrahimi, M.; Panunto, T. W. *J. Am. Chem. Soc.* **1990**, *112*, 8415. (d) Laurence, C.; Berthelot, M.; Lucon, M.; Morris, D. G. *J. Chem. Soc., Perkin Trans. 2* **1994**, 491.

example, H-bonding by chiral thiourea catalysts to the nitro functionality has been proposed to promote asymmetric cycloadditions of nitro-containing heterocycles (Figure 4.4, a)[134] and Michael additions to nitroolefins.[135] Alternatively, the nitro group has been shown to be an inhibitor in some reactions catalyzed by H-bond donors (Figure 4.4, b).[136]

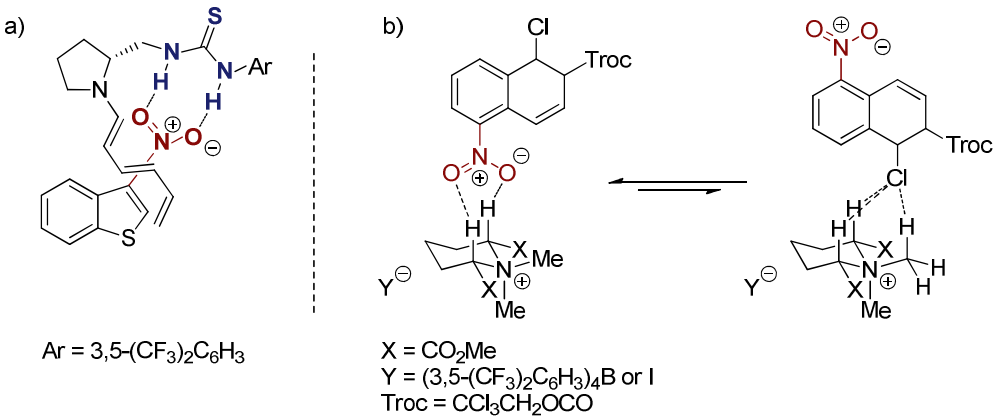
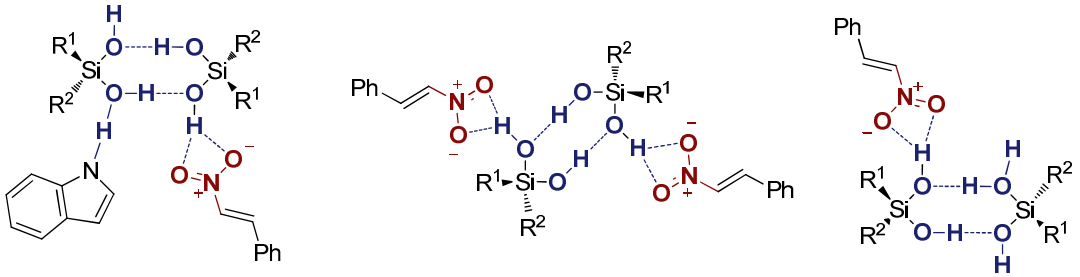


Figure 4.4. *Nitro functionality as hydrogen bond acceptor in catalysis: a) activated as a leaving group in formal [2+4] cycloaddition to 3-nitrobenzothiophenes; b) as a competitor for chloride activation by tetraalkylammonium salts.*

In a particularly interesting example from the Franz group,[137] cooperative H-bonding effects in silanediol-catalyzed addition of indole and 2-methoxy-*N*,*N*-dimethylaniline to *trans*-*β*-nitrostyrene were investigated. A collection of NMR, X-ray and ESMS experiments together with computational studies has revealed the formation of hydrogen-bonding adducts between the H-bond donor and nitro components. The authors proposed the possible simultaneous activation of two nitrostyrene molecules by a silanediol dimer **67** (Figure 4.5).



66 **67** **68**

[134] Li, Y.; Tur, F.; Nielsen, R. P.; Jiang, H.; Jensen, F.; Jørgensen, K. A. *Angew. Chemie Int. Ed.* **2016**, *55*, 1020.
[135] Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672.
[136] Shirakawa, S.; Liu, S.; Kaneko, S.; Kumatabara, Y.; Fukuda, A.; Omagari, Y.; Maruoka, K. *Angew. Chem. Int. Ed.* **2015**, *54*, 15767.
[137] (a) Jentzsch, K. I.; Min, T.; Etcheson, J. I.; Fettinger, J. C.; Franz, A. K. *J. Org. Chem.* **2011**, *76*, 7065. (b) Tran, N. T.; Wilson, S. O.; Franz, A. K. *Org. Lett.* **2012**, *14*, 186.

Figure 4.5. *Plausible hydrogen-bonding complexes **66**, **67**, **68** in silanediol-catalyzed addition of indole to nitrostyrene.*

4.4 Discussion: part 2. Co-catalysis by nitro compounds and Brønsted acid

Although nitro solvents have been shown to be particularly effective in several Brønsted acid catalyzed reactions, the active involvement of the nitro functionality, a well-known weak dual H-bond acceptor, has to the best of our knowledge not been taken into consideration. However, the strong electronic effects of the nitro co-catalysts in our azidation reaction and their observed effect in switching a reaction from one that previously exhibited first order concentration dependence in acid to one that exhibits seconds order concentration dependence in acid as well as second order dependence in nitromethane itself, lead us to conclude that the nitro component play a more active role in the observed catalysis. Thus, the following section aims to provide additional evidence and build the discussion around the concept of nitro-assisted Brønsted acid catalysis.

4.4.1 Hydrogen bonding between $B(C_6F_5)_3 \bullet H_2O$ and nitro compounds

The direct spectroscopic observation of hydrogen bonding and associated supramolecular aggregates in diluted solution is extremely challenging due to the weak H-bond accepting ability of nitro compounds and the subsequent fast rate of dynamic exchange of the components.[138] Our attempts to detect hydrogen bonding between nitro compounds and $B(C_6F_5)_3 \bullet H_2O$ in diluted C_6D_6 solutions in the presence or in the absence of $TMSN_3$ by NMR (^1H, ^{19}F, ^{15}N, ^{11}B and ^{29}Si) or by mass spectrometry (ESMS, MALDI) typically resulted in the observation of the individual components, with some exception for ^{19}F NMR, where the signal corresponding to the *para*-F resonance of $B(C_6F_5)_3 \bullet H_2O$ shifts significantly in the presence of nitro compounds.

However, IR experiments show clear evidence of hydrogen bonding between the OH group of $B(C_6F_5)_3 \bullet H_2O$ and the nitro compounds. The magnitudes of the changes in frequency and broadness of the OH stretch increase with greater electron-rich character of the nitro compound, correlating with their co-catalytic activity. The $B(C_6F_5)_3 \bullet H_2O$ OH stretch at 3546 cm^{-1} in toluene shifts to 3523, 3480, and 3465 cm^{-1} in the presence of 4-nitrobenzotrifluoride, $PhNO_2$, and 4-nitroanisole, respectively. The observed peak

[138] Lehn, J.-M. *Supramolecular Chemistry: Concepts and Perspectives*; Wiley-VCH, Weinheim, **1995**.

broadening in the case of electron-rich nitro compounds indicates that a larger number of intermolecular interactions between $B(C_6F_5)_3 \bullet H_2O$ and the nitro compounds are accessible, an observation characteristic of aggregation (Figure 4.6).

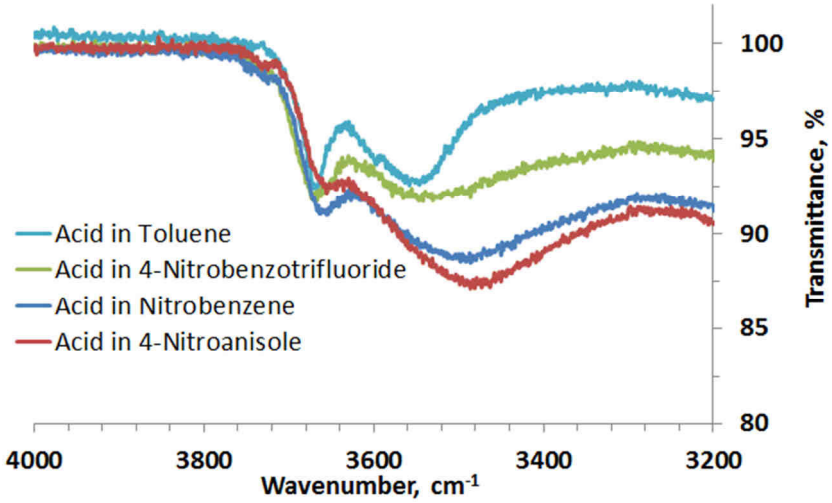


Figure 4.6. *IR experiments showing the effect of various nitro compounds on the OH stretch of* $B(C_6F_5)_3 \bullet H_2O$.

4.4.2 Effect of nitro compound and $B(C_6F_5)_3 \bullet H_2O$ on $TMSN_3$

The influence of nitro compounds on the activation of $TMSN_3$ by $B(C_6F_5)_3 \bullet H_2O$ can be observed by monitoring the azide stretch at 2136 cm^{-1}. No interactions between $PhNO_2$ and $TMSN_3$ were observed in the absence of acid. Mixing catalytic amounts of $B(C_6F_5)_3 \bullet H_2O$ and 1 equiv of $TMSN_3$ in toluene results in a slight decrease of intensity of the peak at 2136 cm^{-1} and the appearance of a new peak at 2200 cm^{-1}. In the presence of $PhNO_2$, the new peak shifts slightly to 2207 cm^{-1}. The peak grows with increasing concentration of $B(C_6F_5)_3 \bullet H_2O$ at the expense of the peak at 2136 cm^{-1} (Figure 4.7). Mixing all three components had no effect on the N–O stretch of $PhNO_2$, ruling out the possibility that the nitro compound becomes silylated and functions as a silyl transfer catalyst.

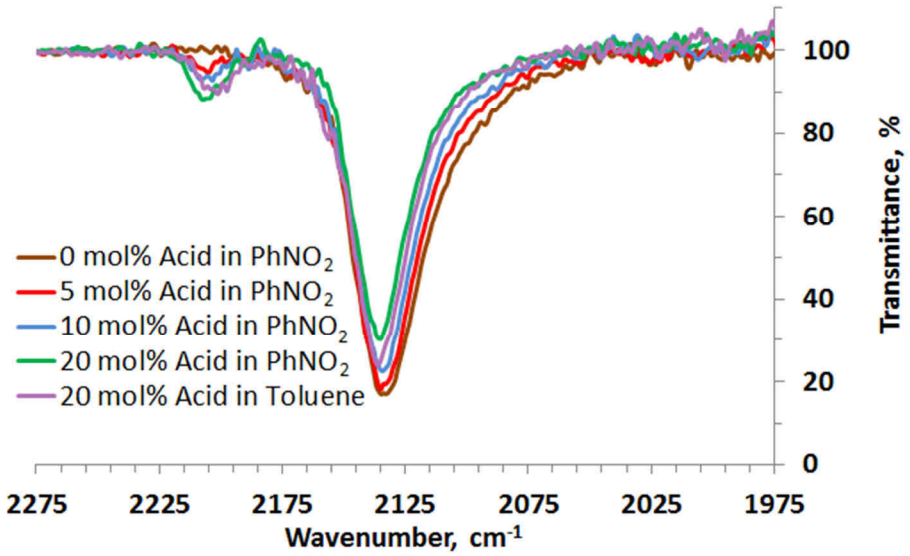
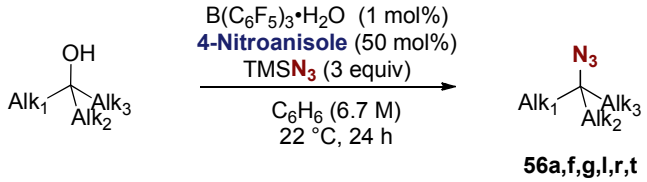


Figure 4.7. *IR experiments showing the effect of $B(C_6F_5)_3$•H_2O and $PhNO_2$ on the azide stretch of $TMSN_3$.*

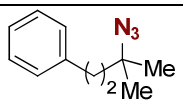
4.4.3 **Scope for dehydroazidation with catalytic amount of nitro compound**

The results of the kinetic and spectroscopic experiments raised a curious question as to whether the loading of nitro compound could be rendered co-catalytic. Based on the previously studied rate dependence on the electronics of the nitro compound, we selected 4-nitroanisole as the most potent co-catalyst for substoichiometric azidation reactions. After the brief reoptimization of reaction conditions, several tertiary aliphatic alcohols were surveyed with 1 mol% of $B(C_6F_5)_3$•H_2O and 50 mol% of 4-nitroanisole co-catalyst in benzene. Indeed, the substitution products could once again be isolated after column chromatography typically in yields higher than 50%, indicating catalytic turnover in the system (Table 4.3).

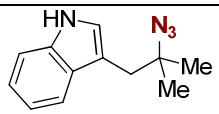
Table 4.3. *Azidation of tertiary aliphatic alcohols with catalytic amount of 4-nitroanisole.*[a]



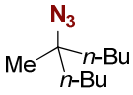
56a,f,g,l,r,t



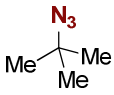
56a, 65%



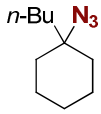
56g, 92%



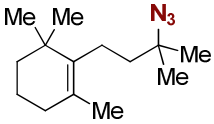
56f, 70%



56l, 93%



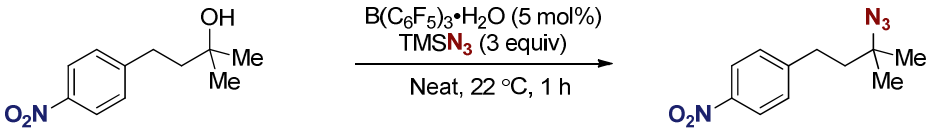
56r, 81%



56t, 42%

[a]Isolated yield

Notably, dehydroazidation was possible at room temperature in the absence of nitro additives when nitro-containing substrate **69** was reacted under neat reaction conditions (Scheme 4.9).



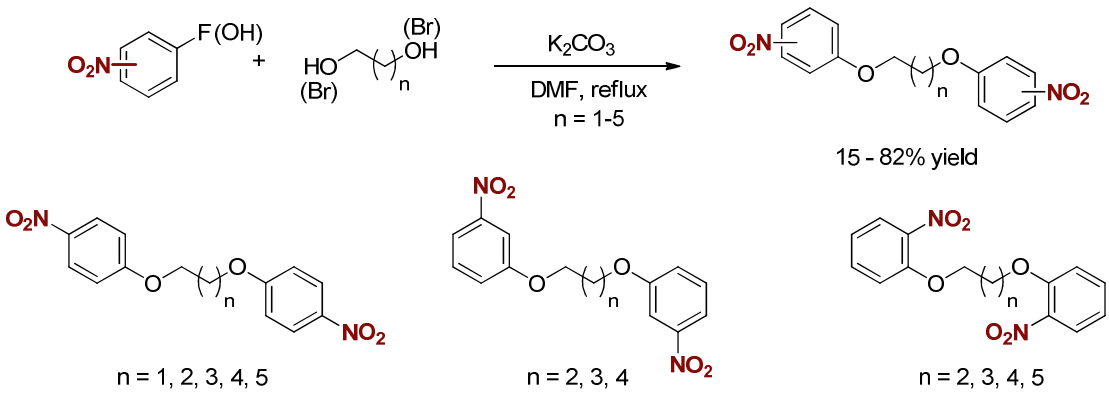
69 **70**, 44% yield

Scheme 4.9. *Azidation of nitro-containing substrate **69** in the absence of external nitro additive.*

4.4.4 Accelerated substitution with bis-nitro compound

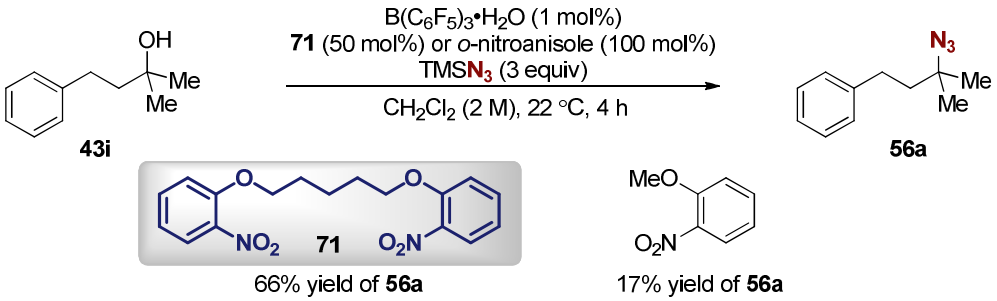
The experimentally confirmed feasibility of nitro co-catalysis in benzene, alongside second order rate dependence on the concentration of nitro compound, prompted the hypothesis as to whether appropriately designed bis-nitro compounds could serve as superior second-generation catalysts. To test this hypothesis, a library of aromatic bis-nitro compounds was prepared, consisting of molecules with two nitrobenzene motifs separated in space by an aliphatic linker where the position of nitro group on the aromatic ring and the

length of the linker have been independently varied. The general synthetic strategy was built on the nucleophilic substitution reaction (Scheme 4.10).



Scheme 4.10. *General strategy for synthesis of the library of bis-nitro compounds.*

With the library in hand, the effect of these bis-nitro compounds on the rate of the azidation reaction was compared with that of simple mono-nitro compounds. Under reaction conditions reoptimized to overcome the poor solubility of the bis-nitro component, compound **71** showed a significantly higher promoting effect on the reaction rate compared to an equivalent amount of mono-nitro co-catalyst (Scheme 4.11). Together with the abovementioned effects, this valuable initial result implies an important role of H-bonded mixed aggregates of nitro compound and Brønsted acid in the observed catalysis and forms a basis for further mechanistic discussion. Notably, none of the other bis-nitro compounds displayed in Scheme 4.10 showed greater catalytic activity than *o*-nitroanisole, indicating that the relative geometry of the two nitro groups is critical to catalysis.



Scheme 4.11. *Rate acceleration in the presence of bis-nitro compound.*

4.4.5 **Mechanistic discussion on nitro-assisted Brønsted acid catalysis**

Taken together, the kinetic, electronic, and spectroscopic evidence suggest that mixed hydrogen-bonded aggregates of Brønsted acid and nitro compound catalyze the reaction and that the catalytically competent Brønsted acid likely contains two molecules of each component. Among several possibilities, we propose two generic structures of molecular aggregates (**A**) and (**Z**), which are expected to be superior hydrogen-bond donor (**A**) and Brønsted acid (**Z**) compare to the parent monomeric $B(C_6F_5)_3$•H_2O (Figure 4.8).

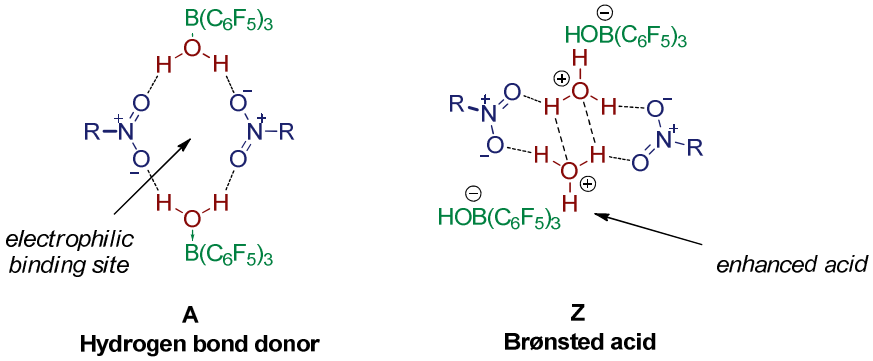
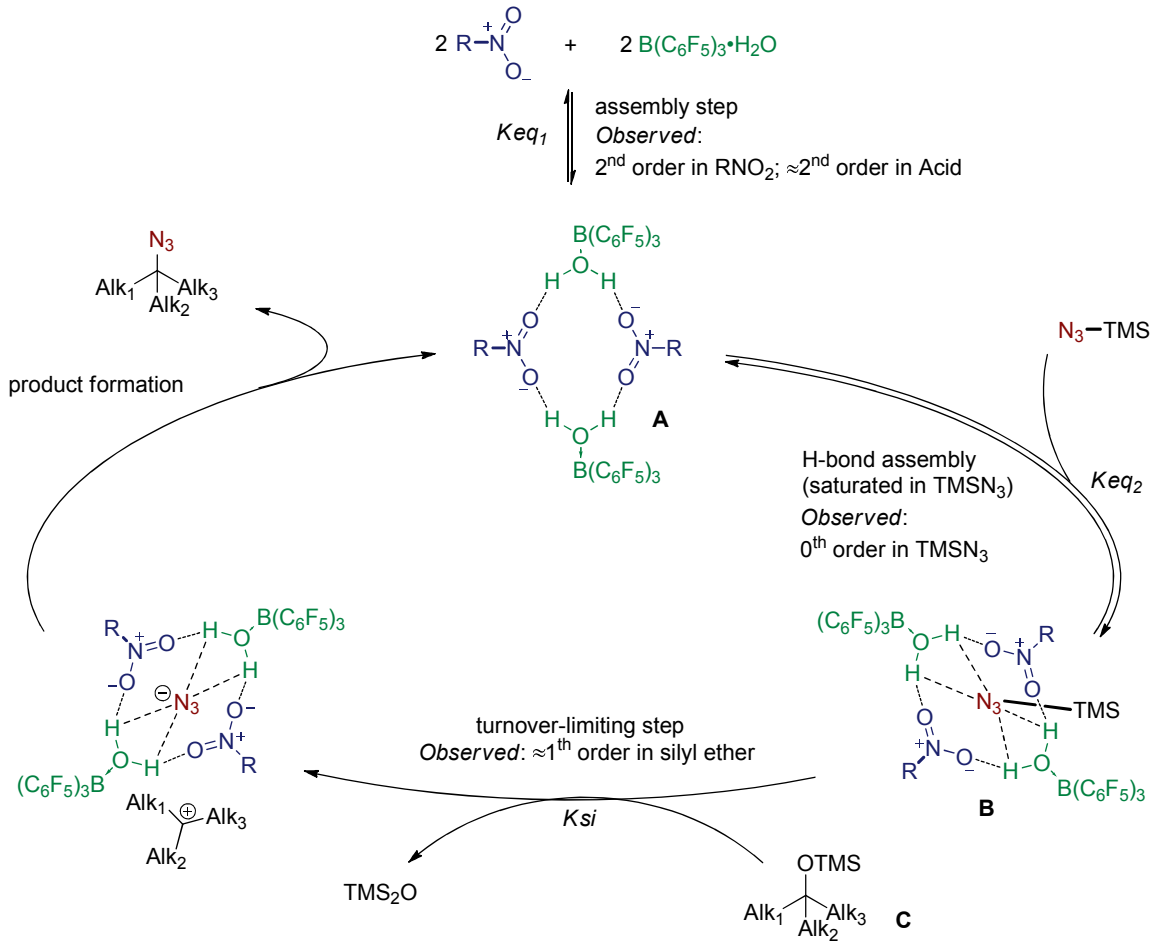


Figure 4.8. *Proposed structures of catalytically active mixed hydrogen-bonded aggregates.*

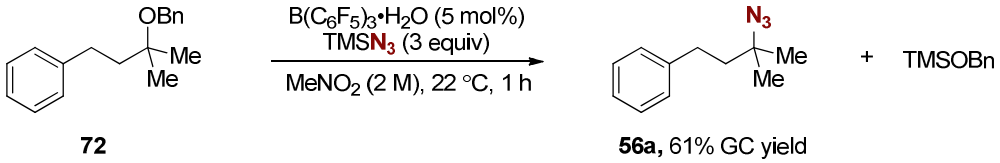
In a plausible catalytic cycle (Scheme 4.12) depicted for the case of (**A**), a rapid and reversible preorganization of two nitro compounds and two molecules of $B(C_6F_5)_3$•H_2O is taking place to form an electrophilic supramolecular pocket (**A**), which is also a superior H-bond donor than the initial Brønsted acid. Reversible hydrogen bonding of (**A**) with nucleophilic $TMSN_3$ generates an aggregate (**B**) that is in the saturation regime for the latter component. (**B**) is expected to be a superior silyl donor compared to a $TMSN_3$ that is activated by only a single molecule of acid. Turnover-limiting silylation of (**C**) by (**B**), presumably associated with the intermediacy of a silyl cation, generates a carbocation that is rapidly trapped by an azide anion to give product. The faster observed rates for electron-rich nitroarenes as well as acceleration effect of bis-nitro compound are consistent with an expected larger equilibrium concentration of (**A**).



Scheme 4.12. *Plausible catalytic cycle for nitro-assisted Brønsted acid-catalyzed azidation.*

4.4.6 **Additional mechanistic considerations**

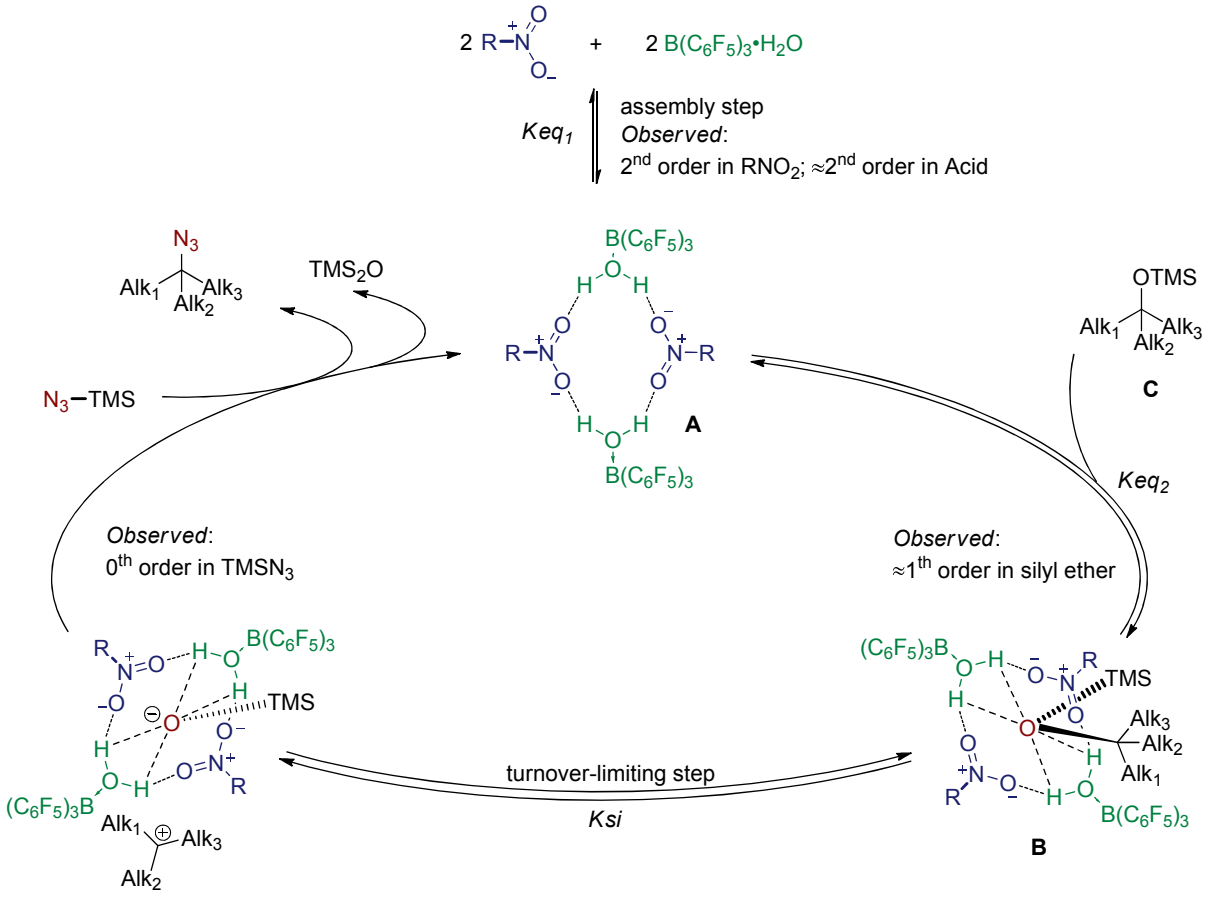
The viability of the mechanism proposed in section 4.4.5 is supported by the observation that other nucleophiles were unable to perform the substitution of alcohol **43i,** nor corresponding silyl ether **55a** under otherwise identical reaction conditions. This outcome is in agreement with the hypothesis that complex (A•$TMSN_3$) acts as a silylating agent, while other types of nucleophiles either are not good hydrogen bond acceptors (allyltrimethylsilane, trimethylsilyl cyanide), or are not able to silylate **55a** (Bu_4NN_3, DPPA). However, tertiary aliphatic benzyl ether **72** reacted with $TMSN_3$ under typical conditions to give **56a** and silyl benzyl ether (Scheme 4.13).



72 **56a,** 61% GC yield

Scheme 4.13. *Reaction of benzyl ether **72** with formation of **56a** and TMSOBn.*

Additionally, 1,4-dimethoxybenzene, acac, and $PhSO_2NH_2$ proved to be ineffective nucleophiles and no product formation was observed. However, in case of silyl ether **55a** reaction with the strongest nucleophiles, such as thiophenol and 1,3-dimethoxybenzene, low yields (<20%) of substitution products were detected by GCMS after prolonged reaction time (3 h), accompanied by minor levels of alkene byproducts. Thus, a slower competing mechanism proceeding through direct ionisation of silyl ethers is likely also operative (Scheme 4.12).



Scheme 4.14. *Additional mechanistic considerations for a slower competing secondary pathway.*

4.5 Conclusion to chapter 4

In conclusion, an unprecedented type of co-catalysis has been described in which nitro compounds dramatically accelerate the $B(C_6F_5)_3 \bullet H_2O$ catalyzed azidation of tertiary aliphatic alcohols and enable low-loading catalysis for the first time under exceptionally mild conditions by inducing a change in the catalyst activation mode. Preliminary mechanistic investigations are consistent with catalysis by transient 2:2 aggregates of nitro compounds and Brønsted acid, highlighting the overlooked organizational role of solvents and additives in Brønsted acid catalysis. Taken more broadly, such a non-covalent preorganization of weak H-bond acceptors and Brønsted acid may represent a general phenomenon in acid catalysis, giving rise to a new modular and tunable approach for acceleration of Brønsted acid catalysts in solution. In this regard, theoretical studies in collaboration with the group of Dr. Marco Cecchini are underway. Initial attempts to model the structures of 2:2 mixed aggregates of nitro compounds and $B(C_6F_5)_3 \bullet H_2O$ by DFT indicate their formation is plausible in vacuum alongside the strong correlation between co-catalytic activity and OH-stretching frequency of assembled supramolecular complexes. Furthermore, the driving force for assembly increases with electron-donating substituents in agreement with the observed reaction kinetics (Figure 4.9).

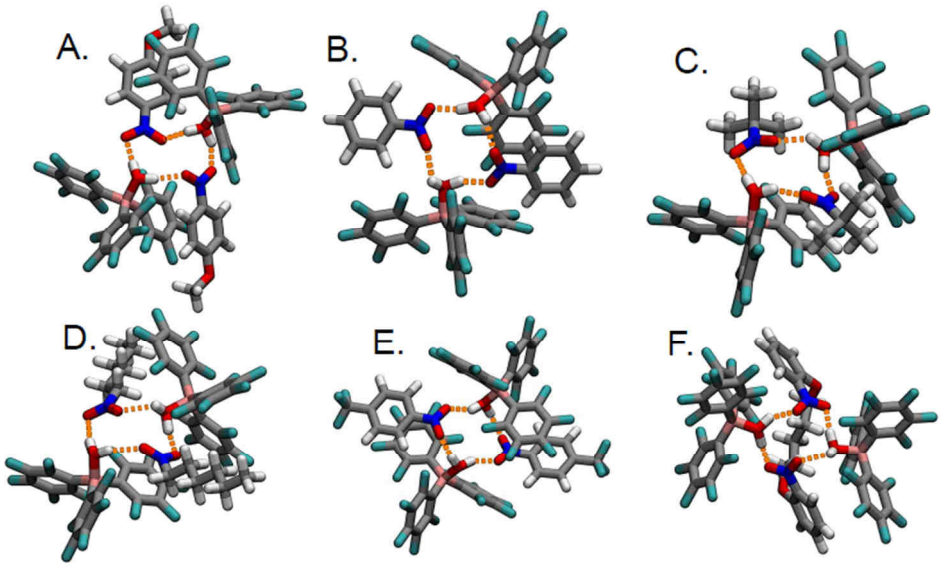


Figure 4.9. *Initial results of computational modeling: wB97X-D/6-31G(d,p) DFT level of theory-optimized structures for the complexes of $B(C_6F_5)_3 \bullet H_2O$ with:4-nitroanisole (A), nitrobenzene (B), 2-methyl-2-nitropropane (C), 1-nitrohexane (D), 4-nitrobenzotrifluoride (E) bis-nitro compound **71** (F). H-white, C-grey, O-red, F-green, B-pink, N-blue*

CHAPTER 5

Friedel-Crafts Alkylation with Tertiary Aliphatic Fluorides

5.1 Introduction

As well as hydroxyl-containing substrates, fluorinated organic molecules are common in biochemistry and medicinal chemistry with approximately one fifth of all pharmaceuticals containing fluorine.[139] Such a tremendous importance of organofluorides is associated with a great impact that the installation of fluorine does on the biological properties of the corresponding molecular scaffolds. Thus, a simple replacement of hydrogen atom on its bioisosteric fluoride often leads to the dramatic changes in drug's metabolic stability and lipophilicity, though also conserving or even increasing its therapeutic effect. Fascinated by remarkable properties of organofluorides, in particular by their inherent stability, we decided to take a closer look into the progress made so far for the cleavage of an unactivated C–F bond.

5.1.1 Properties of organofluorine compounds

The use of organofluorine compounds in material science, medicinal and polymer chemistry is widespread owing to the unique nature of the C–F bond.[140] With the highest electronegativity value ($\chi = 4$ by Pauling scale),[141] a fluorine atom forms the strongest single bond to carbon.[142] This bond is characterized by a short interatomic length ($r_W = 1.47$ Å) as well as high polarity (Figure 5.1).[143] The electrostatic component within this bond stipulates its thermodynamic stability and forms the basis for the inertness of the C–F bond towards selective cleavage in the presence of other, often less robust, functional groups. In addition, low Lewis basicity and nucleofugality conspire to make fluoride a poor leaving group.

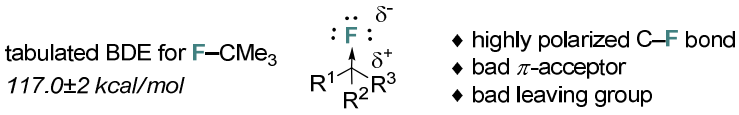
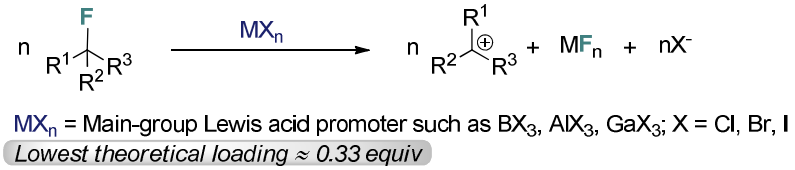


Figure 5.1. *Typical physicochemical features of fluorinated organic molecules*

[139] Thayer, A. M. *Chem. Eng. News* **2006**, *84*, 15.
[140] (a) Hiyama, T. *Organofluorine Compounds: Chemistry and Applications*, Springer, Berlin, **2000**. (b) Gladysz, J.A.; Curran, D. P.; Horváth, I. T. *Handbook of Fluorous Chemistry*, Wiley-VCH: Weinheim, **2004**. (c) Uneyama, K. *Organofluorine Chemistry*, Blackwell Publishing, Oxford, UK, **2006**. (d) Kirsch, P. *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications*, Wiley-VCH, Weinheim, **2013**.
[141] Pauling, L. *The Nature of the Chemical Bond and the Structure of Molecules and Crystals: An Introduction to Modern Structural Chemistry*, Cornell University Press, Ithaca, NY, **1939**.
[142] (a) Smith, D. W. *J. Phys. Chem. A* **1998**, *102*, 7086. (b) Luo, Y.-R. *Handbook of bond dissociation energies in organic compounds*; CRC Press, Boca Raton, Florida, US, **2003**.
[143] O'Hagan, D. *Chem. Soc. Rev.* **2008**, *37*, 308.

5.1.2 **State of the art for non-transition metal-promoted nucleophilic substitution of tertiary aliphatic fluorides**

The constantly growing number of densely functionalized organofluorine compounds has stimulated chemists to develop a range of methods for the selective cleavage of C–F bonds. However, the chemical inertness of the bond needs to be overcome in order to solve noble environmental concerns associated with the accumulation of potentially toxic organofluorine compounds that are resistant towards natural degradation. This demand has resulted in a variety of methods reported for the transformation of polyfluorinated molecules,[144] mono- and polyfluorinated aromatics,[145] as well as benzylic and allylic fluorides.[146] However, despite such notable advances in the area, selective functionalization of aliphatic C(sp^3)–F bonds remains much less established and typically requires the use of stoichiometric amounts of sensitive B or Al Lewis acids or stoichiometric trapping with Si reagents.[147] As might be expected, catalytic turnover is not possible in such systems and the lowest required loading of such a promoter is strictly limited by the number of strong covalent bonds that can be formed with the fluorine abstracting reagent (Scheme 5.1).



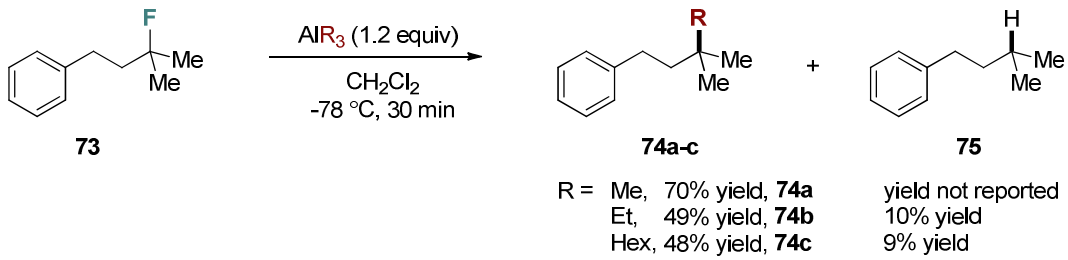
Scheme 5.1. *Stoichiometric reactivity between Lewis acids and alkyl fluorides.*

The following section of this introduction details the state of the art in B-, Al- and Si-promoted activation of alkyl fluorides with a particular focus on the reactivity of tertiary aliphatic fluorides and their Friedel-Crafts reactions.

[144] Ahrens, T.; Kohlmann, J.; Ahrens, M.; Braun, T. *Chem. Rev.* **2015**, *115*, 931.
[145] Amii, H.; Uneyama, K. *Chem. Rev.* **2009**, *109*, 2119.
[146] Unzner, T. A.; Magauer, T. *Tetrahedron Lett.* **2015**, *56*, 877.
[147] Stahl, T.; Klare, H. F. T.; Oestreich, M. *ACS Catal.* **2013**, *3*, 1578.

5.1.2.1 **Activation by Al Lewis acids**

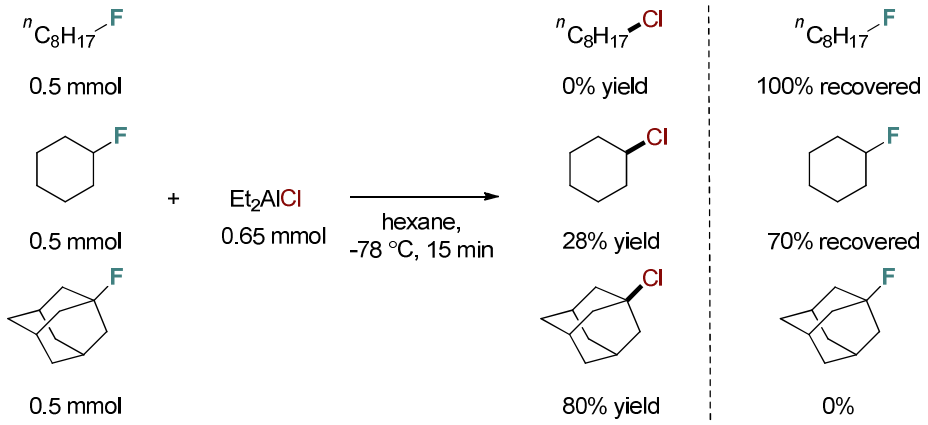
The formation of a strong Al–F bond (159 kcal/mol)[148] could be considered as the thermodynamic driving force for reactions involving fluoride abstraction from organofluorine substrates by a trialkylaluminum or by an aluminum trihalide. In an early report from Maruoka and co-workers,[149] tertiary aliphatic fluorides were shown to react readily with a stoichiometric amount of trialkylaluminum to give the corresponding *tert*-alkylated products (Scheme 5.2). In a representative example, 2-fluoro-2-methyl-4-phenylbutane **73** was successfully functionalized by the direct transfer of an alkyl group from 1.2 equiv of trialkylaluminum at -78 °C to give the alkylated products **74a-c** alongside with the minor hydrodefluorinated by-product **75**.



Scheme 5.2. *Alkylation of tertiary aliphatic fluoride **73** with trialkylaluminum.*

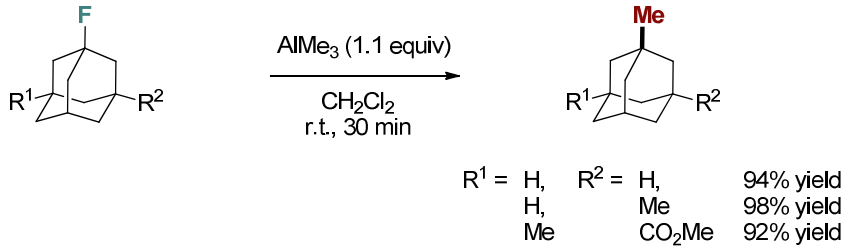
In related work from Terao, Kambe and co-workers,[150] the authors used a hexane solution of organoaluminum reagents of the type $AlX(Alk)_2$ to convert $C(sp^3)$–F bonds to $C(sp^3)$–X bonds, where X = Cl, H, C, O, S, Se, Te or N. Their efforts resulted in the development of a transformation that typically takes place at -78 °C for secondary or tertiary aliphatic fluorides and requires a superstoichiometric amount of the aluminum reagent. Notably, the study provides an important insight into the relative reactivity of monofluorinated substrates, showing that tertiary aliphatic fluorides produce the desired products more readily compared to secondary and primary analogs (Scheme 5.3).

[148] Dean, J. A. *Lange's Handbook of Chemistry*; McGraw-Hill, **1999**.
[149] Ooi, T.; Uraguchi, D.; Kagashima, N.; Maruoka, K. *Tetrahedron Lett.* **1997**, *38*, 5679.
[150] Terao, J.; Begum, S. A.; Shinohara, Y.; Tomita, M.; Naitoh, Y.; Kambe, N. *Chem. Commun.* **2007**, *8*, 855.



Scheme 5.3. *Competition study between alkyl fluorides with $AlEt_2Cl$.*

The reactivity of fluorinated adamantanes has been studied extensively by Aoyama and Hara.[151] In their report, various adamantane derivatives bearing a fluorinated tertiary carbon center have been successfully alkylated by a number of *C*-centered nucleophiles in the presence of stoichiometric $Al(OTf)_3$ or with $AlMe_3$ as an alkylating agent (Scheme 5.4). It is worth emphasizing that ester functionalities are tolerated in the presence of the rather chemically aggressive organoaluminum reagent, likely due to the fast proximal methylation of the nascent carbocation intermediate.



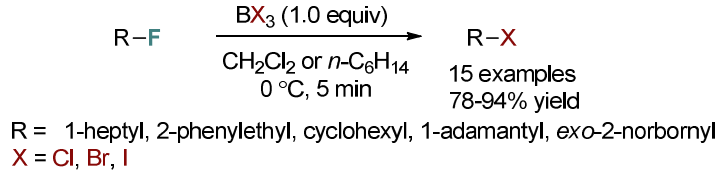
Scheme 5.4. *Methylation of fluoroadamantanes with $AlMe_3$.*

5.1.2.2 **Activation by B Lewis acids**

The high polarity of the C–F bond as well as the significant thermodynamic stability of the B-F bond (183 kcal/mol)[148] enable organoboron reagents to accomplish stoichiometric activation of organofluorine compounds. Satyamurthy and co-workers have reported the halogen exchange reaction between alkyl fluorides and boron trihalides.[152] In their study, equimolar amounts of Lewis acids and fluorinated substrates were mixed in dichloromethane

[151] Aoyama, M.; Hara, S. *Tetrahedron* **2009**, *65*, 3682.
[152] Namavari, M.; Satyamurthy, N.; Barrio, J. R. *J. Fluorine Chem.* **1995**, *72*, 89.

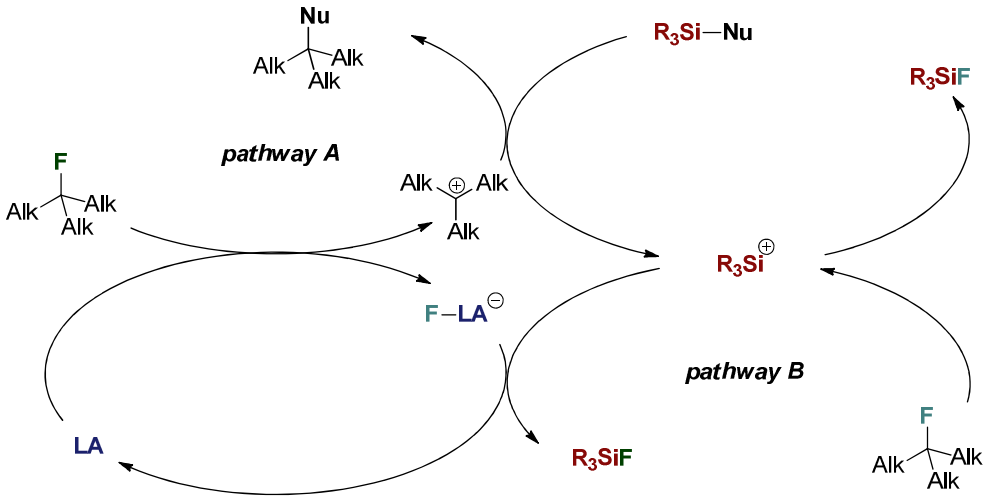
or hexane at 0 °C and under inert atmosphere to give the corresponding products in good yields (Scheme 5.5).



Scheme 5.5. *Halogen exchange reactions of alkyl fluorides with boron trihalides.*

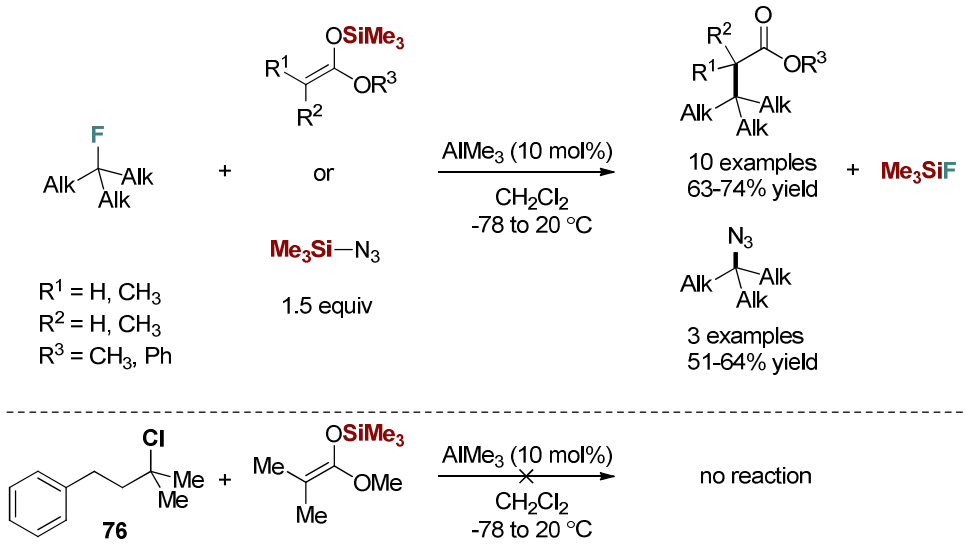
5.1.2.3 **Stoichiometric trapping with Si**

Main-group Lewis acid-triggered reactions of alkyl fluorides could be rendered catalytic if coupled with the stoichiometric formation of another strong covalent bond to fluorine in order to drive the thermodynamics of the overall transformation. As an implementation of this principle, the active Lewis acid catalyst, such as a B- or Al-based compound, could be successfully regenerated after heterolytic cleavage of the C–F bond by fluoride transfer to generate a strong F–Si bond (129 kcal/mol).[148] In a typical catalytic cycle (Scheme 5.6), the ionisation of the C–F bond is followed by nucleophilic addition to the nascent carbocation to deliver the substitution product while a stoichiometric amount of trialkylsilyl cation regenerates the catalyst (Pathway A). Alternatively, the silyl cation itself may abstract the fluorine from the alkyl fluoride to give rise to pathway B, which is potentially difficult to decouple under standard reaction conditions. Additionally, depending on the nucleophilic motif, the catalyst might activate the organosilane reagent itself, thus delivering a more electrophilic silicon that is a superior fluoride abstracting agent (not shown).



Scheme 5.6. *Alkyl fluoride activation/substitution in the presence of stoichiometric silicon-based trap.*

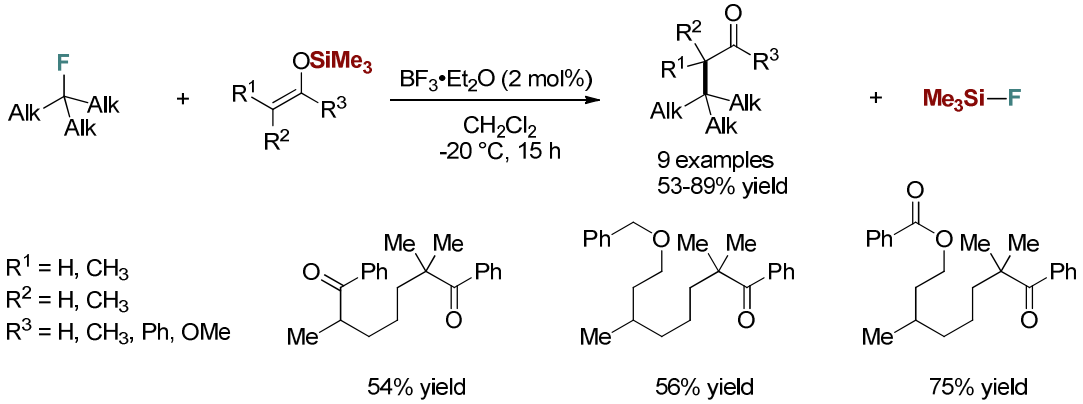
Thus, in a previously mentioned report from the Maruoka group,[149] the alkylation and azidation of tertiary alkyl fluorides has been shown to proceed with 10 mol% of pyrophoric $AlMe_3$ if $TMSN_3$ or silyl ketene acetal were employed as the sources of both nucleophile and silicon trap in order to maintain catalyst turnover (Scheme 5.7). Importantly, the subjection of the analogous chlorinated substrate **76** to the same conditions resulted in no reaction.



Scheme 5.7. *$AlMe_3$-catalyzed substitution of tert-alkyl fluorides.*

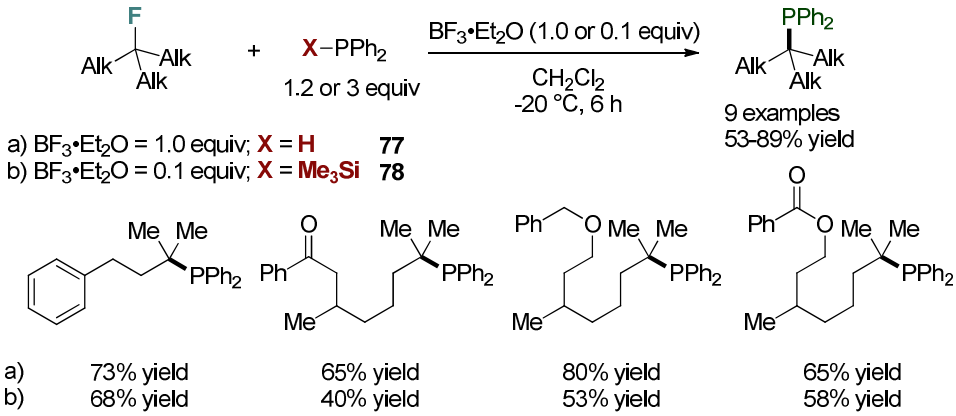
Closely related to the abovementioned study, tertiary aliphatic fluorides were reacted with silyl enol ethers, as well as with allylsilanes and hydrosilanes, in the presence of 2 mol%

of boron trifluoride diethyl etherate complex (Scheme 5.8).[153] The reaction is reported to work efficiently at -20 °C, tolerating ketone, ether and ester functionalities to furnish the desired products in good yields.



Scheme 5.8. *BF_3•Et_2O-catalyzed substitution of tert-alkyl fluorides.*

In 2004, Oshima and co-workers reported an example of how reactions of alkyl fluorides that previously required stoichiometric activating agent could be rendered catalytic by employing a nucleophile that contains a built-in fluoride-trapping agent in the form of a silyl group.[154] Whereas 1.0 equiv of BF_3•Et_2O was required if diphenylphosphine **77** was used as nucleophile for P-alkylation with tertiary aliphatic fluorides, only 0.1 equiv was necessary when diphenyl(trimethylsilyl)phosphine **78** was the nucleophile (Scheme 5.9). Remarkably, the boron catalyst operates effectively at substoichiometric loading despite the presence of the basic phosphine reagents.

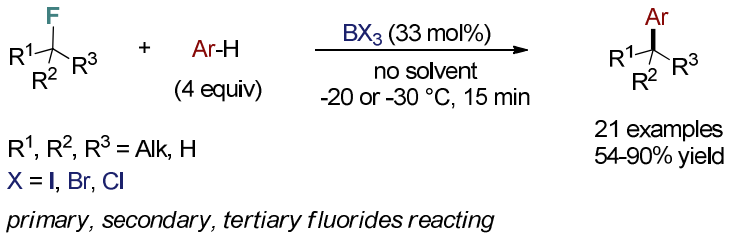


Scheme 5.9. *Stoichiometric and substoichiometric activation of tertiary aliphatic fluorides for the alkylation of diphenylphosphines **77** and **78**.*

[153] Hirano, K.; Fujita, K.; Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Tetrahedron Lett.* **2004**, *45*, 2555.
[154] Hirano, K.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2004**, *6*, 4873.

5.1.2.4 **Friedel-Crafts reactions of unactivated alkyl fluorides**

The boron trihalide promoted alkylation of aromatics with alkyl fluorides has been examined in seminal reports from Olah and co-workers.[155] After evaluating a series of alkylation and haloalkylation reactions with alkylfluorides and fluorohaloalkanes, it was noted that the C–F bond reacts preferentially over the C–Cl, C–Br and C–I bonds. The order of catalyst activity has been assigned as BI_3>BBr_3>BCl_3>BF_3. Although high levels of reactivity towards electron-neutral arenes have been observed in Olah's system, none of these reagents are capable of catalyst turnover as they react stoichiometrically with fluoride (Scheme 5.10). Moreover, in order to control the reactivity of boron, the transformation required the use of cryogenic conditions and showed no selectivity with respect to primary, secondary and tertiary alkyl fluorides, thus leaving room for further improvements.

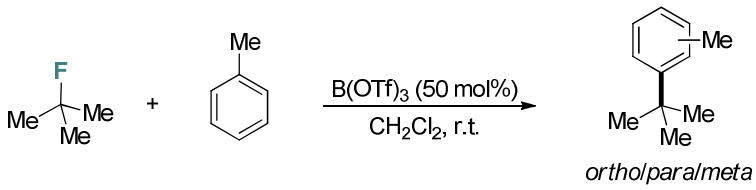


Scheme 5.10. *Friedel-Crafts alkylation with alkyl fluorides promoted by boron halides.*

In a subsequent study from the same group,[156] it was found that the triflate salts of boron, aluminum and gallium are also effective stoichiometric activators for Friedel-Crafts reactions in CH_2Cl_2 or $MeNO_2$ at room temperature. $B(OTf)_3$ has been the most active reagent followed by gallium triflate and then by aluminum triflate. The distribution of regioisomers for the toluene alkylation products after treatment with *tert*-butyl fluoride was examined in detail, as well as relative rates of isomerization of *tert*-butyltoluenes in CH_2Cl_2. Interestingly, it was concluded that the reaction initially formed a relatively high amount of *meta*-substituted regioisomer, the content of which was observed to rapidly decrease throughout the reaction and only 4 mol% of it remained after 25 min of reaction time (Table 5.1). The authors argue this to be a result of extensive intermolecular isomerization with an excess of toluene which delivers the predominant *para*-substituted product.

[155] (a) Olah, G.; Kuhn, S.; Olah, J. *J. Chem. Soc.* **1957**, 2174. (b) Olah, G. A.; Kuhn, S. J. *J. Org. Chem.* **1964**, *29*, 2317.
[156] Olah, G. A.; Farooq, O.; Farnia, S. M. F.; Olah, J. A. *J. Am. Chem. Soc.* **1988**, *110*, 2560.

Table 5.1. *Alkylation of toluene with tert-butyl fluoride using $B(OTf)_3$ and product distribution in CH_2Cl_2.*



Time, min	GCMS yield, (%)	*ortho, (%)*	*meta, (%)*	*para,(%)*
5	42	0	60	40
10	44	0	54	46
15	38	0	37	63
25	46	0	4	96

5.1.3 Critical conclusion and aim of the chapter

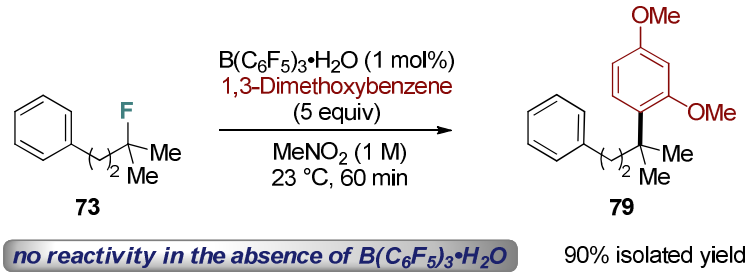
Clearly, the field of chemoselective activation of seemingly inert C(sp^3)–F bonds has significantly advanced over the last 50 years. The major breakthrough here has been achieved based on the chemistry of main-group Lewis acids, which combine high Lewis acidity and fluoride affinity. However, many aspects of this research still require further development. As a rule, successful substitution of the C(sp^3)–F bond requires stoichiometric amounts of sensitive or harsh organoboron or aluminum compounds. Consequently, cryogenic conditions, use of dry solvents, inert atmospheres and strict time control, are often associated with these methods. Representative Friedel-Crafts reactions of alkyl fluorides require stoichiometric amounts of boron trihalides or pseudohalides and furnish products alongside a high level of isomerization without catalyst turnover. The development of catalytic variants of these transformations remains an open challenge.

5.2 Discussion

5.2.1 Reaction discovery

Given the success of our recently discovered azidodehydration reaction of tertiary aliphatic alcohols, we hypothesized that a related catalytic system could be applied to the selective activation of the much stronger C(sp^3)–F bond. As a target reaction we selected the Friedel-Crafts alkylation of (hetero)arenes with tertiary aliphatic fluorides – a challenging transformation given the nature of the unactivated C–F bond and the clear lack of reports

involving non-transition metal-based catalysis. After the multigram-scale preparation of a model tertiary aliphatic fluoride **73**, we quickly observed the desired reactivity by using 1,3-dimethoxybenzene as a common Friedel-Crafts nucleophile in the presence of $B(C_6F_5)_3•H_2O$ in nitromethane at room temperature. After a brief optimization of concentration and catalyst loading, the Friedel-Crafts product could be prepared after 1 h of reaction time in 90% isolated yield following Kugelrohr distillation. No reactivity was observed in the absence of the catalyst even after 30 h of reaction time (Scheme 5.11).



Scheme 5.11. *Friedel-Crafts reaction discovery with tertiary aliphatic fluorides.*

5.2.2 **Solvent screen**

This result encouraged us to study the effects of solvent and of the nature of the catalyst on the reaction outcome, notably with regards to the concomitant formation of alkenes and bisalkylation product.

In contrast to the activation of tertiary aliphatic alcohols in nitromethane, the effect of solvent on the consumption of tertiary aliphatic fluorides was less pronounced (Figure 5.2). While no conversion was observed in 5 of 11 tested solvents (from dioxane to acetone on the figure), in "neutral" (benzene, toluene) or slightly "acidic" (DCM, DCE) solvents, the cleavage of alkyl fluoride was commonplace, though often proceeding slowly and leading to a higher degree of elimination by-product compared to nitromethane.

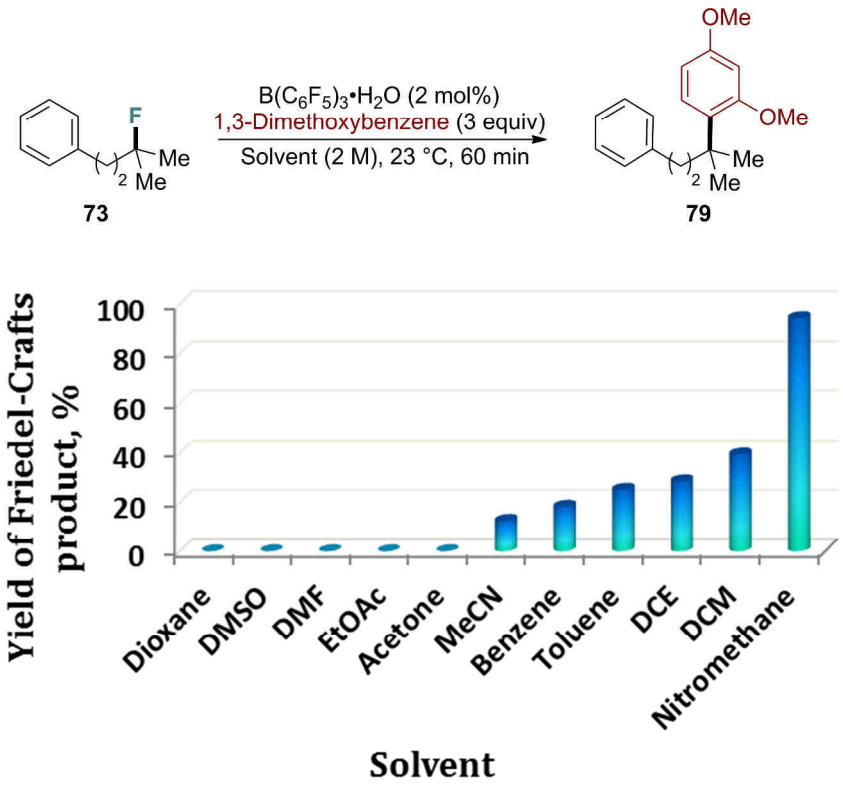


Figure 5.2. *Solvent screen (NMR yield).*

5.2.3 **Catalyst screen**

In order to probe the scope of catalysts able to cleave C(sp^3)–F bonds in nitromethane, tertiary aliphatic fluoride **80a** was employed as a model substrate. This substrate is considered to be particularly suitable for this study, as upon heterolytic cleavage of the C–F bond, the nascent carbocation possesses an enhanced tendency for E1 elimination to form the conjugated styrene-type product.

A survey of common Lewis acids (1 mol%), Brønsted acids (1 mol%) and hydrogen-bond donating catalysts (5 mol%) was carried out under standard reaction conditions (Figure 5.3). While most of the tested Lewis and Brønsted acids were found to catalyze this transformation with a full consumption of **80a** in 1 h, the best chemoselectivity was observed with $B(C_6F_5)_3•H_2O$, which gave the highest conversion to the Friedel-Crafts product but also a minimal amount of alkene by-product. In contrast, typical H-donors such as BINOL derivatives, thioureas or tartaric acid were not suitable catalysts for this reaction.

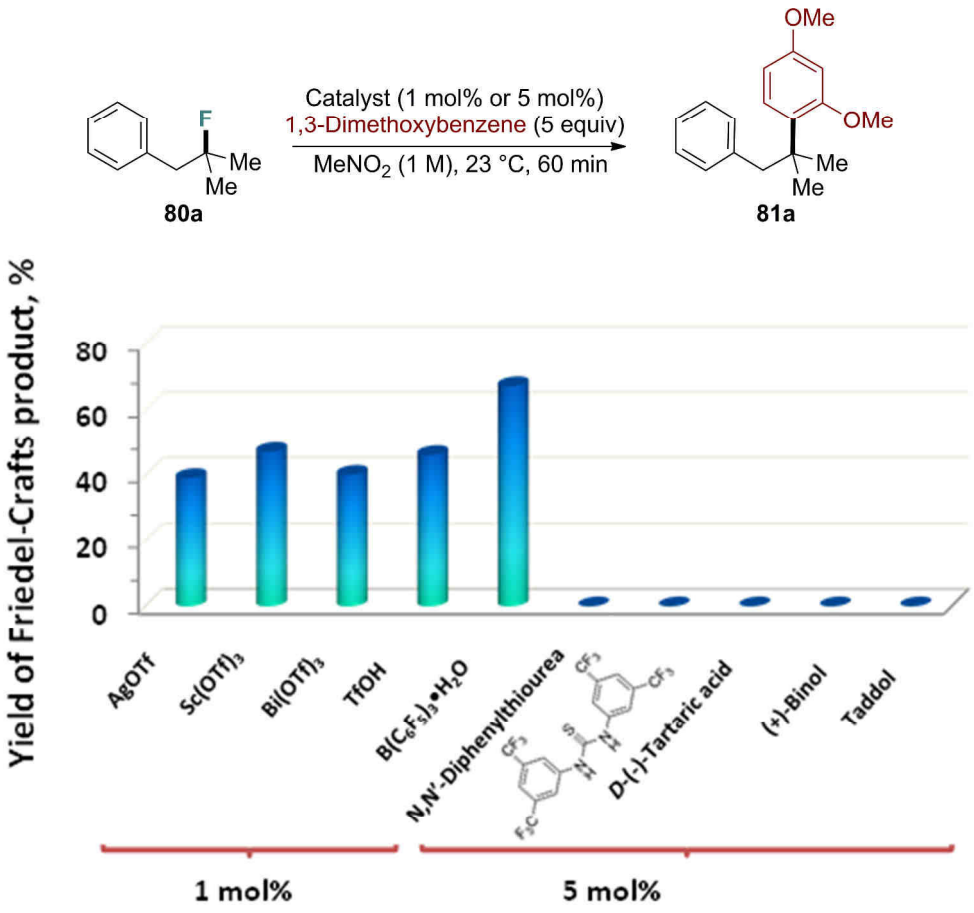
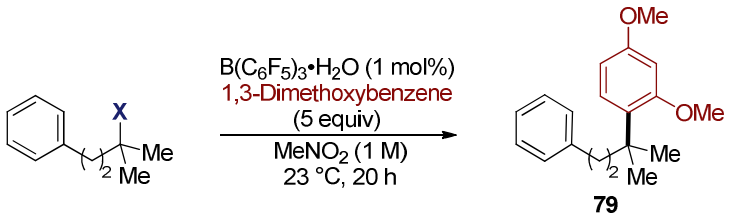


Figure 5.3. *Catalyst screen (NMR yield).*

5.2.4 **Leaving group selectivity**

Chemoselectivity is of vital importance when it is desirable to activate one strong covalent bond in the presence of others that are much weaker. With suitable reaction conditions in hand, we speculated that selective activation of tertiary aliphatic fluorides could be favored over other leaving groups such as halides or alkoxides. Thus, a library of tertiary aliphatic halides and alkyl ethers was prepared and tested. As anticipated, the $B(C_6F_5)_3$•H_2O catalyst showed complete selectivity for the activation of the fluoride over other leaving groups even after prolonged reaction time, emphasizing the importance of acid–fluorine interactions. (Table 5.2).

Table 5.2. *Leaving group selectivity.*



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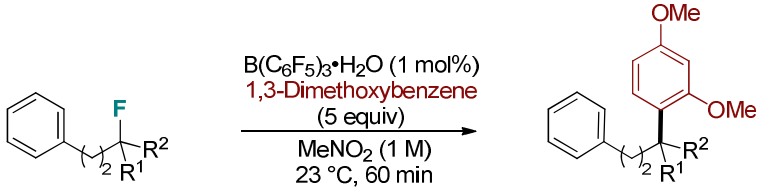
Entry	*Substrate, leaving group*	*NMR conversion, (%)*
1	**73**, F	>99
2	**82**, Br	0
3	**76**, Cl	0
4	**43i**, OH	0
5	**83**, OMe	0
6	**72**, OBn	0

5.2.5 **Effect of the substitution pattern of the substrate**

The relative reactivity of alkyl fluorides with different substitution patterns was next investigated. Though tertiary aliphatic fluorides tend to react preferentially compared to secondary or primary alkyl fluorides in halogen exchange reactions with Et_2AlCl (see the introduction section of this chapter), relative reactivity with respect to the substitution pattern, to the best of our knowledge, has never been addressed directly in the Friedel-Crafts reactions of alkyl fluorides. In fact, under Olah's Friedel-Crafts alkylation conditions, primary, secondary and tertiary aliphatic fluorides were all observed to react with arenes under identical conditions without discussion concerning relative reactivity. To attack this problem, a library of mono- and disubstituted alkyl fluorides was synthesized and tested under our standard reaction conditions (Table 5.3). Reflecting an order of stability of the corresponding carbocations, only tertiary aliphatic fluoride **73** reacted well, while primary and secondary fluorides, as well as difluorinated analogs, were unreactive under the catalytic conditions.

Table 5.3. *Substitution pattern selectivity.*



Entry	*Substrate*	*R¹*	*R²*	*NMR conversion, %*
1	**73**	**Me**	**Me**	>99
2	**82**	**Me**	**H**	0
3	**83**	**H**	**H**	0

Table 5.3 (continued)

Entry	*Substrate*	*R^1*	*R^2*	*NMR conversion, (%)*
4	**84**	**F**	**H**	0
5	**85**	**F**	**Me**	0

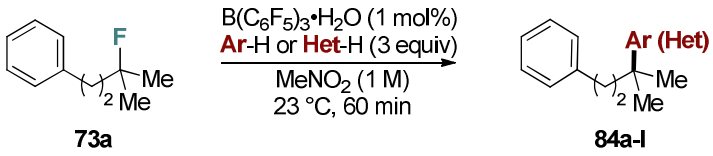
5.2.6 **Nucleophile scope**

With knowledge of leaving group selectivity in hand, and after confirming the favorable reactivity of tertiary aliphatic fluorides over secondary and primary organofluorides, the scope of suitable nucleophiles was next examined (Table 5.4). As a rule, common electron rich Friedel-Crafts nucleophiles proved to be well tolerated by the method, furnishing substitution products in good to high yields. Halogen bearing arenes, phenols and naphthols could be used as nucleophiles to furnish corresponding products **84a,b,e,f**. It was noticed that addition of HFIP as an additive or as a co-solvent was in some cases beneficial to the reaction outcome, as in the case of **84d** and **84h**. Likewise, the reaction was confirmed to tolerate heteroarenes such as indoles to deliver products **84i** and **84j**, though an elevated temperature was necessary to suppress the quenching effect of the Lewis basic nitrogen. Interestingly, in the case of **84j**, both *C*- (major) and *N*- (minor) alkylated products in ratio of 11 to 1 respectively could be separately isolated (combined yield is showcased in the table). Thiophene and furan could also be employed in this transformation, though a diminished yield of product **84l** was isolated in the latter case as a result of the fast competitive polymerization of the furan under the acidic reaction conditions. Remarkably, only minor (<5 %) levels of bisalkylation were observed in the described reactions.

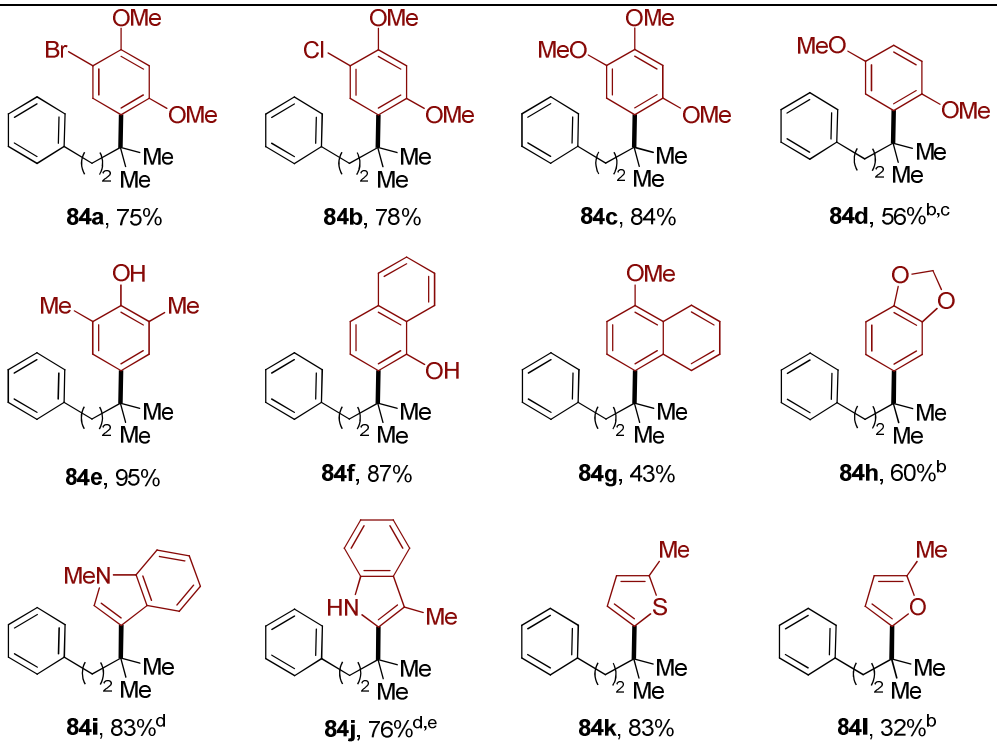
As summarized above, the Friedel-Crafts reaction with tertiary aliphatic fluorides provided best results when electron rich (hetero)arenes were employed as nucleophiles. In the case of electron poor analogs, no desired reaction or minor Friedel-Crafts product formation was observed alongside with the major product being that of elimination. These results highlight the fact that the actual "feasibility" of fluoride activation is not a problem here but efficient trapping of the carbocation is the limiting factor under standard reaction conditions. Carbocation lifetime could be prolonged to a certain extent by addition of stabilizing additives or co-solvents, such as HFIP, however in general fast nucleophilic addition is crucial to suppress the E1 process. Generally, these results are in agreement with the electrophilicity and nucleophilicity scales developed by Mayr and co-workers, though tertiary aliphatic carbocations were not specifically considered in their studies.[11] The list of representative unsuccessful nucleophiles tried in this study is shown in Figure 5.4.

1,3,5-Trimethoxybenzene, albeit being an electron rich arene, did not react with tertiary aliphatic coupling partner **73** almost certainly due to steric hindrance between the bulky electrophile and nucleophile and elimination was found to be the major reaction pathway. This observation highlights the importance of steric considerations in Friedel-Crafts reactions, as can clearly be deduced by comparison with the electron rich, but less sterically constrained nucleophile 1,2,4-trimethoxybenzene, which furnishes the corresponding product **84c** in 84% isolated yield (Table 5.4).

Table 5.4. *Nucleophile scope.*[a]



73a **84a-l**



84a, 75% **84b**, 78% **84c**, 84% **84d**, 56%[b,c]

84e, 95% **84f**, 87% **84g**, 43% **84h**, 60%[b]

84i, 83%[d] **84j**, 76%[d,e] **84k**, 83% **84l**, 32%[b]

[a]Isolated yield. [b]1/1 of $MeNO_2$/HFIP was used as a solvent. [c]5 equiv of nucleophile used. [d]Reaction was run at 90 °C. [e]11 to 1 ratio of *C*- to *N*- alkylated products

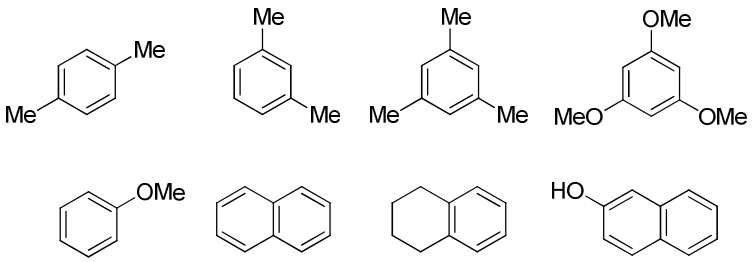
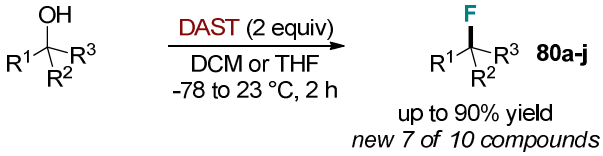


Figure 5.4. *Unsuccessful nucleophiles* .

5.2.7 **Substrate scope**

Next, efforts were undertaken to test the range of tertiary aliphatic fluorides compatible with the productive Friedel-Crafts reaction. The synthesis of new fluorinated starting materials was accomplished by deoxygenative fluorination of the corresponding alcohols (Scheme 5.12).



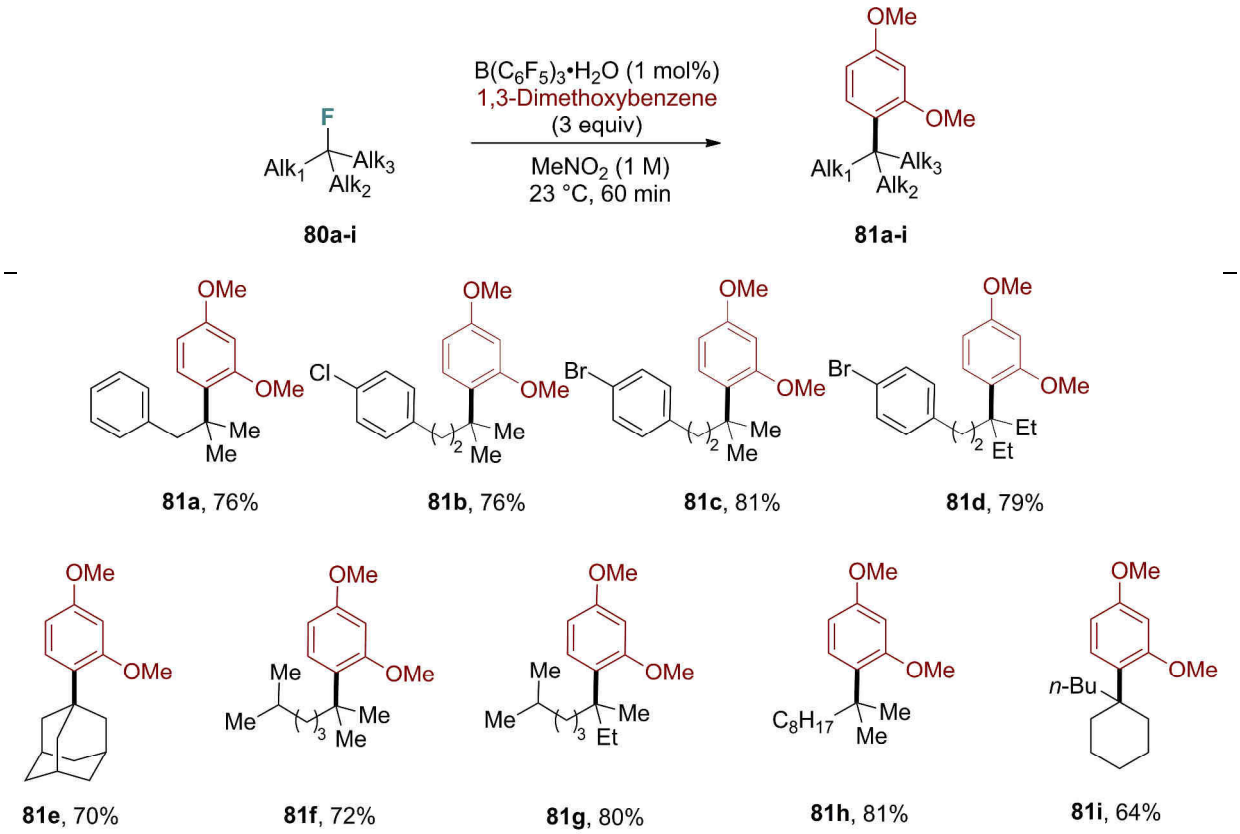
Scheme 5.12. *Synthesis of library of tertiary aliphatic fluorides*

With the library of fluorides in hand, we subjected them to standard catalytic conditions in reaction with 3 equiv of 1,3-dimethoxybenzene as a standard nucleophile. The results are summarized in Table 5.5. Alkyl fluoride **80a**, prone to elimination, furnished the desired product **81a** in 76% yield. Halogen bearing products **81b** and **81c** could also be obtained in good yields as well as more sterically demanding **81d**. Adamantyl fluoride reacted well to give product **81e**, just as substrates with elongated aliphatic chain were successfully coupled to furnish **81f-h**. Cyclohexyl-derived product **81i** could be obtained as well from the corresponding fluoride in this reaction.

5.2.8 **Kinetic investigation: role of HF**

The results presented above give an important insight into the feasibility of Friedel-Crafts reactions with alkyl fluorides. For the first time this reaction has been performed using as little as 1 mol% of catalyst in the absence of stoichiometric trapping agent, thus representing a significant step forward towards substoichiometric alkyl fluoride activation. However, the nature of the catalytic species and the kinetic profile of the reaction remain unexplored. The fast reaction kinetics observed at room temperature pose some difficulties for studying the earliest parts of the reaction by NMR; typically reactions were complete within 10 min at room temperature, though, in order to assure full conversion, the standard isolation was performed after 1 h. Thus, reoptimization of reaction conditions was necessary. Reaction at 4 °C in deuterated nitromethane provided the possibility to continuously monitor the reactivity by ^{1}H NMR within a reasonable time scale (Figure 5.5).

Table 5.5. *Alkyl fluoride scope.*[a]



[a]Isolated yield.

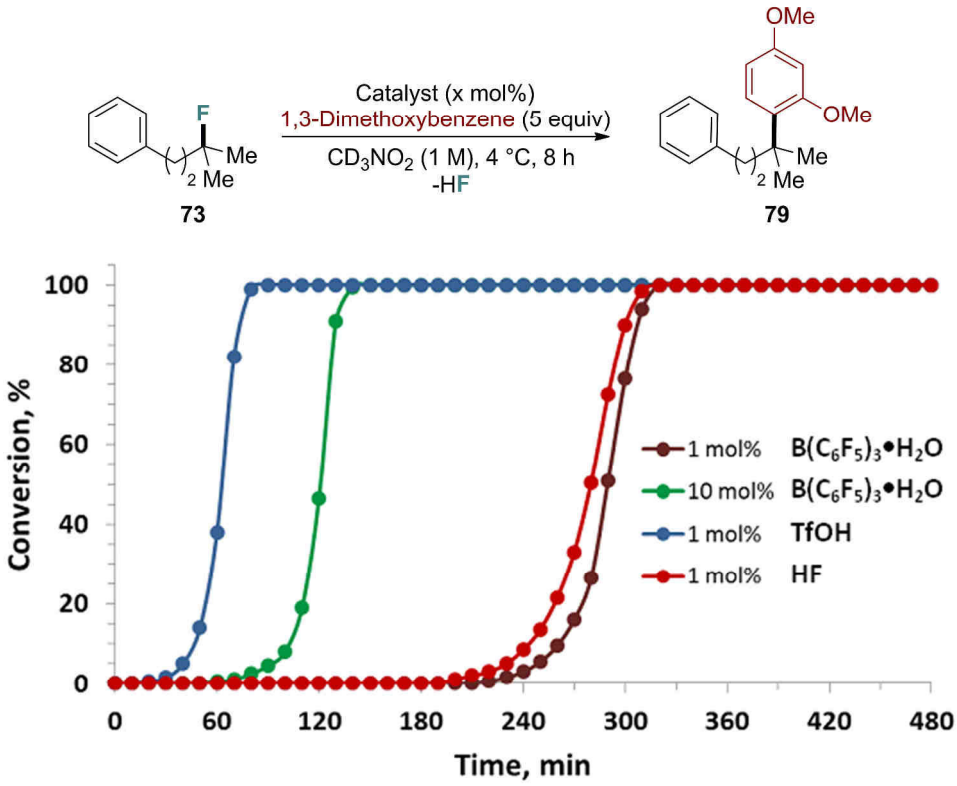
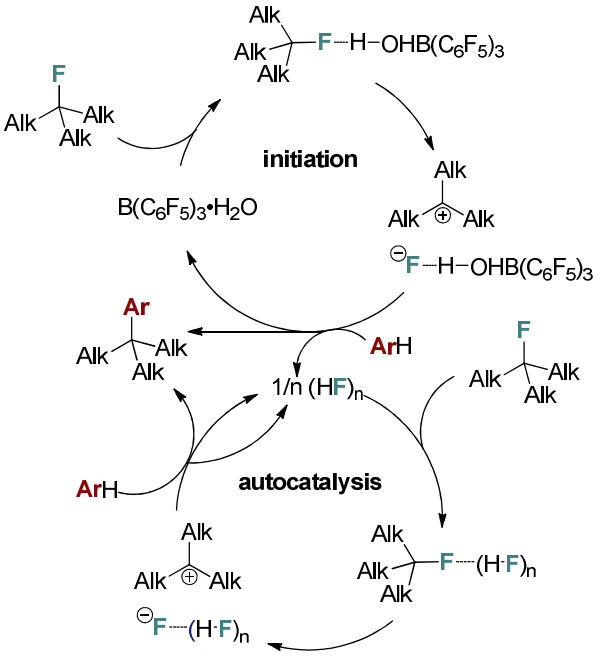


Figure 5.5. *Time-dependent NMR study at 4 °C revealing an autocatalytic kinetic profile.*

In all cases, the reactions display an induction period and a sigmoid kinetic profile characteristic of autocatalytic systems. Increasing the catalyst loading from 1 to 10 mol% decreased the induction period from about 220 to 60 minutes, but resulted in a comparable kinetic profile once the induction period had expired (Figure 5.5, green vs. maroon points). For comparison with $B(C_6F_5)_3 \bullet H_2O$ (pKa = 8.6 in MeCN),[89] initiating the reaction with 1 mol% TfOH (pKa = 0.7 in MeCN)[157] and HF (calculated pKa = 25.2 in MeCN)[158] resulted in induction periods of about 25 minutes and 200 minutes, respectively (Figure 5.5, blue and red points). Thus, despite the fact that the reaction is autocatalytic in HF, the initiating catalyst plays an essential role. Autocatalytic reaction kinetics were previously observed by Paquin and co-workers for Friedel-Crafts reactions of benzylic fluorides using HFIP solvent as a H-bond donor to initiate the reaction after several hours.[159] Though the comparable kinetic profiles of $B(C_6F_5)_3 \bullet H_2O$ and HF might initially be viewed as surprising since the former is a stronger acid by more than 14 orders of magnitude, HF is well known to undergo concentration-dependent homoassociation to form higher order aggregates that are much stronger Brønsted acids than the monomeric species.[160] A plausible set of catalytic cycles that accounts for all observations is shown in Scheme 5.13.



Scheme 5.13. *Proposed autocatalytic mechanism.*

[157] Raamat, E.; Kaupmees, K.; Ovsjannikov, G.; Trummal, A.; Kütt, A.; Saame, J.; Koppel, I.; Kaljurand, I.; Lipping, L.; Rodima, T.; Pihl, V.; Koppel, I. A.; Leito, I.; *J. Phys. Org. Chem.* **2013**, *26*, 162.
[158] Nicoleti, C. R.; Marini, V. G. ; Zimmermann, L. M.; Machado, V. G. *J. Braz. Chem. Soc.* **2012**, *23*, 1488.
[159] Champagne, P. A.; Benhassine, Y.; Desroches, J.; Paquin, J.-F. *Angew. Chemie Int. Ed.* **2014**, *53*, 13835.
[160] Lisy, J. M.; Tramer, A.; Vernon, M. F.; Lee, Y. T. *J. Chem. Phys.* **1981**, *75*, 4733.

5.2.9 **Kinetic investigation: $B(C_6F_5)_3$•H_2O turnover**

Taking into account the abovementioned discoveries and our previous experience in $B(C_6F_5)_3$•H_2O-catalyzed alcohol activation in nitromethane, we raised the question of whether $B(C_6F_5)_3$•H_2O turnover could be possible under reaction conditions where the autocatalytic function of HF is suppressed. In such a system, the fluoride anion formed upon heterolytic cleavage of the $C(sp^3)$–F bond must be immediately trapped before triggering an "undesirable" autocatalytic cycle. With this goal in mind, several potential silicon-based fluoride acceptors were examined based on their compatibility with the catalyst and with the alkyl fluoride. Among those assayed, including trimethylsilanol, hexamethyldisiloxane, *N*,*O*-bis(trimethylsilyl)trifluoroacetamide (BSTFA), diphenylsilane, triphenylsilane and triethylsilane, only triethoxysilane proved to be compatible with both organofluorine and substoichiometric catalyst. Under *de novo* reoptimized conditions, the consumption of tertiary aliphatic fluoride was monitored by ^{19}F NMR in the presence of overstoichiometric fluoride trap (Figure 5.6).

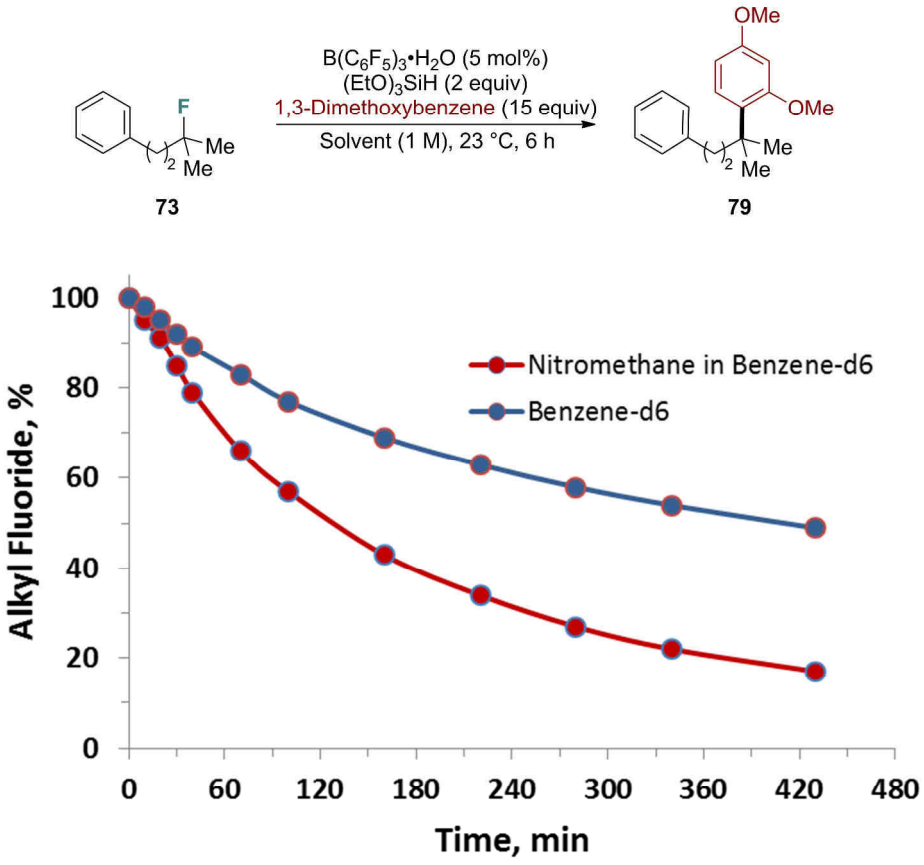


Figure 5.6. *Profiles of alkyl fluoride consumption in the presence of fluoride trap.*

While the consumption of alkyl fluoride **73** in d^6-benzene still reaches approximately 45% in 7 h, in the presence of nitromethane this rate is accelerated and only 15% of starting material remains by the end of experiment. More importantly, the autocatalytic profile has been suppressed in the presence of $(EtO)_3SiH$, therefore demonstrating the potential for $B(C_6F_5)_3 \bullet H_2O$ to operate with catalytic turnover. The last statement is supported by the fact that the full amount of the catalyst is clearly observed without change over the period of experimentation when the reaction is monitored by ^{19}F NMR.

5.3 **Conclusion to Chapter 5**

Chapter 5 summarized our exploration of the catalytic Friedel-Crafts reaction of tertiary aliphatic fluorides, a transformation previously limited to activation by stoichiometric amount of Lewis acids or with silicon-based trapping agents. A range of tertiary aliphatic fluorides was successfully coupled with a variety of electron rich arenes and heterocyclic compounds. The potential utility of this transformation is showcased by the fact that more than 90% of the Friedel-Crafts products synthesized herein are new compounds.

In this study, fluoride was a better leaving group compared to other halides or oxygen-based nucleofuges. In accordance with the scale of relative carbocation stability, tertiary aliphatic fluorides proved to be the sole reactive electrophile, while secondary or primary aliphatic fluorides, as well as difluorinated substrates, are not reactive in this Friedel-Crafts transformation. From a more fundamental perspective, the observed autocatalytic kinetics are likely due to the formation of a highly active in situ generated HF-derived Brønsted acid catalyst.

CHAPTER 6

Conclusions and Outlook

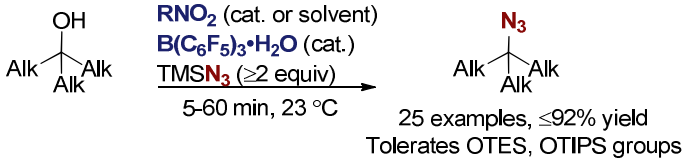
As widely available, easily prepared and highly tractable compounds, alcohols have long been recognized as ideal electrophilic partners for direct nucleophilic substitution reactions. Only in the early 21st century, in light of the growing demand for highly efficient catalytic transformations, has progress been made in the direct substitution of π-activated alcohols, though the scope of reactions performed by a given catalyst remains largely limited to certain combinations of alcohols and nucleophiles. Moreover, the field as a whole suffers from recurring limitations with respect to functional group compatibility that need to be addressed. In this context, efforts towards a more general approach to the catalytic dehydrative substitution of alcohols were made in this thesis.

To date, alcohol activation has been to a large extent regarded as the matter of finding a sufficiently strong catalyst which is able to ionize the C–O bond. However in this thesis, practice shows the importance of taking into account factors beyond the properties of the catalyst, electrophile or nucleophile, but also to consider catalyst interactions with the solvent which should not be regarded as an innocent chemical space.

An essence of this principle has been exemplified in chapter 4, where a co-catalytic effect of nitro compounds was described for the $B(C_6F_5)_3 \bullet H_2O$ catalyzed azidation of tertiary aliphatic alcohols, enabling catalyst turnover for the first time. Although distinct reactivity in nitromethane might be vaguely dismissed as an effect of the reaction medium, kinetic investigations reveal that the nitro component induces a switch from first order concentration dependence in Brønsted acid to second order concentration dependence in Brønsted acid and second order dependence in the nitro compound.

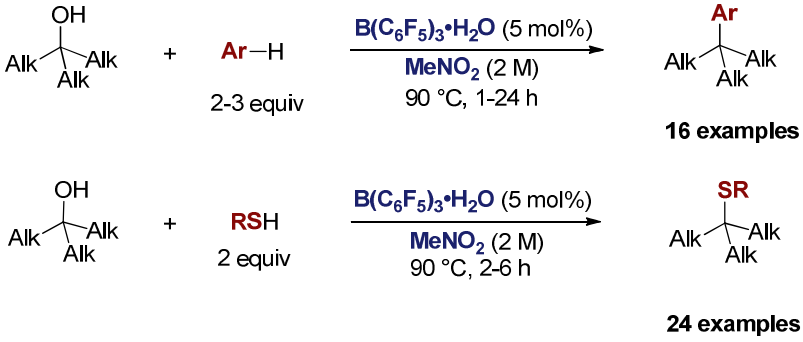
Kinetic, electronic, and spectroscopic evidence suggests that higher order hydrogen-bonded aggregates of nitro compounds and acids are the kinetically competent Brønsted acid catalysts. These results serve as a reminder that “simple” Brønsted acid catalysis can be surprisingly complex in solution, illustrating the need for detailed mechanistic investigations.

The disclosed nitro-assisted Brønsted acid catalysis resulted in mild and chemoselective azidation of tertiary aliphatic alcohols using nitromethane as solvent or using 50 mol % of nitro co-catalyst in benzene and provided access to valuable products. The utility of the method is emphasized by the fact that 18 of 25 synthesized azides are new compounds with elaborate functionalities, such as silyl ethers, alkenes, *N*-containing heterocycles, which would be otherwise difficult to access by alternative stoichiometric methods (Scheme 6.1).



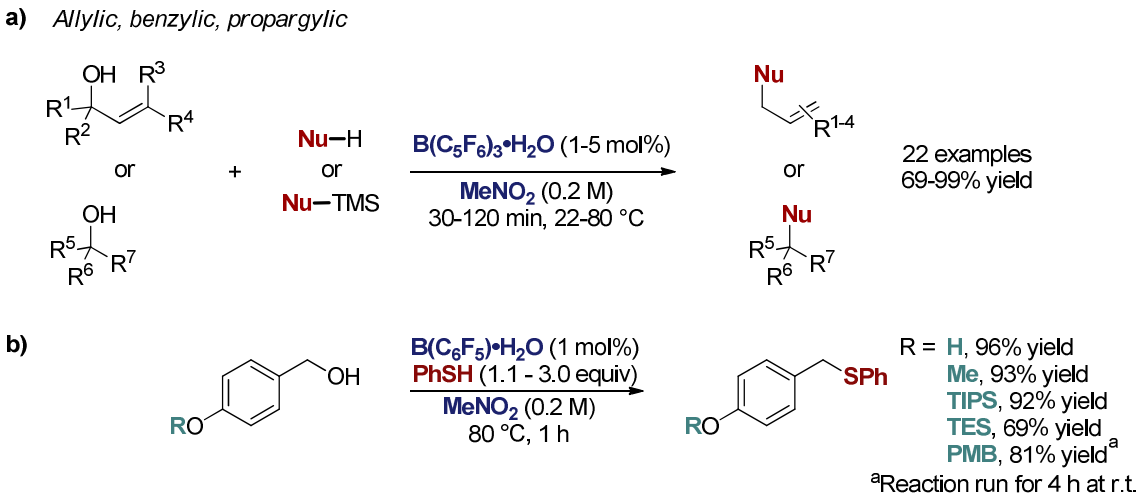
Scheme 6.1. *Nitro-assisted Brønsted acid catalyzed azidation of tertiary aliphatic alcohols.*

At higher temperatures, nitromethane was shown to enhance the substitution of unactivated hydroxyl groups under acid catalysis with nucleophiles beyond $TMSN_3$. Substoichiometric amounts of $B(C_6F_5)_3•H_2O$ in nitro solvent proved remarkably efficient and a wide variety of tertiary aliphatic alcohols was successfully activated in Friedel-Crafts alkylation and thiodehydration reactions with a range of electron-rich arenes and thiols, respectively (Scheme 6.2). Once again, in contrast to activation by commonly used stoichiometric Brønsted or Lewis acids, $B(C_6F_5)_3•H_2O$ catalysis in the presence of nitromethane allows desired reactivity alongside superior chemoselectivity as acid-sensitive functionalities are well tolerated under standard reaction conditions.



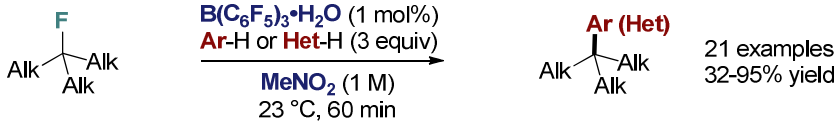
Scheme 6.2. *$B(C_6F_5)_3•H_2O$ in nitromethane allows catalytic substitution of tertiary aliphatic alcohols.*

A more systematic comparison of common Brønsted and Lewis acid catalysts performed in Chapter 2, a set of experiments that led to the aforementioned discovery, revealed the combination of $B(C_6F_5)_3•H_2O/MeNO_2$ as an optimal catalytic system for the dehydrative coupling of π-activated alcohols as well as cyclodehydration reaction of non-activated aliphatic substrates. The broad substrate scope of substitution with *C*-, *N*-, *S*-, and *O*-nucleophiles (Scheme 6.3, a) highlights the power of the catalysis developed herein. On the other hand, the high level of tolerance to silyl ether protecting groups (Scheme 6.3, b) and acid sensitive alkenes indicates the enhanced level of molecular recognition between the hydroxyl group and the catalyst system.



Scheme 6.3. *$B(C_6F_5)_3$•H_2O catalysis in nitromethane allows broad and chemoselective substitution of π-activated alcohols.*

Furthermore, the powerful catalysis by $B(C_6F_5)_3$•H_2O in $MeNO_2$ has been extended beyond alcohol activation to the cleavage of strong C–F bonds that allowed Friedel-Crafts reactions of tertiary aliphatic fluorides to be rendered catalytic for the first time. In that particular case, $B(C_6F_5)_3$•H_2O initiates a reaction with an autocatalytic kinetic profile, which is likely a result of the formation of a highly active *in situ*-generated HF-derived Brønsted acid catalyst. A range of tertiary aliphatic fluorides was successfully coupled with a variety of electron rich arenes and heterocyclic compounds (Scheme 6.4). The utility of the disclosed methodology is highlighted by the fact that, despite the nearly 140-year history of the Friedel-Crafts reaction, more than 90% of the apparently simple products in this study are new compounds.



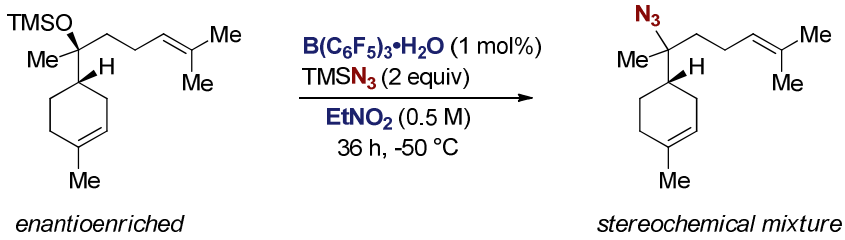
Scheme 6.4. *Friedel-Crafts arylation of tertiary aliphatic fluorides enabled by $B(C_6F_5)_3$•H_2O catalysis in nitromethane*

In summary, the unique catalytic profile of $B(C_6F_5)_3$•H_2O in nitromethane allowed us to address major challenges in substitution of unfunctionalized hydroxyl groups and provided valuable synthetic methodology for the selective activation of tertiary aliphatic fluorides. On

the other hand, this thesis emphasizes the complex nature of "simple" catalysis in solution and the necessity to consider catalytic species, not in isolation, but as part of a larger system that interacts with the chemical environment.

Looking forward, aggregation between weak H-bond acceptors and Brønsted acids may constitute a new modular and tunable approach to accelerating Brønsted acid catalysis in solution. The generation of supramolecular H-bond donating catalysts by interaction of strong Brønsted acids with solvents that produce H-bond network, such as HFIP, could be anticipated as an extension of our current studies.

In terms of asymmetric transformations, a kinetic resolution of racemic alcohols via an asymmetric alcohol substitution co-catalyzed by an enantioenriched chiral nitro component could be envisioned. In the context of stereoselective alcohol substitutions, Shenvi has recently reported an inversion of stereochemistry in tertiary aliphatic trifluoroacetates with TMSCN.[161] In principle, fine tuning of our catalyst system could allow for a similar transformation directly from the alcohol. Unfortunately, thus far we have only observed substitution leading to the racemization of the corresponding stereogenic center (Scheme 6.5). However, overcoming solubility issues of electrophiles at lower temperature as well as the employment of second generation of nitro co-catalysts is anticipated to provide exciting results in this area.



Scheme 6.5. *Attempts for stereoinversion of tertiary aliphatic alcohols.*

[161] Pronin, S. V; Reiher, C.; Shenvi, R. *Nature* **2013**, *501*, 195.

EXPERIMENTAL SECTION

EXPERIMENTAL SECTION – CHAPTER 2

General information. All reactions were performed in air-dried flasks under nitrogen atmosphere, unless otherwise noted. All dehydrative transformations were performed in 10 mL sealed tubes under an air atmosphere. Purification of reaction products was carried out by flash column chromatography using Merck silica gel (40-63 μm). Analytical thin layer chromatography (TLC) was performed on aluminum sheets pre-coated with silica gel 60 F254 (E. Merck), cut to size. Visualization was accomplished with UV light followed by dipping in a potassium permanganate and/or Seebach's staining solutions and heating.
^{1}H NMR spectra were recorded on a Bruker Avance400 (400 MHz) spectrometer at ambient temperature unless otherwise noted and are reported in ppm using solvent as the internal standard ($CDCl_3$ at 7.26 ppm, C_6D_6 at 7.15 ppm). Data are reported as: multiplicity (ap = apparent, br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration and coupling constant(s) in Hz. ^{13}C NMR spectra were recorded on a Bruker Avance400 (100 MHz) spectrometer. Chemical shifts are reported in ppm from tetramethylsilane, with the residual solvent resonance employed as the internal standard ($CDCl_3$ at 77.0 ppm, C_6D_6 at 128.0 ppm).

Materials. Unless otherwise noted, all commercial materials were purchased from *Sigma-Aldrich* and used without further purification. 1-vinyl-1-cyclohexanol **5**,[162] 4-(triisopropylsilyloxy)benzyl alcohol **16c**,[163] 4-(4'-methoxybenzyloxy)benzyl alcohol **16e**,[164] (*E*)-1-phenylhex-2-ene-1,6-diol **11a**,[165] (*E*)-6-phenylhex-5-ene-1,4-diol **11b**,[165] 1,1-diphenylprop-2-en-1-ol **18d**,[166] 1-phenylcyclohex-2-enol **18e**,[167] 6-phenylhex-5-yne-1,4-diol

[162] Albrecht, U; Langer, P. *Tetrahedron* **2007**, *63*, 4648.
[163] Lee, H. Y.; Jiang, X.; Lee, D. *Org. Lett.* **2009**, *11*, 2065.
[164] Taguchi, H.; Yosioka, I.; Yamasaki, K.; Kim, I. H. *Chem. Pharm. Bull.* **1981**, *29*, 55.
[165] Zheng, H.; Ghanbari, S.; Nakamura, S.; Hall, D. G. *Angew. Chem. Int. Ed.* **2012**, *51*, 6187.
[166] Zheng, H.; Lejkowski, M.; Hall, D. G. *Chem. Sci.* **2011**, *2*, 1305.
[167] Shibuya, M.; Tomizawa, M.; Iwabuchi,Y. *J. Org. Chem.* **2008**, *73*, 4750.

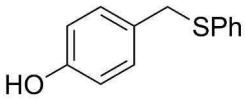
21,[165] 4-benzyl-5-phenylpentane-1,4-diol **23**,[165] *N*-tosyl butanolamine **25**[168] were prepared following a literature procedure. Tris(pentafluorophenyl)borane was purchased from *Strem Chemicals Inc.* and used under air, without any precaution to exclude moisture or air. $B(C_6F_5)_3$ is known to rapidly hydrate to $B(C_6F_5)_3{\bullet}H_2O$ under these conditions.[89]

General procedure A.
To a 10 mL reaction tube containing the alcohol (0.5 mmol) in nitromethane (2.5 mL) was added the nucleophile (1.1 to 3 equiv), followed by $B(C_6F_5)_3{\bullet}H_2O$ (1 to 5 mol%). The vial was capped and the mixture allowed to stir for 0.5 to 2 h at r.t., 80 or 100 °C. After cooling to room temperature, the reaction mixture was diluted with water and extracted twice with EtOAc. The organic layers were combined, washed with brine, dried over Na_2SO_4, filtered and volatiles were removed *in vacuo*. The residue was purified by flash chromatography on SiO_2.

General procedure B.
To a 10 mL reaction tube containing the alcohol (0.5 mmol) in nitromethane (2.5 mL) was added the nucleophile (1.1 to 3 equiv), followed by $B(C_6F_5)_3{\bullet}H_2O$ (1 to 5 mol%). The vial was capped and the mixture allowed to stir for 0.5 to 2 h at r.t., 80 or 100 °C. After cooling to room temperature, volatiles were removed *in vacuo*. The residue was purified by flash chromatography on SiO_2.

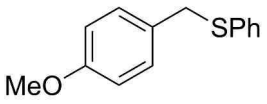
General procedure C.
To a 10 mL reaction tube containing the alcohol (0.5 mmol) in nitromethane (2.5 mL) was added $B(C_6F_5)_3{\bullet}H_2O$ (1 to 15 mol%). The vial was capped and the mixture allowed to stir for 1 to 18 h at r.t., 80 or 100 °C. After cooling to room temperature, volatiles were removed *in vacuo*. The residue was purified by flash chromatography on SiO_2.

Chemoselective Substitution

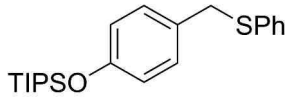


4-Hydroxybenzyl-phenyl sulfide (**17a**). Synthesized according to *general procedure A* after 2 h at 80 °C starting with the alcohol **16a** (62 mg, 0.5 mmol), thiophenol **19m** (103 µL, 110 mg, 1.00 mmol) and $B(C_6F_5)_3{\bullet}H_2O$ (2.6 mg, 5.0 µmol, 1.0 mol%). Isolated (105 mg, 96%) as a white solid after column chromatography (15% EtOAc in Petroleum ether). R_f = 0.24 (Petroleum ether/EtOAc 6:1).
^{1}H NMR (400 MHZ, $CDCl_3$): δ 7.35–7.14 (m, 7H), 6.77–6.73 (m, 2H), 4.77 (s, 1H), 4.07 (s, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 154.8, 136.5, 130.3, 130.0 129.8, 129.0, 126.5, 115.5, 38.6. **HRMS** (ESI) for $C_{13}H_{12}OS$: calcd. 216.0608; found 216.0604.

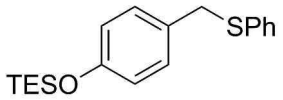
[168] Elliott, L. D.; Wrigglesworth, J. W.; Cox, B.; Lloyd-Jones, G. C.; Booker-Milburn, K. I. *Org. Lett.* **2011**, *13*, 728.



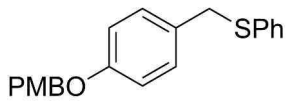
4-Methoxybenzyl-phenyl sulfide (**17b**).[169] Synthesized according to *general procedure A* after 2 h at 80 °C starting with the alcohol **16b** (62 µL, 69 mg, 0.5 mmol), thiophenol **19m** (56 µL, 61 mg, 0.55 mmol) and $B(C_6F_5)_3$•H_2O (2.6 mg, 5.0 µmol, 1.0 mol%). Isolated (116 mg, 93%) as a white solid after column chromatography (10% CH_2Cl_2 in Petroleum ether). R_f = 0.23 (Petroleum ether/CH_2Cl_2 9:1).
^{1}H NMR (400 MHZ, $CDCl_3$): δ 7.36–7.17 (m, 7H), 6.87–6.81 (m, 2H), 4.10 (s, 2H), 3.80 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 158.9, 136.7, 130.0, 129.9, 129.5, 128.9, 126.4, 114.0, 55.4, 38.6. The analytical data are in accordance with those reported in the literature.



4-Triisopropylsiloxybenzyl-phenyl sulfide (**17c**). Synthesized according to *general procedure A* after 2 h at 80 °C starting the alcohol **16c** (140 mg, 500 µmol), thiophenol **19m** (56 µL, 61 mg, 0.55 mmol) and $B(C_6F_5)_3$•H_2O (2.6 mg, 5.0 µmol, 1.0 mol%). Isolated (171 mg, 92%) as a colorless oil after column chromatography (Petroleum ether). R_f = 0.71 (Petroleum ether/CH_2Cl_2 8:2).
^{1}H NMR (400 MHZ, $CDCl_3$): δ 7.32–7.16 (m, 5H), 7.13 (d, *J* = 8.5 Hz, 2H), 6.80 (d, *J* = 8.5 Hz, 2H), 4.06 (s, 2H), 1.32–1.20 (m, 3H), 1.11 (d, *J* = 7.1 Hz, 18H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 155.3, 136.5, 130.3, 130.0, 129.9, 128.9, 126.5, 120.0, 38.9, 18.0, 12.8. **HRMS** (ESI) for $C_{22}H_{32}OSSi$: calcd. 372.1943; found 372.1960.



4-Triethylsiloxybenzyl-phenyl sulfide (**17d**). Synthesized according to *general procedure A* after 2h at 80 °C starting with the alcohol **16d** (119 mg, 500 µmol), thiophenol **19m** (154 µL, 165 mg, 1.50 mmol) and $B(C_6F_5)_3$•H_2O (2.6 mg, 5.0 µmol, 1.0 mol%). Isolated (113 mg, 69%) as a colorless oil after column chromatography (10% CH_2Cl_2 in Petroleum ether). R_f = 0.33 (Petroleum ether/CH_2Cl_2 8:2).
^{1}H NMR (400 MHZ, $CDCl_3$): δ 7.32–7.16 (m, 5H), 7.13 (d, *J* = 8.3 Hz, 2H), 6.76 (d, *J* = 8.3 Hz, 2H), 4.06 (s, 2H), 0.99 (t, *J* = 7.9 Hz, 9H), 0.73 (q, *J* = 7.9 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 154.9, 136.6, 130.2, 130.1, 130.1, 128.9, 126.4, 120.1, 38.8, 6.7, 5.1. **HRMS** (ESI) for $C_{19}H_{26}OSSi$: calcd. 330.1473; found 330.1466.

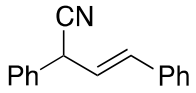


p-Methoxybenzyl-4-oxybenzyl-phenyl sulfide (**17e**). Synthesized according to *general procedure A* after 4 h at 22 °C starting with the alcohol **16e** (122 mg, 0.500 mmol), thiophenol **19m** (56 µL, 61 mg, 0.55 mmol) and $B(C_6F_5)_3$•H_2O (2.6 mg, 5.0 µmol, 1.0 mol%).

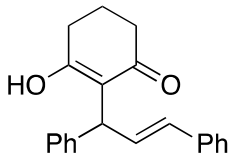
[169] Nishimoto, Y.; Okita, A.; Yasuda, M.; Baba, A. *Org. Lett.* **2012**, *14*, 1846.

Isolated (136 mg, 81%) as a colorless solid after column chromatography (25% CH_2Cl_2 in Petroleum ether). R_f = 0.21 (Petroleum ether/CH_2Cl_2 8:2).
^{1}H NMR (400 MHZ, $CDCl_3$): δ 7.39–7.16 (m, 9H), 6.93 (d, *J* = 8.8 Hz, 2H), 6.90 (d, *J* = 8.8 Hz, 2H), 4.97 (s, 2H), 4.09 (s, 2H), 3.82 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 159.6, 158.2, 136.7, 130.1, 129.9, 129.7, 129.3, 129.2, 128.9, 126.4, 115.0, 114.2, 70.0, 55.4, 38.6. **HRMS** (ESI) for $C_{21}H_{20}O_2S$: calcd. 336.1184; found 330.1183.

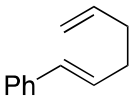
Substrate Scope for Substitution of π–Activated Alcohols



α-[(*E*)-2-Phenylethenyl]-benzeneacetonitrile **(20a)**.[170] Synthesized according to *general procedure A* after 0.5 h at 22 °C starting with the alcohol **18b** (105 mg, 500 μmol), trimethylsilyl cyanide **19a** (125 μL, 99.0 mg, 1.00 mmol) and $B(C_6F_5)_3$•H_2O (2.6 mg, 5.0 μmol, 1.0 mol%). Isolated (100 mg, 91%) as a white solid after column chromatography (0 to 5% EtOAc in Petroleum ether). R_f = 0.42 (Petroleum ether/EtOAc 9:1).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50-7.33 (m, 10H), 6.89 (dd, *J* = 15.8, 1.3 Hz, 1H), 6.26 (dd, *J* = 15.8, 6.3 Hz, 1H), 4.74 (dd, *J* = 6.3, 1.3 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 135.5, 134.7, 133.3, 129.4, 128.8, 128.5, 127.6, 126.8, 123.4, 118.9, 40.1. The analytical data are in accordance with those reported in the literature.



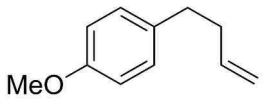
2-[(2*E*)-1,3-Diphenyl-2-propen-1-yl]-3-hydroxy-2-cyclohexen-1-one **(20b)**.[171] Synthesized according to *general procedure B* after 2 h at 22 °C starting with the alcohol **18b** (105 mg, 500 μmol), 1,3-cyclohexanedione **19b** (168 mg, 1.50 mmol) and $B(C_6F_5)_3$•H_2O (2.6 mg, 5.0 μmol, 1.0 mol%). Isolated (146 mg, 96%) as a white solid after column chromatography (20 to 50% EtOAc in Petroleum ether). R_f = 0.20 (Petroleum ether/EtOAc 1:1).
^{1}H NMR (400 MHz, $CDCl_3$) δ 10.13 (br, 1H), 7.51-7.24 (m, 10H), 7.00 (dd, *J* = 15.9 and 8.3 Hz, 1H), 6.57 (d, *J* = 15.9 Hz, 1H), 5.28 (d, *J* = 8.3 Hz, 1H), 2.53-2.39 (m, 4H), 2.01-1.90 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 143.3, 137.7, 131.2, 131.1, 128.6, 128.2, 127.7, 127.2, 126.4, 125.9, 117.8, 42.4, 33.2, 20.7. The analytical data are in accordance with those reported in the literature.



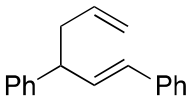
(*E*)-1-Phenyl-1,5-hexadien **(20c)**.[172] Synthesized according to *general procedure A* after 2 h at 80 °C starting with the alcohol **18a** (67 mg, 0.50 mmol), allyltrimethylsilane **19c** (238 μL,

[170] Chen, G.; Wang, Z.; Wu, J.; Ding, K. *Org. Lett.* **2008**, *10*, 4573.
[171] Sanz, R.; Martínez, A.; Miguel, D.; Álvarez-Gutiérrez, J. M.; Rodríguez, F. *Adv. Synth. Catal.* **2006**, *348*, 1841.
[172] Jiménez-Aquino, A.; Flegeau, E. F.; Schneider, U.; Kobayashi, S. *Chem. Comm.* **2011**, *47*, 9456.

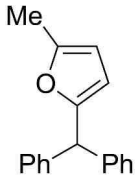
171 mg, 1.50 mmol) and $B(C_6F_5)_3$•H_2O (7.8 mg, 15 μmol, 3.0 mol%). Isolated (78 mg, 99%) as a colorless liquid without further purification. R_f = 0.35 (Petroleum ether).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.18 (m, 5H), 6.42 (d, *J* = 15.9 Hz, 1H), 6.29-6.20 (m, 1H), 5.94-5.82 (m, 1H), 5.12-4.99 (m, 2H), 2.37-2.21 (m, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 138.1 137.8, 130.2, 130.1, 128.5, 126.9, 126.0, 114.9, 33.5, 32.4. The analytical data are in accordance with those reported in the literature.



4-(4-Methoxyphenyl)-1-butene (**20d**).[173] Synthesized according to *general procedure A* after 2 h at 80 °C starting with the alcohol **16b** (62 μL, 69 mg, 0.50 mmol), allyltrimethylsilane **19c** (159 μL, 114 mg, 1.00 mmol) and $B(C_6F_5)_3$•H_2O (2.6 mg, 5.0 μmol, 1.0 mol%). Isolated (79 mg, 97%) as a colorless liquid after column chromatography (10% CH_2Cl_2 in Petroleum ether). R_f = 0.30 (Petroleum ether/CH_2Cl_2 9:1).
^{1}H NMR (400 MHZ, $CDCl_3$): δ 7.12 (d, *J* = 8.8 Hz, 2H), 6.84 (d, *J* = 8.8 Hz, 2H), 5.93–5.80 (m, 1H), 5.05 (dq, *J* = 17.5, 1.6 Hz, 1H), 4.98 (dq, *J* = 10.1, 1.6 Hz, 1H), 3.80 (s, 3H), 2.67 (t, *J* = 7.8 Hz, 2H), 2.39–2.32 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 157.9, 138.3, 134.1, 129.4, 115.0, 113.9, 55.4, 35.9, 34.6. The analytical data are in accordance with those reported in the literature.



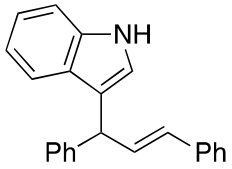
(*E*)-Hexa-1,5-diene-1,3-diyldibenzene **(20e)**.[174] Synthesized according to *general procedure A* after 1 h at 22 °C starting with the alcohol **18b** (105 mg, 0.5 mmol), allyltrimethylsilane **19c** (238 μL, 171 mg, 1.50 mmol) and $B(C_6F_5)_3$•H_2O (7.8 mg, 15 μmol, 3.0 mol%). Isolated (116 mg, 99%) as a colorless liquid without further purification. R_f = 0.33 (Petroleum ether).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49-7.27 (m, 10H), 6.56-6.45 (m, 2H), 5.96-5.84 (m, 1H), 5.23-5.10 (m, 2H), 3.69-3.61 (m, 1H), 2.78-2.65 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 144.0, 137.6, 136.6, 133.6, 129.9, 128.6, 128.6, 127.9, 127.2, 126.5, 126.3, 116.5, 49.1, 40.3. The analytical data are in accordance with those reported in the literature.



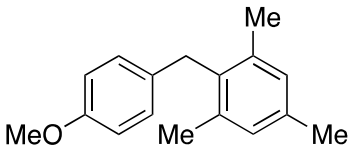
2-Benzhydryl-5-methylfuran (**20f**).[175] Synthesized according to *general procedure A* after 2 h at 80 °C starting with the alcohol **18h** (92 mg, 0.50 mmol), 2-methylfuran **19d** (90 μL, 82 mg, 1.0 mmol) and $B(C_6F_5)_3$•H_2O (2.6 mg, 5.0 μmol, 1.0 mol%). Isolated (123 mg, 99%) as a colorless oil after column chromatography (5% EtOAc in Petroleum ether). R_f = 0.38 (Petroleum ether/CH_2Cl_2 20:1).

[173] Onodera, G.; Yamamoto, E.; Tonegawa, S.; Iezumi, M.; Takeuchi, R. *Adv. Synth. Catal.* **2011**, *353*, 2013.
[174] Narayana Kumar, G. G. K. S.; Laali, K. K. *Org. Biomol. Chem.* **2012**, *10*, 7347.
[175] Li, H.; Li, W.; Liu, W.; He, Z.; Li, Z. *Angew. Chem. Int. Ed.* **2011**, *50*, 2975.

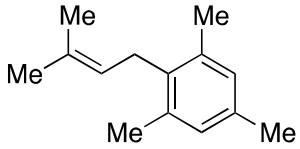
^{1}H NMR (400 MHZ, $CDCl_3$): δ 7.31–7.25 (m, 4H), 7.24–7.15 (m, 6H), 5.87 (d, *J* = 3.0 Hz, 1H), 5.74 (d, *J* = 3.0 Hz, 1H), 5.38 (s, 1H), 2.24 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 154.9, 151.6, 142.2, 128.9, 128.5, 126.7, 109.2, 106.1, 51.1, 13.7. The analytical data are in accordance with those reported in the literature.



3-[(2*E*)-1,3-Diphenyl-2-propen-1-yl]-(*1H*)-indole **(20g)**.[176] Synthesized according to *general procedure B* after 1 h at 22 °C starting with the alcohol **18b** (105 mg, 500 µmol), indole **19e** (58 mg, 0.55 mmol) and $B(C_6F_5)_3$•H_2O (5.2 mg, 10 µmol, 2.0 mol%). Isolated (149 mg, 96%) as a yellow oil after column chromatography (0 to 10% EtOAc in Petroleum ether). R_f = 0.26 (Petroleum ether/EtOAc 9:1).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (br, 1H), 7.66 (d, *J* = 7.8 Hz, 1H), 7.57-7.21 (m, 13H), 6.95 (d, *J* = 7.3 Hz, 1H), 6.93-6.88 (m, 1H), 6.65 (d, *J* = 15.8 Hz, 1H), 5.31 (d, *J* = 7.3 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 143.6, 137.7, 136.8, 132.8, 130.7, 128.7, 128.7, 128.6, 127.4, 127.0, 126.6, 126.5, 122.9, 122.3, 120.1, 119.6, 118.7, 111.4, 46.4. The analytical data are in accordance with those reported in the literature.



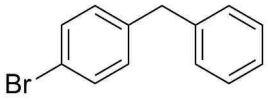
1-(4-Methoxybenzyl)-2,4,6-trimethylbenzene (**20h**).[177] Synthesized according to *general procedure A* after 2 h at 80 °C starting with the alcohol **16b** (62 µL, 69 mg, 0.50 mmol), mesitylene **19f** (139 µL, 120 mg, 1.00 mmol) and $B(C_6F_5)_3$•H_2O (2.6 mg, 5.0 µmol, 1.0 mol%). Isolated (119 mg, 99%) as a white solid after column chromatography (10 % CH_2Cl_2 in Petroleum ether). R_f = 0.42 (Petroleum ether/EtOAc 20:1).
^{1}H NMR (400 MHZ, $CDCl_3$): δ 7.01–6.93 (m, 4H), 6.86–6.81 (m, 2H), 4.01 (s, 2H), 3.80 (s, 3H), 2.35 (s, 3H), 2.26 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 157.8, 137.1, 135.7, 134.3, 132.2, 129.0, 128.9, 113.9, 55.3, 33.9, 21.0, 20.2. The analytical data are in accordance with those reported in the literature.



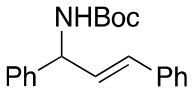
1-(3-Methylbut-2-en-1-yl)-2,4,6-trimethylbenzene **(20i)**. Synthesized according to *general procedure A* after 1 h at 80 °C starting with the alcohol **18g** (43 mg, 0.50 mmol), mesitylene **19f** (180 mg, 1.50 mmol) and $B(C_6F_5)_3$•H_2O (2.6 mg, 5.0 µmol, 1.0 mol%). Isolated (65 mg, 69%) as a colorless liquid after column chromatography (100% Petroleum ether). R_f = 0.57 (Petroleum ether).

[176] Yasuda, M.; Somyo, T.; Baba, A.; *Angew. Chem. Int. Ed.* **2006**, *45*, 7393.
[177] Hofmann, M.; Hampel, N.; Kanzian, T.; Mayr, H. *Angew. Chem. Int. Ed.* **2004**, *43*, 5402.

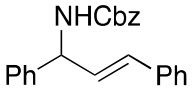
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.91 (s, 2H), 5.06 (t, *J* = 6.6 Hz, 1H), 3.36 (d, *J* = 6.6 Hz, 2H), 2.33 (s, 6H), 2.32 (s, 3H), 1.84 (s, 3H), 1.75 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 136.2, 135.5, 135.1, 131.4, 128.9, 122.4, 28.5, 25.7, 20.8, 20.0, 18.0; **HRMS** (ESI) for $C_{14}H_{20}$: calcd. 188.1565; found 188.1570.



4-Benzyl-bromobenzene (**20j**).[178] Synthesized according to *general procedure A* after 2 h at 100 °C starting with the alcohol **18o** (93.5 mg, 0.5 mmol), benzene **19g** (223 μL, 195 mg, 2.50 mmol) and $B(C_6F_5)_3$•H_2O (7.8 mg, 15 μmol, 3.0 mol%). Isolated (121 mg, 98%) as a white solid after column chromatography (Petroleum ether). R_f = 0.38 (Petroleum ether).
^{1}H NMR (400 MHZ, $CDCl_3$): δ 7.43–7.37 (m, 2H), 7.33–7.13 (m, 5H), 7.09–7.03 (m, 2H), 3.94 (s, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 140.6, 140.2, 131.7, 130.8, 129.0, 128.7, 126.5, 120.1, 41.4. The analytical data are in accordance with those reported in the literature.

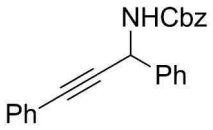


tert-Butyl *N*-[(2E)-1,3-diphenyl-2-propen-1-yl]-carbamate **(20k)**.[179] Synthesized according to *general procedure B* after 1 h at 22 °C starting with the alcohol **18b** (105 mg, 500 μmol), *tert*-butyl carbamate **19h** (117 mg, 1.00 mmol) and $B(C_6F_5)_3$•H_2O (5.2 mg, 10 μmol, 2.0 mol%). Isolated (146 mg, 94%) as a white solid after column chromatography (1 to 10% EtOAc in Petroleum ether). R_f = 0.39 (Petroleum ether/EtOAc 9:1).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43-7.24 (m, 10H), 6.58 (dd, *J* = 15.9 and 1.0 Hz, 1H), 6.36 (dd, *J* = 15.9, 6.0 Hz, 1H), 5.50 (br, 1H), 5.03 (br, 1H), 1.50 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 155.0, 141.4, 136.6, 131.0, 129.6, 128.7, 128.6, 127.7, 127.5, 127.0, 126.5, 79.8, 56.3, 28.4. The analytical data are in accordance with those reported in the literature.

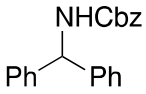


Benzyl *N*-[(2E)-1,3-diphenyl-2-propen-1-yl]-carbamate **(20l)**.[180] Synthesized according to *general procedure B* after 1 h at 22 °C starting with the alcohol **18b** (105 mg, 500 μmol), benzyl carbamate **19i** (151 mg, 1.00 mmol) and $B(C_6F_5)_3$•H_2O (5.2 mg, 10 μmol, 2.0 mol%). Isolated (169 mg, 99%) as a white solid after column chromatography (0 to 10% EtOAc in Petroleum ether). R_f = 0.22 (Petroleum ether/EtOAc 9:1).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49-7.27 (m, 15H), 6.63 (d, *J* = 15.8 Hz, 1H), 6.39 (dd, *J* = 15.8, 5.3 Hz, 1H), 5.72-5.52 (m, 2H), 5.26-5.15 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 157.8, 141.1, 136.5, 131.3, 129.3, 128.9, 128.7, 128.6, 128.2, 127.9, 127.8, 127.1, 126.7, 67.1, 56.9. The analytical data are in accordance with those reported in the literature.

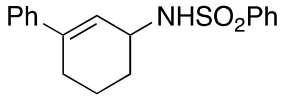
[178] Bedford, R. B.; Gower, N. J.; Haddow, M. F.; Harvey, J. N.; Nunn, J.; Okopie, R. A.; Sankey, R. F. *Angew. Chem. Int. Ed.* **2012**, *51*, 5435.
[179] Das, K; Shibuya, R.; Nakahara, Y.; Germain, N.; Ohshima, T.; Mashima, K. *Angew. Chem. Int. Ed.* **2012**, *51*, 150.
[180] Qin, H.; Y. N.; Matsunaga, S.; Shibasaki, M. *Angew. Chem. Int. Ed.* **2007**, *46*, 409.



N-(1,3-Diphenylpropynyl)-benzyl carbamate (**20m**).[181] Synthesized according to *general procedure A* after 2 h at 80 °C starting with the alcohol **18l** (104 mg, 500 μmol), benzyl carbamate **19i** (151 mg, 1.00 mmol) and 1 mol% of $B(C_6F_5)_3$•H_2O (2.6 mg, 5.0 μmol, 1.0 mol%). Isolated (167 mg, 98%) as a white solid after column chromatography (5% CH_2Cl_2 in Petroleum ether). R_f = 0.16 (Petroleum ether/CH_2Cl_2 20:1).
^{1}H NMR (400 MHZ, $CDCl_3$): δ 7.63 (d, *J* = 6.7 Hz, 2H), 7.55–7.47 (m, 2H), 7.46–7.31 (m, 11H), 6.03 (d, *J* = 8.3 Hz, 1H), 5.55 (d, *J* = 8.3 Hz, 1H), 5.28–5.13 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 155.5, 139.2, 136.3, 131.9, 128.8, 128.6, 128.6, 128.4, 128.3, 127.1, 122.5, 87.1, 85.2, 67.2, 47.5. The analytical data are in accordance with those reported in the literature.

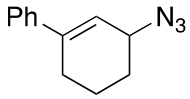


N-Benzhydryl-benzyl-carbamate (**20n**).[182] Synthesized according to *general procedure A* after 2 h at 80 °C starting with the alcohol **18h** (92 mg, 0.50 mmol), benzyl carbamate **19i** (151 mg, 1.00 mmol) and $B(C_6F_5)_3$•H_2O (7.8 mg, 15 μmol, 3.0 mol%). Isolated (139 mg, 88%) as a white solid after column chromatography (10% EtOAc in Petroleum ether). R_f = 0.32 (Petroleum ether/EtOAc 10:1).
^{1}H NMR (400 MHZ, $CDCl_3$): δ 7.41–7.23 (m, 15H), 6.03 (d, *J* = 7.0 Hz, 1H), 5.55 (s, 1H), 5.14 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.7, 141.7, 136.4, 128.8, 128.6, 128.3, 127.6, 127.3, 67.1, 59.0. The analytical data are in accordance with those reported in the literature.

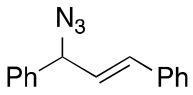


(3-Phenylcyclohex-2-en-1-yl)benzenesulfonamide **(20o)**. Synthesized according to *general procedure B* after 2 h at 22 °C starting with the alcohol **18e** (87 mg, 0.50 mmol), benzenesulfonamide **19j** (157 mg, 1.00 mmol) and $B(C_6F_5)_3$•H_2O (7.8 mg, 15 μmol, 3.0 mol%). Isolated (127 mg, 81%) as a white solid after column chromatography (10 to 20% EtOAc in Petroleum ether). R_f = 0.32 (Petroleum ether/EtOAc).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (m, 2H), 7.64-7.49 (m, 3H), 7.38-7.23 (m, 5H), 5.79-5.73 (m, 1H), 5.22 (d, *J* = 8.5 Hz, 1H), 4.06 (br, 1H), 2.47-2.27 (m, 2H), 1.89-1.53 (m, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 141.4, 141.0, 132.6, 129.2, 128.3, 127.6, 127.0, 125.3, 123.7, 50.0, 29.8, 27.0, 19.9; **HRMS** (ESI) for $C_{18}H_{19}NO_2S$: calcd. 313.1137; found 313.1157. R_f = 0.43 (Petroleum ether/EtOAc 4:1).

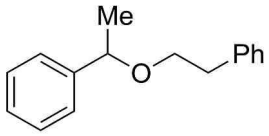
[181] Das, B. G.; Nallagonda, R.; Ghorai, P. *J. Org. Chem.* **2012**, *77*, 5577.
[182] Shirakawa, S.; Kobayashi, S. *Org Lett.* **2007**, *9*, 311.



5-Azido-3-phenylcyclohex-2-ene **(20p)**.[183] Synthesized according to *general procedure A* after 2 h at 22 °C starting with the alcohol **18e** (87 mg, 0.50 mmol), trimethylsilyl azide **19k** (115 mg, 1.00 mmol) and $B(C_6F_5)_3$•H_2O (13 mg, 25 μmol, 5.0 mol%). Isolated (89 mg, 90%) as a colorless liquid after column chromatography (0 to 3% EtOAc in Petroleum ether). R_f = 0.28 (Petroleum ether/EtOAc 49:1).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45-7.28 (m, 5H), 6.11-6.07 (m, 1H), 4.13-4.06 (m, 1H), 2.56-2.38 (m, 2H), 2.02-1.74 (m, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 142.6, 141.1, 128.4, 127.8, 125.5, 121.4, 56.9, 28.3, 27.4, 19.8. The analytical data are in accordance with those reported in the literature.

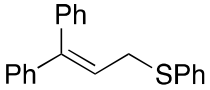


(*E*)-(3-Azidoprop-1-ene-1,3-diyl)dibenzene **(20q)**.[184] Synthesized according to *general procedure A* after 2 h at 22 °C starting with the alcohol **18b** (105 mg, 0.500 mmol), trimethylsilyl azide **19k** (115 mg, 1.00 mmol) and $B(C_6F_5)_3$•H_2O (13 mg, 25 μmol, 5.0 mol%). Isolated (112 mg, 95%) as a yellow liquid after column chromatography (0 to 3% EtOAc in Petroleum ether). R_f = 0.25 (Petroleum ether/EtOAc 49:1).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51-7.31 (m, 10H), 6.79 (d, *J* = 15.7 Hz, 1H), 6.37 (dd, *J* = 15.7, 7.2 Hz, 1H), 5.27 (d, *J* = 7.2 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 138.7, 136.0, 133.0, 128.9, 128.7, 128.4, 128.3, 127.2, 127.0, 126.9, 67.3. The analytical data are in accordance with those reported in the literature.

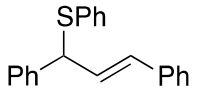


1-(2-Phenylethoxy)ethyl-benzene (**20r**).[185] Synthesized according to *general procedure A* after 2 h at 80 °C starting with the alcohol **18k** (61 mg, 0.50 mmol), 2-phenyl ethanol **19l** (122 mg, 1.00 mmol) and $B(C_6F_5)_3$•H_2O (5.2 mg, 10 μmol, 2.0 mol%). Isolated (109 mg, 96%) as a white solid after column chromatography (3% EtOAc in Petroleum ether). R_f = 0.34 (Petroleum ether/EtOAc 30:1).
^{1}H NMR (400 MHZ, $CDCl_3$): δ 7.45–7.21 (m, 10H), 4.47 (q, *J* = 6.4 Hz, 1H), 3.58 (t, *J* = 7.4 Hz, 2H), 3.03–2.88 (m, 2H), 1.50 (d, *J* = 1.5 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 144.1, 139.2, 129.1, 128.5, 128.4, 127.5, 126.2, 126.2, 78.2, 69.7, 36.7, 24.2. The analytical data are in accordance with those reported in the literature.

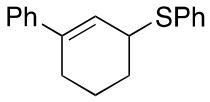
[183] Hassner, A.; Dehaen, W. *J. Org. Chem.* **1990**, *55*, 2243.
[184] Rueping, M.; Vila, C.; Uria, U. *Org Lett.* **2012**, *14*, 768.
[185] Rosenfeld, D. C.; Shekhar, S.; Takemiya, A.; Utsunomiya, M.; Hartwig, J. F. *Org. Lett.* **2006**, *8*, 4179.



3,3-Diphenylallyl-phenyl sulfide **(20s)**.[186] Synthesized according to *general procedure A* after 1 h at 80 °C starting with the alcohol **18d** (105 mg, 500 μmol), thiophenol **19m** (56 μL, 61 mg, 0.55 mmol) and $B(C_6F_5)_3•H_2O$ (2.6 mg, 5.0 μmol, 1.0 mol%). Isolated (149 mg, 99%) as a white solid after column chromatography (0 to 10% EtOAc in Petroleum ether). R_f = 0.29 (Petroleum ether/EtOAc 20:1).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50-7.19 (m, 15H), 6.30 (t, *J* = 7.8 Hz, 1H), 3.76 (d, *J* = 7.8 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 144.5, 142.0, 139.0, 135.9, 130.4, 130.0, 128.9, 128.4, 128.3, 127.6, 127.5, 126.4, 124.3, 34.0. The analytical data are in accordance with those reported in the literature.

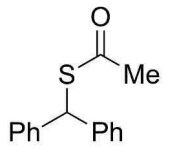


1-[(2*E*)-1,3-Diphenyl-2-propen-1-yl]phenyl sulfide **(20t)**.[187] Synthesized according to *general procedure A* after 0.5 h at 22 °C starting with the alcohol **18b** (105 mg, 0.500 μmol), thiophenol **19m** (56 μL, 61 mg, 0.55 mmol) and $B(C_6F_5)_3•H_2O$ (2.6 mg, 5.0 μmol, 1.0 mol%). Isolated (150 mg, 99%) as a yellow liquid after column chromatography (0 to 5% EtOAc in Petroleum ether). R_f = 0.31 (Petroleum ether/EtOAc 30:1).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62-7.30 (m, 15H), 6.65 (dd, *J* = 15.7, 8.3 Hz, 1H), 6.47 (d, *J* = 15.7 Hz, 1H), 5.11 (d, *J* = 8.3 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 140.4, 136.8, 135.0, 133.2, 131.7, 129.3, 128.9, 128.8, 128.6, 128.1, 127.8, 127.7, 127.6, 126.6, 56.8. The analytical data are in accordance with those reported in the literature.



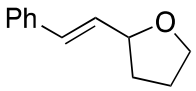
(3-Phenylcyclohex-2-en-1-yl)phenyl sulfide (**20u**). Synthesized according to *general procedure A* after 0.5 h at 22 °C starting with the alcohol **18e** (87 mg, 0.50 mmol), thiophenol **19m** (56 μL, 61 mg, 0.55 mmol) and $B(C_6F_5)_3•H_2O$ (2.6 mg, 5.0 μmol, 1.0 mol%). Isolated (120 mg, 90%) as a white solid after column chromatography (0 to 2% EtOAc in Petroleum ether). R_f = 0.35 (Petroleum ether/EtOAc 49:1).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57-7.51 (m, 2H), 7.49-7.43 (m, 2H), 7.41-7.27 (m, 6H), 6.28-6.23 (m, 1H), 4.16-4.10 (m, 1H), 2.54-2.47 (m, 2H), 2.18-1.80 (m, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 141.7, 139.9, 135.9, 131.6, 129.0, 128.4, 127.4, 126.8, 125.4, 124.0, 45.1, 28.6, 27.5, 20.0; **HRMS** (ESI) for $C_{18}H_{18}S$: calcd. 266.1129; found 266.1123.

[186] Ravikumar, P. C.; Yao, L.; Fleming, F. F. *J. Org. Chem.* **2009**, *74*, 7294.
[187] Zaitsev, A. B.; Caldwell, H. F.; Pregosin, P. S.; Veiros, L. F. *Chem. Eur. J.* **2009**, *15*, 6468.

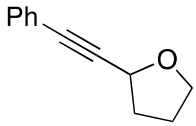


S-Benzhydryl-ethanethioate (**20v**).[188] Synthesized according to *general procedure A* after 3 h at 22 °C starting with the alcohol **18h** (92 mg, 0.50 mmol), thioacetic acid **19n** (107 µL, 114 mg, 1.50 mmol) and $B(C_6F_5)_3 \bullet H_2O$ (2.6 mg, 5.0 µmol, 1.0 mol%). Isolated (103 mg, 85%) as a white solid after column chromatography (10% CH_2Cl_2 to 20% CH_2Cl_2 in Petroleum ether). R_f = 0.28 (Petroleum ether/CH_2Cl_2 8:2).
^{1}H NMR (400 MHZ, $CDCl_3$): δ 7.38–7.21 (m, 10H), 5.97 (s, 1H), 2.35 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 193.9, 141.1, 128.7, 128.5, 127.4, 52.0, 30.4. The analytical data are in accordance with those reported in the literature.

Scope of dehydrative cyclizations



(*E*)-2-Styryltetrahydrofuran **(12)**.[165] Synthesized according to *general procedure C* after 1 or 2 h at 22 °C starting with alcohol **11a** or **11b** (39 mg, 0.20 mmol) and $B(C_6F_5)_3 \bullet H_2O$ (1.0 mg, 2.0 µmol, 1.0 mol%). Isolated (32 and 29 mg, 91 and 82 %, respectively) as a colorless liquid after column chromatography (0 to 5% EtOAc in Petroleum ether). R_f = 0.35 (Petroleum ether/EtOAc 20:1).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46-7.24 (m, 5H), 6.64 (d, *J* = 15.9 Hz, 1H), 6.25 (dd, *J* = 15.9 and 6.6 Hz, 1H), 4.56-4.48 (m, 1H), 4.05-3.98 (m, 1H), 3.93-3.85 (m, 1H), 2.22-1.92 (m, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 136.9, 130.6, 130.4, 128.5, 127.5, 126.5, 79.7, 68.2, 32.4, 25.9. The analytical data are in accordance with those reported in the literature.



2-(Phenylethynyl)tetrahydrofuran **(22)**.[189] Synthesized according to *general procedure C* after 18 h at 80 °C starting with the alcohol **21** (95 mg, 0.50 mmol) and $B(C_6F_5)_3 \bullet H_2O$ (2.6 mg, 5.0 µmol, 1.0 mol%). Isolated (75 mg, 87%) as a colorless liquid after column chromatography (0 to 5% EtOAc in Petroleum ether). R_f = 0.31 (Petroleum ether/EtOAc 20:1).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50-7.42 (m, 2H), 7.35-7.28 (m, 3H), 4.87-4.79 (m, 1H), 4.08-3.98 (m, 1H), 3.92-3.82 (m, 1H), 2.30-1.88 (m, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 131.7, 128.2, 128.8, 122.8, 89.1, 84.5, 68.6, 67.9, 33.4, 25.5. The analytical data are in accordance with those reported in the literature.

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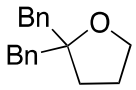
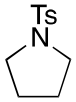
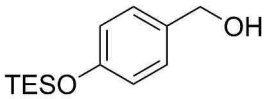
[188] Liu, C.; Li, M.-B.; Yang, C.-F.; Tian, S.-K. *Chem. Eur. J.* **2009**, *15*, 793.
[189] Daniels, D. S. B.; Thompson, A. L.; Anderson, E. A. *Angew. Chem. Int. Ed.* **2011**, *50*, 11506.



2,2-Dibenzyltetrahydrofuran **(24)**.[165] Synthesized according to *general procedure C* after 4 h at 100 °C starting with the alcohol **23** (27 mg, 0.1 mmol) and $B(C_6F_5)_3$•H_2O (1.0 mg, 2.0 μmol, 2.0 mol%). Isolated (20 mg, 79%) as a colorless liquid after column chromatography (0 to 4% EtOAc in Petroleum ether). R_f = 0.42 (Petroleum ether/EtOAc 20:1).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.21 (m, 10H), 3.64 (t, *J* = 6.7 Hz, 2H), 2.93 (d, *J* = 13.5 Hz, 2H), 2.80 (d, *J* = 13.5 Hz, 2H), 1.78 (t, *J* = 7.2 Hz, 2H), 1.43-1.35 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 138.3, 130.7, 127.9, 126.1, 85.3, 68.3, 46.2, 32.9, 26.2. The analytical data are in accordance with those reported in the literature.



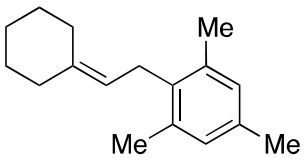
N-Tosyl pyrrolidine **(26)**.[190] Synthesized according *to general procedure C* after 4 h at 100 °C starting with the alcohol **25** (49 mg, 0.2 mmol) and $B(C_6F_5)_3$•H_2O (5.2 mg, 10 μmol, 5.0 mol%). Isolated (45 mg, 99%) as a white solid after column chromatography (10 to 20% EtOAc in Petroleum ether). R_f = 0.25 (Petroleum ether/EtOAc 10:1).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.1 Hz, 2H), 7.30 (d, *J* = 8.1 Hz, 2H), 3.26-3.14 (m, 4H), 2.41 (s, 3H), 1.78-1.68 (m, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 143.3, 134.0, 129.6, 127.5, 47.9, 25.2, 21.5. The analytical data are in accordance with those reported in the literature.



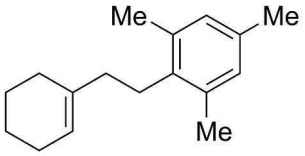
4-(Triethylsilyloxyphenyl)methanol (**16b**)**.** To a stirred solution of 4-hydroxybenzaldehyde (1.00 g, 7.34 mmol) in anhydrous DCM (50 mL) was added imidazole (1.00 g, 14.7 mmol). Then the reaction was cooled down to 0 °C and TES-Cl (1.48 mL, 1.33 g, 8.81 mmol) was added in several portions. After complete addition, the reaction mixture was allowed to warm up to room temperature and stirred for 20 h. The crude reaction was filtered through Celite, rinsed with DCM and the solvent was removed *in vacuo* obtaining a white solid. The residue was dissolved in anhydrous DCM (10 mL) and cooled to -78 °C. A solution of diisobutylaluminum hydride (14.7 mL, 1.0 M in DCM, 14.7 mmol) was added dropwise. The reaction mixture was stirred for 90 min at -78 °C, and was quenched with MeOH (1 mL), warmed up to room temperature and a 1M aqueous solution of potassium tartrate was added. The aqueous layer was extracted with DCM (3 x 50 mL). The organic layer was washed with water and brine, then dried over Na_2SO_4, filtered and the solvent was removed *in vacuo*. The residue was purified by column chromatography on silica gel (10% EtOAc in petroleum ether) affording a colorless oil (1.25 g, 72%). R_f = 0.33 (10% EtOAc in petroleum ether).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (d, *J* = 7.8 Hz, 2H), 6.81 (d, *J* = 7.8 Hz, 2H), 4.58 (s, 2H), 0.98 (t, *J* = 7.7 Hz, 9H), 0.72 (q, *J* = 15.4 Hz, 7.7 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 155.1, 133.8, 128.5, 119.9, 64.8, 6.59, 5.09; **HRMS** (ESI) for $C_{13}H_{22}OSi$: calcd. 238.1389; found 238.1398.

[190] Nishikata, T.; Nagashima, H. *Angew. Chem. Int. Ed.* **2012**, *51*, 5363.

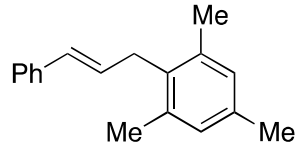
Selected procedures for catalyst screen; products 6a, 6b and 15



1-(2-Cyclohexylidenethyl)-2,4,6-trimethylbenzene **(6a)**. Synthesized according to *general procedure A* after 1 h at 80 °C starting with the alcohol **5** (63 mg, 0.50 mmol), mesitylene (180 mg, 1.5 mmol) and $B(C_6F_5)_3$•H_2O (2.6 mg, 5.0 μmol, 1.00 mol%). Isolated (105 mg, 92%) as a colorless liquid after column chromatography (100% Petroleum ether). R_f = 0.64 (Petroleum ether).
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.92 (s, 2H), 5.03 (t, *J* = 6.8 Hz, 1H), 3.39 (d, *J* = 6.8 Hz, 2H), 2.41-2.37 (m, 2H), 2.36 (s, 6H), 2.33 (s, 3H), 2.16-2.10 (m, 2H), 1.70-1.34 (m, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 139.2, 136.2, 135.5, 135.1, 128.9, 118.9, 37.2, 29.0, 28.6, 27.8, 27.6, 27.0, 20.9, 20.0; **HRMS** (ESI) for $C_{17}H_{24}$: calcd. 228.1878; found 228.1888.



2-(2-(Cyclohex-1-en-1-yl)ethyl)-1,3,5-trimethylbenzene (**6b**). 1-(2-Cyclohexylidenethyl)-2,4,6-trimethylbenzene **6a**. Synthesized according to *general procedure A* after 1 h at 80 °C starting with the alcohol **5** (63 mg, 0.50 mmol), mesitylene (180 mg, 1.5 mmol) and $Bi(OTf)_3$ (3.3 mg, 5.0 μmol, 1.00 mol%). Isolated (95 mg, 83%) as a colorless liquid after column chromatography; product contains approximately 7% of 6a (100% Petroleum ether). R_f = 0.62 (Petroleum ether).
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.97 (s, 2H), 5.65 (s, 1H), 2.87-278 (m, 2H), 2.44 (s, 6H), 2.39 (s, 3H), 2.22-2.13 (m, 6H), 1.85-1.70 (m, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 138.0. 136.2, 135.9, 134.9, 128.9, 120.9, 37.5, 28.4, 28.4, 25.3, 23.1, 22.6, 20.1, 19.7. HRMS (ESI) for $C_{17}H_{24}$: calcd. 228.1878; found 228.1888.



1-Cinnamyl-2,4,6-trimethylbenzene **(15)**.[191] Synthesized according to *general procedure A* after 1 h at 80 °C starting with the alcohol 14 (67 mg, 0.5 mmol), mesitylene (180 mg, 1.5 mmol) and $B(C_6F_5)_3$•H_2O (2.6 mg, 5.0 μmol, 1.0 mol%). Isolated (102 mg, 86% respectively) as a colorless liquid after column chromatography (100% Petroleum ether). R_f = 0.24 (Petroleum ether).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.14 (m, 5H), 6.88 (s, 2H), 6.31-6.21 (m, 2H), 2.78 (d, *J* = 4.0 Hz, 1H), 2.31 (s, 6H), 2.28 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 137.8, 136.7, 135.6,

[191] Tang, X.-L.; Wu, Z.; Li, M.-B.; Gu, Y.; Tian, S.-K. *Eur. J. Org. Chem.* **2012**, *22*, 4107.

133.2, 130.0, 129.0, 128.5, 127.8, 127.0, 126.1, 32.7, 21.0, 20.0. The analytical data are in accordance with those reported in the literature.

EXPERIMENTAL SECTION – CHAPTER 3

General Information. All reactions were performed in air-dried flasks under an nitrogen atmosphere, unless otherwise noted. All dehydrative transformations were performed in 10 mL sealed tubes under an air atmosphere. Purification of reaction products was carried out by flash column chromatography using Merck silica gel (40-63 μm). Analytical thin layer chromatography (TLC) was performed on aluminum sheets pre-coated with silica gel 60 F254 (E. Merck), cut to size. Visualization was accomplished with UV light followed by dipping in a potassium permanganate, p-anisaldehyde and/or Seebach's staining solutions and heating.

^{1}H NMR spectra were recorded on a Bruker Avance400 (400 MHz) spectrometer at ambient temperature unless otherwise noted and are reported in ppm using solvent as the internal standard ($CDCl_3$ at 7.26 ppm). Data are reported as: multiplicity (ap = apparent, br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration and coupling constant(s) in Hz. ^{13}C NMR spectra were recorded on a Bruker Avance400 (100 MHz) spectrometer. Chemical shifts are reported in ppm from tetramethylsilane, with the residual solvent resonance employed as the internal standard ($CDCl_3$ at 77.2 ppm).

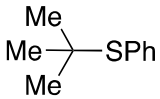
Materials. Unless otherwise noted, all commercial materials were purchased from *Sigma-Aldrich* and used without further purification. The alcohols **43c**[192], **43d**[193], **43e**[194], **43j**[195], **43k**[196], **43l**[197] and **42m**[198] were prepared following a literature procedure. Tris(pentafluorophenyl)borane was purchased from *Strem Chemicals Inc.* and used under air, without any precaution to exclude moisture or air.

Procedures for the Thiodehydration Reaction

General procedure A.
To a 10 mL reaction tube containing the alcohol (0.5 mmol) in nitromethane (250 µL) was added the nucleophile (2 equiv), followed by $B(C_6F_5)_3 \bullet H_2O$ (5 mol%). The vial was capped and the mixture allowed to stir for 30 minutes to 2 h at 90 °C. After cooling to room temperature, the volatiles of the reaction mixture were removed in vacuo. The residue was purified by flash chromatography on SiO_2.

General procedure B.
To a 10 mL reaction tube containing the alcohol (0.5 mmol) in nitromethane (250 µL) was added the nucleophile (2 equiv), followed by $B(C_6F_5)_3 \bullet H_2O$ (5 mol%). The vial was capped and the mixture allowed to stir for 30 minutes to 2 h at 90 °C. After cooling to room temperature, the reaction mixture was diluted with NaOH (50%) and extracted twice with EtOAc. The organic layers were combined, washed with brine, dried over Na_2SO_4, filtered and volatiles were removed in vacuo. The residue was purified by flash chromatography on SiO_2.

Alcohol Scope of Catalytic Thiodehydration with Thiophenol



(tert-Butyl)-phenyl sulfide **44**.[199] Synthesized according to *general procedure A* after 2 h at 90 °C starting with *tert*-butanol (37 mg, 48 µL, 0.50 mmol), thiophenol (103 µL, 110 mg, 1.00 mmol) and $B(C_6F_5)_3 \bullet H_2O$ (13.3 mg, 25.0 µmol, 5.00 mol%). Isolated (74 mg, 89%) as a colorless oil after column chromatography (Petroleum ether). R_f = 0.58 (Petroleum ether).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56-7.52 (m, 2H), 7.38-7.30 (m, 3H), 1.29 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 137.6, 132.8, 128.8, 128.6, 45.9, 31.1. The analytical data are in accordance with those reported in the literature.

[192] Aycock, D.F. *Org. Process. Res. Dev.*, **2007**, *11*, 156.
[193] Jung, M. E.; Abrecht, S. *J. Org. Chem.*, **1988**, *53*, 423.
[194] Lipshutz, B. H.; Kozlowski, J. A.; Breneman, C. M. *J. Am. Chem. Soc.* **1985**, *107*, 3197.
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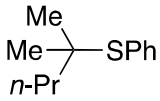
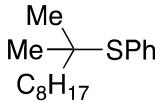
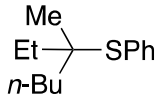
[196] Saito, T.; Nishimoto, Y.; Yasuda, M.; Baba, A. *J. Org. Chem.* **2007**, 77, 8588.
[197] Reeder, M. D.; Srikanth, G. S. C.; Jones, S. B.; Castle, S. L. O*rg. Lett.*, **2005**, *7*, 1089.
[198] Suzuki, N.; Rousset, C. J.; Aoyagi, K.; Kotora, M.; Takahashi, T.; Hasegawa, M.; Nitto, Y.; Saburi, M. *J. Organomet. Chem.* **1994**, *473*, 117.
[199] Ranu, B.C.; Mandal, T. *J. Org. Chem.* **2004**, *69*, 5793.



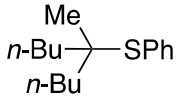
(2-Methylpentan-2-yl)-phenyl sulfide **45a**. Synthesized according to *general procedure A* after 2 h at 90 °C starting with the alcohol **43a** (51 mg, 0.50 mmol), thiophenol (103 µL, 110 mg, 1.00 mmol) and $B(C_6F_5)_3 \bullet H_2O$ (13.3 mg, 25.0 µmol, 5.0 mol%). Isolated (77 mg, 79%) as a colorless oil after column chromatography (Petroleum ether). R_f = 0.44 (Petroleum ether).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55-7.47 (m, 2H), 7.38-7.27 (m, 3H), 1.54-1.41 (m, 4H), 1.23 (s, 6H), 0.92 (t, *J* = 7.0, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 137.7, 132.6, 128.7, 128.5, 49.6, 44.9, 28.9, 18.2, 14.6. **HRMS** (ESI) for $C_{12}H_{18}S$: calcd. 194.1129; found 194.1131.



(2-Methyldecan-2-yl)-phenyl sulfide **45b**. Synthesized according to *general procedure A* after 2 h at 90 °C starting with the alcohol **43c** (86 mg, 0.50 mmol), thiophenol (103 µL, 110 mg, 1.00 mmol) and $B(C_6F_5)_3 \bullet H_2O$ (13.3 mg, 25.0 µmol, 5.00 mol%). Isolated (132 mg, 99%) as a colorless oil after column chromatography (Petroleum ether). R_f = 0.38 (Petroleum ether).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55-7.49 (m, 2H), 7.39-7.27 (m, 3H), 1.51-1.42 (m, 4H), 1.35-1.25 (m, 10H), 1.23 (s, 6H), 0.91 (t, *J* = 7.1, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 137.7, 132.6, 128.6, 128.5, 49.5, 42.6, 32.0, 30.2, 29.8, 29.5, 28.9, 24.9, 22.8, 14.3. **HRMS** (ESI) for $C_{17}H_{28}S$: calcd. 264.1912; found 264.1908.



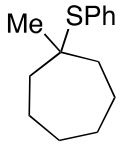
(3-Methylheptan-3-yl)-phenyl sulfide **45c**.[200] Synthesized according to *general procedure A* after 2 h at 90 °C starting with the alcohol **43c** (65 mg, 0.50 mmol), thiophenol (103 µL, 110 mg, 1.0 mmol) and $B(C_6F_5)_3 \bullet H_2O$ (13.3 mg, 25.0 µmol, 5.0 mol%). Isolated (102 mg, 92%) as a colorless oil after column chromatography (0 to 2% EtOAc in Petroleum ether). R_f = 0.54 (Petroleum ether).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57-7.51 (m, 2H), 7.41-7.27 (m, 3H), 1.56-1.30 (m, 8H), 1.20 (s, 3H), 1.03 (t, *J* = 7.4 Hz, 3H), 0.98 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 137.5, 132.4, 128.5, 128.4, 53.4, 38.9, 32.2, 26.4, 26.0, 23.2, 14.2, 8.8. The analytical data are in accordance with those reported in the literature.



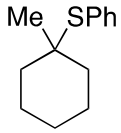
(5-Methylnonan-5-yl)-phenyl sulfide **45d**. Synthesized according to *general procedure A* after 2 h at 90 °C starting with the alcohol **43d** (79 mg, 0.50 mmol), thiophenol (103 µL, 110 mg, 1.00 mmol) and $B(C_6F_5)_3 \bullet H_2O$ (13.2 mg, 25.0 µmol, 5.0 mol%). Isolated (118 mg, 94%)

[200] Screttas, C.G.; Micha-Screttas, M. *J. Org. Chem.* **1979**, *44*, 713.

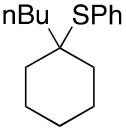
as a colorless after column chromatography (0 to 2% EtOAc in Petroleum ether). R_f = 0.58 (Petroleum ether).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57-7.51 (m, 2H), 7.41-7.30 (m, 3H), 1.53-1.28 (m, 12H), 1.21 (s, 3H), 0.97 (t, *J* = 7.3 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 137.5, 132.4, 128.5, 128.3, 53.1, 39.5, 26.6, 26.5, 23.2, 14.2; **HRMS** (ESI) for $C_{16}H_{26}S$: calcd. 250.1755; found 250.1740.



(1-Methylcycloheptyl)-phenyl sulfide **45e**. Synthesized according to *general procedure A* after 2 h at 90 °C starting with the alcohol **45e** (64 mg, 0.50 mmol), thiophenol (103 µL, 110 mg, 1.00 mmol) and $B(C_6F_5)_3$•H_2O (13.2 mg, 25.0 µmol, 5.0 mol%). Isolated (110 mg, 99%) as a colorless oil after column chromatography (Petroleum ether). R_f = 0.50 (Petroleum ether).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56-7.48 (m, 2H), 7.39-7.28 (m, 3H), 1.82-1.40 (m, 12H), 1.23 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 137.8, 132.7, 128.7, 128.5, 53.5, 41.2, 30.6, 30.3, 23.3. **HRMS** (ESI) for $C_{14}H_{20}S$: calcd. 220.1286; found 220.1293.



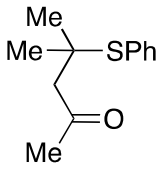
(1-Methylcyclohexyl)-phenyl sulfide **45f**.[201] Synthesized according to *general procedure A* after 2 h at 90 °C starting with the alcohol **43f** (57 mg, 0.50 mmol), thiophenol (103 µL, 110 mg, 1.0 mmol) and $B(C_6F_5)_3$•H_2O (13.3 mg, 25.0 µmol, 5.00 mol%). Isolated (99 mg, 96%) as a colorless oil after column chromatography (Petroleum ether). R_f = 0.70 (Petroleum ether).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55-7.50 (m, 2H), 7.38-7.28 (m, 3H), 1.84-1.73 (m, 2.H), 1.72-1.63 (m, 2H), 1.54-1.31 (m, 6H), 1.23 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 137.8, 132.2, 128.6, 128.5, 50.2, 38.4, 28.9, 26.0, 22.7. The analytical data are in accordance with those reported in the literature.



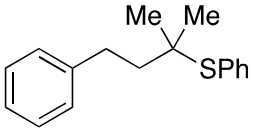
(1-Butylcyclohexyl)-phenyl sulfide **45g**. Synthesized according to *general procedure A* after 2 h at 90 °C starting with the alcohol **43g** (78 mg, 0.50 mmol), thiophenol (103 µL, 110 mg, 1.0 mmol) and $B(C_6F_5)_3$•H_2O (13.3 mg, 25.0 µmol, 5.00 mol%). Isolated (123 mg, 99%) as a colorless liquid after column chromatography (0 to 2% EtOAc in Petroleum ether). R_f = 0.42 (Petroleum ether).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57-7.50 (m, 2H), 7.40-7.29 (m, 3H), 1.92-1.30 (m, 16H), 0.99 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 137.5, 132.2, 128.4, 128.4, 54.2,

[201] Takeuchi, M.; Shimakoshi, H.; Kano, K. *Organometallics* **1994**, *13*, 1208.

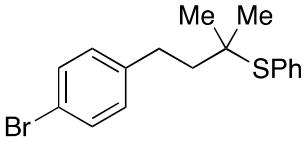
38.9, 36.3, 26.1, 25.7, 23.2, 22.3, 14.3; **HRMS** (ESI) for $C_{16}H_{24}S$: calcd. 248.1599; found 248.1600.



4-Methyl-4-(phenylthio)pentan-2-one **45h**.[202] Synthesized according to *general procedure A* after overnight at 90 °C starting with the alcohol **43h** (58 mg, 0.50 mmol), thiophenol (103 µL, 110 mg, 1.00 mmol) and $B(C_6F_5)_3$•H_2O (13.3 mg, 25.0 µmol, 5.00 mol%). Isolated (64 mg, 62%) as a colorless oil after column chromatography (Petroleum ether). R_f = 0.09 (Petroleum ether).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56-7.50 (m, 2H), 7.41-7.31 (m, 3H), 2.67 (s, 2H), 2.14 (s, 3H), 1.39 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 206.7, 137.7, 131.5, 129.2, 128.7, 54.5, 47.2, 32.3, 28.3. The analytical data are in accordance with those reported in the literature.

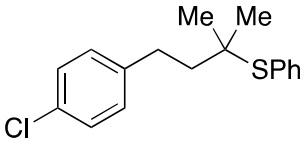


(2-Methyl-4-phenylbutan-2-yl)-phenyl sulfide **45i**.[169] Synthesized according to *general procedure A* after 2 h at 90 °C starting with the alcohol **43i** (82 mg, 0.50 mmol), thiophenol (103 µL, 110 mg, 1.00 mmol) and $B(C_6F_5)_3$•H_2O (13.2 mg, 25.0 µmol, 5.00 mol%). Isolated (124 mg, 97%) as a colorless oil after column chromatography (0 to 2% EtOAc in Petroleum ether). R_f = 0.28 (Petroleum ether).
^{1}H NMR (400 MHz, $CDCl_3$) δ7.71-7.63 (m, 2H), 7.50-7.25 (m, 8H), 2.99-2.90 (m, 2H), 1.95-1.83 (m, 2H), 1.43 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 142.5, 137.6, 132.3, 128.8, 128.6, 128.5, 128.4, 125.8, 49.2, 44.3, 31.4, 29.0. The analytical data are in accordance with those reported in the literature.

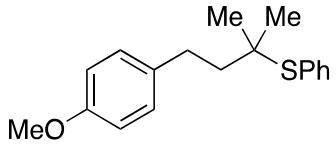


(4-(4-Bromophenyl)-2-methylbutan-2-yl)-phenyl sulfide **45j**. Synthesized according to *general procedure A* after 2 h at 90 °C starting with the alcohol **43j** (121 mg, 500 µmol), thiophenol (103 µL, 110 mg, 1.00 mmol) and $B(C_6F_5)_3$•H_2O (13.3 mg, 25.0 µmol, 5.00 mol%). Isolated (168 mg, 99%) as a waxy solid after column chromatography (Petroleum ether). R_f = 0.25 (Petroleum ether).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57-7.51 (m, 2H), 7.42-7.30 (m, 5H), 7.09-7.02 (d, *J* = 8.3, 2H), 2.83-2.75 (m, 2H), 1.77-1.69 (m, 2H), 1.31 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 141.5, 137.6, 132.2, 131.6, 130.2, 129.0, 128.7, 119.6, 49.2, 44.1, 30.9, 29.1. **HRMS** (ESI) for $C_{17}H_{19}BrS$: calcd. 334.0391; found 334.0395. m.p. = 52-53 °C.

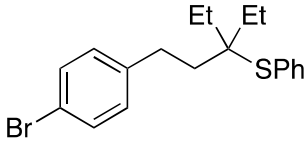
[202] Spruce, L. W.; Gale, J. B.; Berlin, K. D.; Verma, A. K.; Breitman, T. R.; Ji, X.; Van der Helm, D. *J. Med. Chem.* **1991**, *34*, 430.



(4-(4-Chlorophenyl)-2-methylbutan-2-yl)-phenyl sulfide **45k**. Synthesized according to *general procedure A* after 2 h at 90 °C starting with the alcohol **43k** (99 mg, 0.50 mmol), thiophenol (103 µL, 110 mg, 1.00 mmol) and $B(C_6F_5)_3$•H_2O (13.2 mg, 25.0 µmol, 5.00 mol%). Isolated (141 mg, 97%) as a waxy solid after column chromatography (Petroleum ether). R_f = 0.39 (Petroleum ether).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61-7.55 (m, 2H), 7.42-7.32 (m, 2H), 7.30-7.24 (m, 2H), 7.16-7.10 (m, 2H), 2.87-2.79 (m, 2H), 1.80-1.73 (m, 2H), 1.34 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 140.9, 137.5, 132.2, 131.5, 129.8, 128.9, 128.6, 128.5, 49.1, 44.1, 30.8, 29.0. **HRMS** (ESI) for $C_{17}H_{19}ClS$: calcd.290.0896; found 290.0902. m.p. = 49-50 °C.

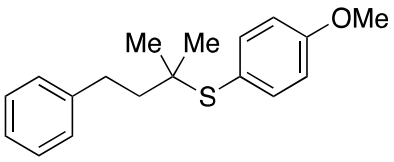


(4-(4-Methoxyphenyl)-2-methylbutan-2-yl)-phenyl sulfide **45l**. Synthesized according to *general procedure A* after 2 h at 90 °C starting with the alcohol **43l** (97 mg, 0.50 mmol), thiophenol (103 µL, 110 mg, 1.00 mmol) and $B(C_6F_5)_3$•H_2O (13.2 mg, 25.0 µmol, 5.00 mol%). Isolated (139 mg, 96%) as a waxy solid after column chromatography (0 to 5% EtOAc in Petroleum ether). R_f = 0.46 (Petroleum ether/EtOAc 10%).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68-7.62 (m, 2H), 7.47-7.38 (m, 3H), 7.19 (d, *J* = 8.6 Hz, 2H), 6.92 (d, *J* = 8.6 Hz, 2H), 3.86 (s, 3H), 2.92-2.82 (m, 2H), 1.88-1.80 (m, 2H), 1.40 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 157.8, 137.6, 134.5, 132.3, 129.3, 128.7, 128.6, 113.9, 55.9, 49.2, 44.5, 30.4, 29.5; **HRMS** (ESI) for $C_{18}H_{22}OS$: calcd. 286.1391; found 286.1384. m.p. = 36-37 °C.

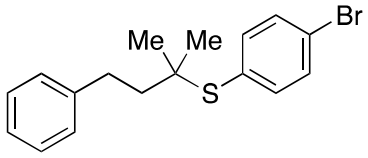


(1-(4-Bromophenyl)-3-ethylpentan-3-yl)-phenyl sulfide **45m**. Synthesized according to *general procedure A* after 2 h at 90 °C starting with the alcohol **43m** (136 mg, 0.5 mmol), thiophenol (103 µL, 110 mg, 1.00 mmol) and $B(C_6F_5)_3$•H_2O (13.3 mg, 25.0 µmol, 5.00 mol%). Isolated (177 mg, 97%) as a colorless oil after column chromatography (Petroleum ether). R_f = 0.28 (Petroleum ether).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53-7.48 (m, 2H), 7.39 (d, *J* = 8.4, 2H), 7.36-7.28 (m, 3H), 7.04 (d, *J* = 8.4, 2H), 2.78-2.71 (m, 2H), 1.63-1.56 (m, 2H), 1.48 (q, *J* = 7.4, 4H), 1.02 (t, *J* = 7.4, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 141.7, 137.4, 132.0, 131.6, 130.2, 128.8, 128.7, 119.6, 57.5, 37.8, 29.8, 28.4, 8.3. **HRMS** (ESI) for $C_{19}H_{23}BrS$: calcd. 362.0704; found 362.0700.

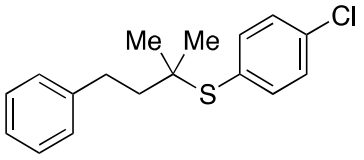
Thiol Scope of Catalytic Thiodehydration Reactions with Alcohol 43i (α,α-dimethylbenzenepropanol)



(4-Methoxyphenyl)(2-methyl-4-phenylbutan-2-yl) sulfide **47a**. Synthesized according to *general procedure B* after 2 h at 90 °C starting with the alcohol **43i** (82 mg, 0.50 mmol), thiol **46a** (123 μL, 140 mg, 1.00 mmol) and $B(C_6F_5)_3•H_2O$ (13.3 mg, 25.0 μmol, 5.00 mol%). Isolated (127 mg, 89%) as a waxy solid after column chromatography (0 to 3% EtOAc in Petroleum ether). R_f = 0.28 (Petroleum ether).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.7 Hz, 2H), 7.40-7.34 (m, 2H), 7.30-7.24 (m, 3H), 6.94 (d, *J* = 8.7 Hz, 2H), 3.87 (s, 3H), 2.94-2.88 (m, 2H), 1.88-1.81 (m, 2H), 1.38 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 160.3, 142.6, 139.0, 128.5, 128.4, 125.8, 123.1, 114.1, 55.3, 48.9, 44.1, 31.4, 28.8; **HRMS** (ESMS) for $C_{18}H_{22}OS$: calcd. 286.1391; found 286.1386. m.p. = 47-48 °C.



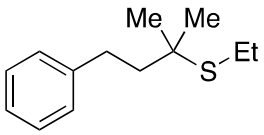
(4-Bromophenyl)(2-methyl-4-phenylbutan-2-yl) sulfide **47b**. Synthesized according to *general procedure B* after 2 h at 90 °C starting with the alcohol **43i** (82 mg, 0.50 mmol), thiol **46b** (189 mg, 1.00 mmol) and $B(C_6F_5)_3•H_2O$ (13.3 mg, 25.0 μmol, 5.00 mol%). Isolated (158 mg, 94%) as a colorless oil after column chromatography (0 to 1% EtOAc Petroleum ether). R_f = 0.30 (Petroleum ether).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.5 Hz, 2H), 7.48 (d, *J* = 8.5 Hz, 2H), 7.40-7.33 (m, 2H), 7.30-7.24 (m, 3H), 2.94-2.84 (m, 2H), 1.90-1.80 (m, 2H), 1.39 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 142.2, 139.0, 131.8, 131.5, 128.5, 128.4, 125.9, 123.6, 49.5, 44.2, 31.4, 28.9; **HRMS** (ESMS) for $C_{17}H_{19}BrS$ + K: calcd. 373.0028; found 373.0022. m.p. = 43-44 °C.



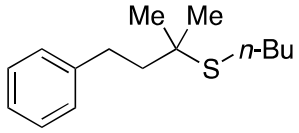
(4-Chlorophenyl)(2-methyl-4-phenylbutan-2-yl) sulfide **47c**.[203] Synthesized according to *general procedure B* after 2 h at 90 °C starting with the alcohol **43i** (82 mg, 0.50 mmol), thiol **47c** (145 mg, 1.00 mmol) and $B(C_6F_5)_3•H_2O$ (13.3 mg, 25.0 μmol, 5.00 mol%). Isolated (142 mg, 98%) as a waxy solid after column chromatography (0 to 1% EtOAc Petroleum ether). R_f = 0.36 (Petroleum ether).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.5 Hz, 2H), 7.44-7.34 (m, 4H), 7.33-7.24 (m, 3H), 2.96-2.87 (m, 2H), 1.91-1.83 (m, 2H), 1.40 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ

[203] Saito, K.; Kondo, K.; Akiyama, T. *Org. Lett.* **2015**, *17*, 3366.

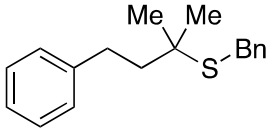
142.3, 138.7, 135.3, 130.9, 128.8, 128.5, 128.4, 125.9, 49.5, 44.2, 31.4, 28.9. The analytical data are in accordance with those reported in the literature. m.p. = 35-36 °C.



Ethyl(2-methyl-4-phenylbutan-2-yl) sulfide **47d**. Synthesized according to *general procedure A* after 2 h at 90 °C starting with the alcohol **43i** (82 mg, 0.50 mmol), thiol **46d** (111 µL, 93.0 mg, 1.50 mmol) and $B(C_6F_5)_3$•H_2O (13.3 mg, 25.0 µmol, 5.00 mol%). Isolated (90 mg, 86%) as a colorless oil after column chromatography (0 to 2% EtOAc Petroleum ether). R_f = 0.24 (Petroleum ether).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.21 (m, 5H), 2.85-2.77 (m, 2H), 2.61 (q, *J* = 7.5 Hz, 2H), 1.92-1.84 (m, 2H), 1.42 (s, 6H), 1.33 (t, *J* =7.5 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 142.7, 128.4, 128.4, 125.8, 45.2, 44.6, 31.4, 28.9, 21.8, 14.7; **HRMS** (ESMS) for $C_{13}H_{20}S$ + K: calcd. 247.0923; found 247.0917.

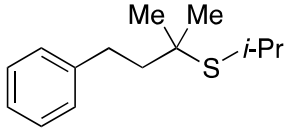


Butyl(2-methyl-4-phenylbutan-2-yl) sulfide **47e**. Synthesized according to *general procedure A* after 2 h at 90 °C starting with the alcohol **43i** (82 mg, 0.50 mmol), thiol **46e** (107 µL, 90.0 mg, 1.00 mmol) and $B(C_6F_5)_3$•H_2O (13.3 mg, 25.0 µmol, 5.0 mol%). Isolated (116 mg, 98%) as a colorless oil after column chromatography (0 to 2% EtOAc Petroleum ether). R_f = 0.24 (Petroleum ether).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.21 (m, 5H), 2.86-2.78 (m, 2H), 2.59 (t, *J* = 7.3 Hz, 2H), 1.93-1.85 (m, 2H), 1.71-1.61 (m, 2H), 1.59-1.47 (m, 2H), 1.43 (s, 6H), 1.01 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 142.7, 128.4, 128.4, 125.8, 45.0, 44.5, 31.8, 31.5, 29.0, 27.5, 22.4, 13.8; **HRMS** (ESMS) for $C_{15}H_{24}S$ + K: calcd. 275.1236; found 275.1230.

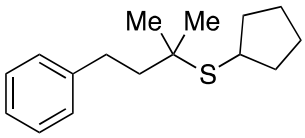


Benzyl(2-methyl-4-phenylbutan-2-yl) sulfide **47f**.[204] Synthesized according to *general procedure A* after 2 h at 90 °C starting with the alcohol **43i** (82 mg, 0.50 mmol), thiol **46f** (117 µL, 124 mg, 1.00 mmol) and $B(C_6F_5)_3$•H_2O (13.3 mg, 25.0 µmol, 5.00 mol%). Isolated (134 mg, 99%) as a colorless oil after column chromatography (0 to 1% EtOAc Petroleum ether). R_f = 0.33 (Petroleum ether).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54-7.26 (m, 10H), 3.88 (s, 2H), 2.93-2.86 (m, 2H), 2.02-1.93 (m, 2H), 1.53 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 142.6, 138.6, 129.1, 128.6, 128.5, 127.0, 125.9, 46.3, 44.6, 33.1, 31.5, 29.0. The analytical data are in accordance with those reported in the literature.

[204] Ikegai, K.; Pluempanupat, W.; Mukaiyama, T. *Bull. Chem. Soc. Japan* **2006**, *79*, 780.



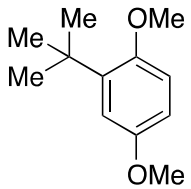
Isopropyl(2-methyl-4-phenylbutan-2-yl) sulfide **47g**. Synthesized according to *general procedure A* after 2 h at 90 °C starting with the alcohol **43i** (82 mg, 0.50 mmol), thiol **46g** (93 μL, 76 mg, 1.0 mmol) and $B(C_6F_5)_3$•H_2O (13.3 mg, 25.0 μmol, 5.00 mol%). Isolated (107 mg, 96%) as a colorless oil after column chromatography (0 to 2% EtOAc Petroleum ether). R_f = 0.24 (Petroleum ether).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.21 (m, 5H), 3.02 (sp, *J* = 6.9, 1H), 2.87-2.79 (m, 2H), 1.95-1.87 (m, 2H), 1.45 (s, 6H), 1.40 (d, *J* = 6.9, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 142.3, 128.4, 128.4, 125.8, 46.4, 45.3, 32.6, 31.5, 29.6, 26.3. **HRMS** (ESMS) for $C_{14}H_{22}S$ + K: calcd. 261.1079; found 261.1074.



Cyclopentyl(2-methyl-4-phenylbutan-2-yl) sulfide **47h**. Synthesized according to *general procedure A* after 2 h at 90 °C starting with the alcohol **43i** (82 mg, 0.50 mmol), thiol **46h** (107 μL, 102 mg, 1.00 mmol) and $B(C_6F_5)_3$•H_2O (13.3 mg, 25.0 μmol, 5.00 mol%). Isolated (123 mg, 99%) as a colorless oil after column chromatography (0 to 2% EtOAc Petroleum ether). R_f = 0.24 (Petroleum ether).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.22 (m, 5H), 3.17-3.06 (m, 1H), 2.89-2.78 (m, 2H), 2.23-2.08 (m, 2H), 1.97-1.88 (m, 2H), 1.87-1.73 (m, 2H), 1.72-1.54 (m, 4H), 1.44 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 142.7, 128.4, 128.4, 125.7, 46.0, 45.3, 40.9, 36.0, 31.5, 29.7, 25.1; **HRMS** (ESMS) for $C_{16}H_{24}S$ + K: calcd. 287.1236; found 287.1230.

General Procedure for the Friedel-Crafts Reactions
To a 10 mL reaction tube containing the alcohol (0.5 mmol) in nitromethane (250 or 75 μL) was added the nucleophile (2 to 3 equiv), followed by $B(C_6F_5)_3$•H_2O (5 mol%). The vial was capped and the mixture allowed to stir for 2 to 24 h at 90 °C. After cooling to room temperature, the volatiles of the reaction mixture were removed in vacuo. The residue was purified by flash chromatography on SiO_2.

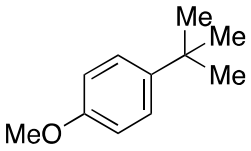
Friedel-Crafts Reactions of Tertiary Aliphatic Alcohols



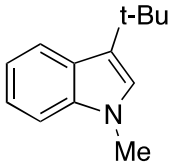
2-*tert*-Butyl-1,4-dimethoxybenzene[205] **39**. Synthesized according to general procedure after 6 h at 90 °C starting with *tert*-butanol (48 μL, 0.50 mmol), 1,4-dimethoxybenzene (207 mg,

[205] Zaytsev, A. V.; Anderson, R J.; Bedernjak, A.; Groundwater, P. W.; Huang, Y.; Perry, J. D.; Orenga, S.; Roger-Dalbert, C.; James, A. *Org. Biomol. Chem.* **2008**, *6*, 682.

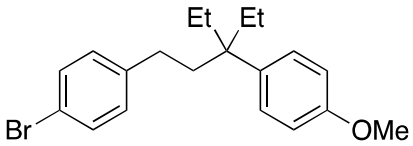
1.50 mmol) and $B(C_6F_5)_3•H_2O$ (13.3 mg, 25.0 μmol, 5.00 mol%). Isolated (88 mg, 91%) as a colorless oil after column chromatography (0 to 5% EtOAc in Petroleum ether). R_f = 0.76 (Petroleum ether/EtOAc 19:1).
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.93 (d, *J* = 3.1 Hz, 1H), 6.84 (d, *J* = 8.6 Hz, 1H), 6.73 (dd, *J* = 8.6, 3.1 Hz, 1H), 3.83 (s, 3H), 3.80 (s, 3H), 1.41 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 153.4, 153.0, 139.9, 114.4, 112.4, 109.9, 55.7, 55.7, 35.0, 29.8. The analytical data are in accordance with those reported in the literature.



4-*tert*-Butyl-anisole[206] **40a**. Synthesized according to general procedure after 6 h at 90 °C starting with *tert*-butanol (48 μL, 0.50 mmol), anisole (163 μL, 162 mg, 1.50 mmol) and $B(C_6F_5)_3•H_2O$ (13.3 mg, 25.0 μmol, 5.00 mol%). Isolated (67 mg, 82%) as a colorless oil after column chromatography (0 to 5% EtOAc in Petroleum ether). R_f = 0.28 (Petroleum ether).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.8 Hz, 2H), 6.89 (d, *J* = 8.8 Hz, 2H), 3.82 (s, 3H), 1.34 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 157.5, 143.5, 126.3, 113.5, 55.3, 34.2, 31.7. The analytical data are in accordance with those reported in the literature.



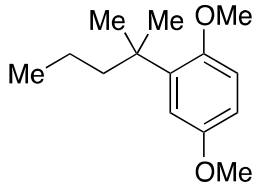
3-*tert*-Butyl-1-methylindole[207] **40b**. Synthesized according to general procedure after 24 h at 90 °C starting with *tert*-butanol (120 μL, 1.25 mmol), N-methylindole (66 mg, 0.50 mmol) and $B(C_6F_5)_3•H_2O$ (13.3 mg, 25.0 μmol, 5.00 mol%). Isolated (80 mg, 85%) as a white solid after column chromatography (0 to 2% EtOAc in Petroleum ether). R_f = 0.46 (Petroleum ether/EtOAc 2%).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.2 Hz, 1H), 7.45-7.18 (m, 3H), 6.90 (s, 1H), 3.82 (s, 3H), 1.58 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 137.9, 126.3, 124.3, 121.4, 121.1, 118.3, 109.4, 32.6, 32.1, 31.0. The analytical data are in accordance with those reported in the literature.



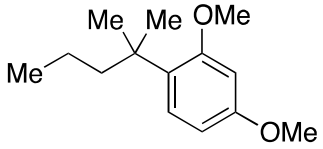
1-(4-Bromophenyl)-3-(4-methoxyphenyl)-3-ethylpentane **40c**. Synthesized according to general procedure after 6 h at 90 °C starting with the alcohol **43m** (136 mg, 0.5 mmol), anisole (161 μL, 162 mg, 1.5 mmol) and $B(C_6F_5)_3•H_2O$ (13.3 mg, 0.025 mmol, 5.0 mol%).

[206] Mahoney, S. J.; Lou, T.; Bondarenko, G.; Fillion, E. *Org. Lett.* **2012**, *14*, 3474.
[207] Davis, P. D.; Neckers, D. C. *J. Org. Chem.* **1980**, *45*, 456-462.

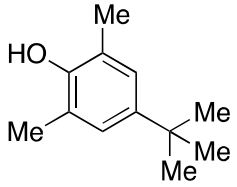
Isolated (9 mg, 10%) as a colorless oil after column chromatography (5% EtOAc in Petroleum ether). R_f = 0.51 (Petroleum ether/EtOAc 20:1).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, *J* = 8.3 Hz, 2H), 7.24 (d, *J* = 8.8 Hz, 2H), 6.97 (d, *J* = 8.3 Hz, 2H), 6.87 (d, *J* = 8.8 Hz, 2H), 3.81 (s, 3H), 2.29-2.21 (m, 2H), 1.89-1.82 (m, 2H), 1.72 (q, *J* = 7.4 Hz, 4H), 0.72 (t, *J* = 7.4 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 157.4, 142.5, 138.9, 131.5, 130.2, 127.8, 119.4, 113.5, 55.3, 43.2, 39.7, 29.9, 29.0, 8.1. **HRMS** (EI) for $C_{20}H_{25}BrO$: calcd. 362.10683; found 362.10574.



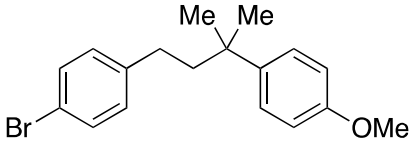
2-(2,5-Dimethoxyphenyl)-2-methylpentane **40d**. Synthesized according to general procedure after 24 h at 90 °C starting with the alcohol **43a** (61 µL, 0.50 mmol), 1,4-dimethoxybenzene (207 mg, 1.50 mmol) and $B(C_6F_5)_3$•H_2O (13.3 mg, 0.025 mmol, 5.00 mol%). Isolated (99 mg, 89%) as a colorless oil after column chromatography (3% EtOAc in Petroleum ether). R_f = 0.53 (Petroleum ether/EtOAc 30:1).
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.83 (d, *J* = 3.2 Hz, 1H), 6.79 (d, *J* = 8.7 Hz, 1H), 6.69 (dd, *J* = 8.7, 3.2 Hz, 1H), 3.78 (s, 3H), 3.77 (s, 3H), 1.80-1.73 (m, 2H), 1.33 (s, 6H), 1.07-0.95 (m, 2H), 0.82 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 153.4, 153.1, 138.8, 115.6, 112.4, 109.8, 55.9, 55.7, 43.5, 38.5, 28.5, 18.6, 15.0. **HRMS** (EI) for $C_{14}H_{22}O_2$: calcd. 222.16198; found 222.16088.



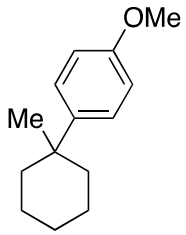
2-(2,4-Dimethoxyphenyl)-2-methylpentane **40e**. Synthesized according to general procedure after 6 h at 90 °C starting with the alcohol **43a** (61 µL, 0.50 mmol), 1,3-dimethoxybenzene (207 mg, 1.50 mmol) and $B(C_6F_5)_3$•H_2O (13.3 mg, 25.0 µmol, 5.00 mol%). Isolated (67 mg, 60%) as a colorless oil after column chromatography (3% EtOAc in Petroleum ether). R_f = 0.49 (Petroleum ether/EtOAc 30:1).
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.85 (d, *J* = 3.2 Hz, 1H), 6.81 (d, *J* = 8.7 Hz, 1H), 6.71 (dd, *J* = 8.7, 3.2 Hz, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 1.82-1.76 (m, 2H), 1.35 (s, 6H), 1.09-0.98 (m, 2H), 0.84 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 153.4, 153.1, 138.8, 115.5, 112.4, 109.8, 55.8, 55.7, 43.5, 38.4, 28.5, 18.6, 15.0. **HRMS** (EI) for $C_{14}H_{22}O_2$: calcd. 222.16198; found 222.16081.



4-*tert*-Butyl-2,6-dimethyl-phenol[208] **40f**. Synthesized according to general procedure after 24 h at 90 °C starting with *tert*-butanol (120 µL, 1.25 mmol), 2,6-dimethyl phenol (62 mg, 0.50 mmol) and $B(C_6F_5)_3$•H_2O (13.3 mg, 25.0 µmol, 5.00 mol%). Isolated (84 mg, 94%) as a colorless oil after column chromatography (5% EtOAc in Petroleum ether). R_f = 0.42 (Petroleum ether/EtOAc 19:1).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (s, 2H), 4.60 (s, 1H), 2.31 (s, 6H), 1.36 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 150.0, 143.0, 125.6, 122.5, 34.0, 31.7, 16.3. The analytical data are in accordance with those reported in the literature.



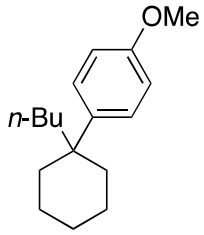
1-(4-Bromophenyl)-3-(4-methoxyphenyl)-3-methylbutane **40g**. Synthesized according to general procedure after 6 h at 90 °C starting with the alcohol **43j** (122 mg, 500 µmol), anisole (161 µL, 162 mg, 1.50 mmol) and $B(C_6F_5)_3$•H_2O (13.3 mg, 25.0 µmol, 5.00 mol%). Isolated (124 mg, 74%) as a colorless oil after column chromatography (5% EtOAc in Petroleum ether). R_f = 0.47 (Petroleum ether/EtOAc 20:1).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.3 Hz, 2H), 7.34 (d, *J* = 8.8 Hz, 2H), 7.00 (d, *J* = 8.3 Hz, 2H), 6.93 (d, *J* = 8.8 Hz, 2H), 3.85 (s, 3H), 2.39-2.31 (m, 2H), 1.95-1.87 (m, 2H), 1.40 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 157.5, 142.2, 140.9, 131.4, 130.1, 126.9 119.3, 113.6, 55.3, 46.8, 37.4, 31.0, 29.2. **HRMS** (EI) for $C_{18}H_{21}BrO$: calcd. 334.07553; found 334.07822.



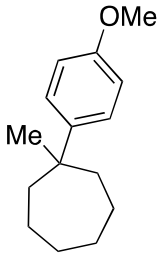
1-(4-Methoxyphenyl)-1-methylcyclohexane[209] **40h**. Synthesized according to general procedure after 6 h at 90 °C starting with the alcohol **43f** (57 mg, 0.50 mmol), anisole (161 µL, 162 mg, 1.50 mmol) and $B(C_6F_5)_3$•H_2O (13.3 mg, 25.0 µmol, 5.00 mol%). Isolated (71 mg, 70%) as a colorless oil after column chromatography (0 to 1% EtOAc in Petroleum ether). R_f = 0.34 (Petroleum ether).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.8 Hz, 2H), 6.92 (d, *J* = 8.8 Hz, 2H), 3.85 (s, 3H), 2.09-1.96 (m, 2H), 1.68-1.41 (m, 8H), 1.23 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$)

[208] Kamitori, Y.; Hojo, M.; Masuda, R.; Izumi, T.; Tsukamoto, S. *J. Org. Chem.* **1984**, *49*, 4165.
[209] Yamamoto, Y.; Itonaga, K. *Chem. Eur. J.* **2008**, *14*, 10705.

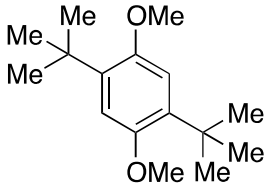
δ 157.1, 142.1, 126.7, 113.5, 55.2, 38.1, 37.3, 26.4, 22.7. The analytical data are in accordance with those reported in the literature.



1-(4-Methoxyphenyl)-1-butylcyclohexane **40i**. Synthesized according to general procedure after 6 h at 90 °C starting with the alcohol **40g** (78 mg, 0.50 mmol), anisole (161 μL, 162 mg, 1.50 mmol) and $B(C_6F_5)_3•H_2O$ (13.3 mg, 25.0 μmol, 5.00 mol%). Isolated (66 mg, 54%) as a colorless oil after column chromatography (0 to 1% EtOAc in Petroleum ether). R_f = 0.36 (Petroleum ether).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, *J* = 8.8 Hz, 2H), 6.90 (d, *J* = 8.8 Hz, 2H), 3.85 (s, 3H), 2.14-2.02 (m, 2H), 1.66-1.34 (m, 10H), 1.24-1.10 (m, 2H), 1.02-0.88 (m, 2H), 0.83 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 156.7, 139.3, 127.8, 113.3, 55.1, 44.0, 40.5, 36.4, 26.8, 25.7, 23.4, 22.4, 14.1; **HRMS** (EI) for $C_{17}H_{26}O$: calcd. 246.19836; found 246.19974.



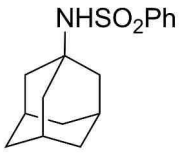
1-(4-Methoxyphenyl)-1-methylcycloheptane **40j**. Synthesized according to general procedure after 6 h at 90 °C starting with the alcohol **40e** (64 mg, 0.50 mmol), anisole (161 μL, 162 mg, 1.50 mmol) and $B(C_6F_5)_3•H_2O$ (13.3 mg, 25.0 μmol, 5.0 mol%). Isolated (73 mg, 67%) as a colorless oil after column chromatography (0 to 1% EtOAc in Petroleum ether). R_f = 0.36 (Petroleum ether).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.8 Hz, 2H), 6.93 (d, *J* = 8.8 Hz, 2H), 3.85 (s, 3H), 2.16-2.08 (m, 2H), 1.76-1.46 (m, 10H), 1.26 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 157.1, 143.4, 126.9, 113.4, 55.2, 41.1, 40.6, 32.5, 30.1, 23.7; **HRMS** (EI) for $C_{15}H_{22}O$: calcd. 218.16706; found 218.16533.



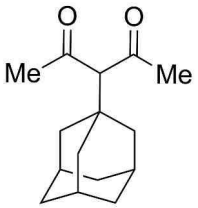
2,5-Di-*tert*-butyl-1,4-dimethoxybenzene[205] **40k**. Synthesized according to general procedure after 6 h at 90 °C starting with *tert*-butanol (120 μL, 1.25 mmol), 1,4-dimethoxybenzene (69 mg, 0.50 mmol) and $B(C_6F_5)_3•H_2O$ (13.3 mg, 25.0 μmol, 5.00 mol%). Isolated (71 mg, 57%)

as a white solid after column chromatography (0 to 5% EtOAc in Petroleum ether). R_f = 0.95 (Petroleum ether/EtOAc 19:1).
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.90 (s, 2H), 3.87 (s, 6H), 1.43 (s, 18H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 152.1, 136.5, 111.8, 56.0, 34.8, 30.0. The analytical data are in accordance with those reported in the literature.
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.48-1.41 (m, 2H), 1.35-1.23 (m, 12H), 1.20 (s, 6H), 0.87 (t, *J* = 6.9, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 71.2, 44.2, 32.0, 30.3, 29.8, 29.4, 29.3, 24.5, 22.8, 14.2. **HRMS** (ESI) for ($C_{11}H_{24}O$ - CH_3): calcd. 157.15924; found 157.16010.

Additional Nucleophile Scope

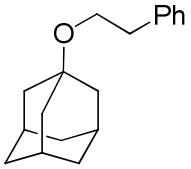


N-1-Adamantylbenzenesulfonamide **51a**.[210] Synthesized according to *general procedure A* after 2 h at 90 °C starting with the 1-adamantol **31** (76 mg, 0.50 mmol), *benzenesulfonamide* **19j** (157 mg, 1.00 mmol) and $B(C_6F_5)_3$•H_2O (13.2 mg, 25.0 μmol, 5.00 mol%). Isolated (135 mg, 93%) as a white solid after column chromatography (10 % EtOAc in Petroleum ether). R_f = 0.45 (Petroleum ether/EtOAc 8:2).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93-7.88 (m, 2H), 7.57-7.45 (m, 3H), 4.50 (s, 1H), 2.00 (s, 1H), 1.79 (d, *J* = 2.6, 6H), 1.64-1.51 (m, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 144.2, 132.1, 128.9, 126.9, 55.2, 43.0, 35.9, 29.5. The analytical data are in accordance with those reported in the literature.

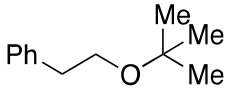


3-(1-Adamantyl)pentane-2,4-dione **51b**.[211] Synthesized according to *general procedure A* after overnight reaction at 90 °C starting with 1-adamantol **31** (76 mg, 0.50 mmol), acetylacetone (102 μL, 100 mg, 1.00 mmol) and $B(C_6F_5)_3$•H_2O (13.2 mg, 25.0 μmol, 5.0 mol%). Isolated (112 mg, 96%) as a white solid after column chromatography (5 to 10 % EtOAc in Petroleum ether). R_f = 0.56 (Petroleum ether/EtOAc 9:1).
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.52 (s, 1H), 2.19 (s, 6H), 1.97 (s, 3H), 1.74-1.57 (m, 12H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 204.4, 78.2, 40.4, 38.5, 36.6, 33.1, 28.7. The analytical data are in accordance with those reported in the literature.

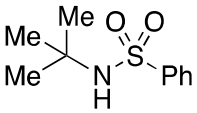
[210] Pelletier, G.; Powell, D. A. *Org. Lett.* **2006**, *8*, 6031.
[211] Gonzalez, A.; Marquet, J.; Moreno-Mañas, M. *Tetrahedron* **1986**, *42*, 4253.



1-Adamantyl 2-phenylethyl ether **51c**. Synthesized according to *general procedure A* after 6 h at 90 °C starting with 1-adamantol **31** (76 mg, 0.50 mmol), 2-phenylethanol (120 µL, 122 mg, 1.00 mmol) and $B(C_6F_5)_3•H_2O$ (13.2 mg, 25.0 µmol, 5.00 mol%). Isolated (116 mg, 91%) as a colorless oil after column chromatography (Petroleum ether). R_f = 0.29 (Petroleum ether).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.18 (m, 5H), 3.63 (t, *J* = 7.7, 2H), 2.86 (t, *J* = 7.7, 2H), 2.15 (s, 3H), 1.76 (d, *J* = 2.2, 6H), 1.70-1.57 (m, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 139.5, 129.1, 128.3, 126.1, 72.2, 61.3, 41.6, 37.6, 36.6, 30.6. **HRMS** (ESI) for $C_{18}H_{24}O$: calcd. 256.1827; found 256.1811.



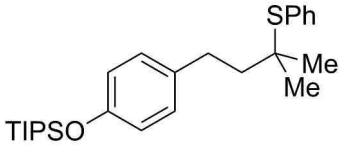
tert-Butyl 2-phenylethyl ether[212] **51d.** Synthesized according to *general procedure A* after 6 h at 90 °C starting with *tert*-butanol (48 µL, 0.50 mmol), 2-phenyl ethanol (120 µL, 122 mg, 1.00 mmol) and $B(C_6F_5)_3•H_2O$ (13.3 mg, 25.0 µmol, 5.0 mol%). Isolated (48 mg, 52%) as a colorless oil after column chromatography (5% EtOAc in Petroleum ether). R_f = 0.56 (Petroleum ether/EtOAc 19:1).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.17 (m, 5H), 3.56 (t, *J* = 7.6 Hz, 2H), 2.85 (t, *J* = 7.6 Hz, 2H), 1.19 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 139.5, 129.1, 128.4, 126.2, 73.0, 63.2, 37.6, 27.7. The analytical data are in accordance with those reported in the literature.



N-(phenylsulfonyl)-*N*-(*tert*-butyl)amine[213] **51e.** Synthesized according to *general procedure A* after 6 h at 90 °C starting with *tert*-butanol (48 µL, 0.50 mmol), phenylsulfonamide (157 mg, 1.0 mmol) and $B(C_6F_5)_3•H_2O$ (13.3 mg, 25.0 µmol, 5.0 mol%). Isolated (89 mg, 84%) as a white solid after column chromatography (15% EtOAc in Petroleum ether). R_f = 0.25 (Petroleum ether/EtOAc 6:1).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93-7.89 (m, 2H), 7.55-7.43 (m, 3H), 5.15 (s, 1H), 1.20 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 143.6, 132.2, 129.0, 127.0, 54.7, 30.2. The analytical data are in accordance with those reported in the literature.

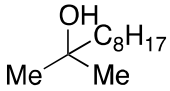
[212] Colombel, V.; Rombouts, F.; Oehlrich, D.; Molander, G. A. *J. Org. Chem.* **2012**, *77*, 2966.
[213] Taniguchi, N. *Eur. J. Org. Chem.* **2010**, 2670.

Chemoselective Thiodehydration Reaction with 48

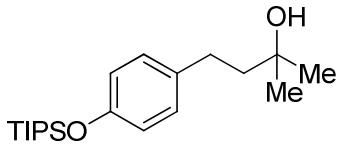


4-(4-Triisopropilsiloxyphenyl)-2-methyl-2-butyl phenyl sulfide **49**. Synthesized according to *general procedure A* after 2 h at 90 °C starting with the alcohol **48** (168 mg, 500 μmol), thiophenol (103 μL, 110 mg, 1.00 mmol) and $B(C_6F_5)_3 \bullet H_2O$ (13.3 mg, 25.0 μmol, 5.00 mol%). Isolated (164 mg, 77%) as a colorless oil after column chromatography (0 to 2% EtOAc in Petroleum ether). R_f = 0.33 (Petroleum ether).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63-7.57 (m, 2H), 7.42-7.32 (m, 3H), 7.07 (d, *J* = 8.3, 2H), 6.85 (d, *J* = 8.3, 2H), 2.85-2.76 (m, 2H), 1.83-1.74 (m, 2H), 1.37-1.25 (m, 9H), 1.16 (d, *J* = 7.5, 18H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 154.1, 137.6, 134,8, 132.4, 129.2, 128.8, 128.6, 119.8, 49.3, 44.4, 30.6, 29.0, 18.1, 12.8; **HRMS** (ESMS) for $C_{26}H_{40}OSSi$ + Na: calcd. 451.2467; found 451.2461.

Preparation of Previously Unreported Starting Materials



2-Methyldecan-2-ol **43b**. A 100 mL three-necked flask fitted with a reflux condenser, dropping funnel, nitrogen inlet, and magnetic stirring bar was charged with degreased magnesium turnings (0.86 g, 36 mmol), dry diethyl ether (10 mL), and a crystal of iodine. A solution of 1-bromooctan (5.79 g, 30.0 mmol) in dry diethyl ether (15 mL) was added dropwise over 2 h to the rapidly stirring suspension so as to maintain a slight but regular reflux in the condenser. The dropping funnel was rinsed with dry diethyl ether (3 mL) and the resulting mixture was stirred overnight at room temperature, to give a brown solution of the Grignard reagent. After cooling with an ice bath, dry acetone (3.8 mL, 52 mmol) in diethyl ether (5 mL) was added dropwise over 1 h. The dropping funnel was washed with diethyl ether (5 mL) and, after stirring at r.t. for 2 hours, the contents of the flask was hydrolyzed with saturated ammonium chloride (25 mL). The organic components were extracted into diethyl ether (3×10 mL), and the combined organic layers were dried with sodium sulfate. Removal of the volatiles with a rotary evaporator afforded crude 2-methyldecan-2-ol as a slightly yellow oil that was purified by column chromatography (10 to 20% EtOAc in heptane) to give an alcohol (2.16 g, 42%, not optimized yield) as a colorless oil. R_f = 0.27 (20% EtOAc in heptane).
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.48-1.41 (m, 2H), 1.35-1.23 (m, 12H), 1.20 (s, 6H), 0.87 (t, *J* = 6.9, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 71.2, 44.2, 32.0, 30.3, 29.8, 29.4, 29.3, 24.5, 22.8, 14.2. **HRMS** (ESI) for ($C_{11}H_{24}O$ - CH_3): calcd. 157.15924; found 157.16010.



4-(4-Triisopropilsiloxyphenyl)-2-methyl-2-butanol **48**.

1.1. To a magnetically stirred solution of 4-(4-hydroxyphenyl)-2-butanone (4.92 g, 30.0 mmol) in dry CH_2Cl_2 (50 mL) was added imidazole (4.08 g, 60.0 mmol) and triisopropylsilyl chloride sequentially (6.95 g, 36.0 mmol). The reaction mixture was allowed to stir overnight at room temperature before being diluted with CH_2Cl_2, filtered and washed with a saturated aqueous $NaHCO_3$ solution and brine. The combined organic layers were then dried over $MgSO_4$, filtered, and concentrated. The obtained material was directly used in the next step without further purification.

1.2. A solution of material from the previous step (15 mmol in 15 mL of ether) was added dropwise to a 3.0 M solution of methyl magnesium iodide (15 mL, 45 mmol) at 0 °C. The solution was allowed to warm to room temperature over 2.5 hours under stirring (TLC control) and quenched with aqueous NH_4Cl, extracted with EtOAc, and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography (10% EtOAc in Petroleum ether) and pure fractions of the product were collected to give (3.79 g, 75%) of colorless oil. R_f = 0.30 (10% EtOAc in Petroleum ether).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (d, 2H, *J* = 8.3 Hz), 6.79 (d, 2H, *J* = 8.3 Hz), 2.68-2.58 (m, 2H), 1.81-1.72 (m, 2H), 1.29-1.21 (m, 9H), 1.10 (d, 18H, *J* = 7.3 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 154.2, 134.9, 129.2, 119.9, 71.1, 46.0, 30.0, 29.5, 18.1, 12.8. **HRMS** (ESI) for $C_{20}H_{36}O_2Si$: calcd. 336.24846; found 336.24978.

EXPERIMENTAL SECTION – CHAPTER 4

General Information. All azidation reactions were performed in 10 mL sealed tubes under an air atmosphere. All other reactions were performed in air-dried flasks under nitrogen atmosphere, unless otherwise noted. Purification of reaction products was carried out by flash column chromatography using Merck silica gel (40-63 μm). Analytical thin layer chromatography (TLC) was performed on aluminum sheets pre-coated with silica gel 60 F254 (E. Merck), cut to size. Visualization was accomplished with UV light followed by dipping in a potassium permanganate, *p*-anisaldehyde and/or Seebach's staining solutions and heating.

^{1}H NMR spectra were recorded on a Bruker Avance400 (400 MHz) spectrometer at ambient temperature unless otherwise noted and are reported in ppm using solvent as the internal standard ($CDCl_3$ at 7.26 ppm). Data are reported as: multiplicity (ap = apparent, br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration and coupling constant(s) in Hz. ^{13}C NMR spectra were recorded on a Bruker Avance400 (100 MHz) spectrometer. Chemical shifts are reported in ppm from tetramethylsilane, with the residual solvent resonance employed as the internal standard ($CDCl_3$ at 77.0 ppm).

GCMS analysis was conducted on a GC System 7820A (G4320) connected to a MSD block 5977E (G7036A) using *Agilent* High Resolution Gas Chromatography Column: PN 19091S – 433UI, HP – 5MS UI, 30m×0.250mm, 0.25 Micron, SN USD 489634H.

IR experiments were performed using *Thermo Scientific* NICOLET 6700 FT-IR spectrometer.

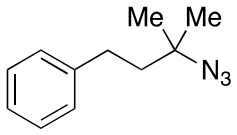
Materials. Unless otherwise noted, all commercial materials were purchased from *Sigma-Aldrich* and used without further purification. The alcohols **54g**[214], **54n**[215], **54o**[216] **54p**[217], **54x**[218], **54t**[219], **54u**[220], **54v**[169], **54w**[221] were prepared following a literature procedure. Tris(pentafluorophenyl)borane $B(C_6F_5)_3$ was purchased from *Alfa Aesar* and used under air, without any precaution to exclude moisture or air.

General Procedure for the Azidation of Tertiary Aliphatic Alcohols

Condition A. To a 10 mL reaction tube containing the alcohol (0.5 mmol, 1 equiv) in nitromethane (250 μL, 2.0 M) was added trimethylsilyl azide (199 µL, 173 mg, 1.50 mmol, 3 equiv), followed by $B(C_6F_5)_3 \bullet H_2O$ (13 mg, 0.025 mmol, 5.0 mol%). The vial was capped and the mixture allowed to stir for 1 h at 23 ^oC. After completion, the volatiles of the reaction mixture were removed *in vacuo*. The residue was purified by flash chromatography on SiO_2.

Condition B. To a 10 mL reaction tube containing the alcohol (0.5 mmol, 1 equiv) in benzene (75 µL, 6.7 M) was added trimethylsilyl azide (199 µL, 173 mg, 1.50 mmol, 3 equiv), followed by 4-nitroanisole (38 mg, 0.25 mmol, 50 mol%) and $B(C_6F_5)_3 \bullet H_2O$ (5.3 mg, 0.010 mmol, 2.0 mol%). The vial was capped and the mixture allowed to stir for 24 h at 23 ^oC. After completion, the volatiles of the reaction mixture were removed *in vacuo*. The residue was purified by flash chromatography on SiO_2.

Spectral Data for all Azide Products 56a-z, 70



(3-Azido-3-methylbutyl)benzene **56a**.[222] Synthesized according to the general procedure (*condition A*) after 1 h at 23 ^oC starting with the alcohol **43i** (82 mg, 0.50 mmol), trimethylsilyl azide (199 µL, 173 mg, 1.50 mmol) and $B(C_6F_5)_3 \bullet H_2O$ (13 mg, 0.025 mmol, 5.0 mol%). Isolated (82 mg, 87%) as a colorless oil after column chromatography (Petroleum ether). R_f = 0.36 (Petroleum ether).

In the simular experiment, 68 mg (72% yield) of the product **56a** was also isolated after 5 min of the reaction time and direct purification of the reaction mixture by column chromatography.

The use of *condition B* furnished 61 mg (65%) of the product **56a**.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.22 (m, 5H), 2.79-2.71 (m, 2H), 1.92-1.83 (m, 2H), 1.41 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 141.9, 128.5, 128.3, 126.0, 61.4, 43.6, 30.8, 26.1. The analytical data are in accordance with those reported in the literature.

[214] Julia, M.; Igolen, H.; Lenzi, J. *Bull. Soc. Chem. Fr.* **1966**, *7*, 2291.
[215] Li, L.; Navasero, N. *Org. Lett.* **2004**, *6*, 3091.
[216] Oshima, K. *Science of synthesis* **2004**, *7*, 573.
[217] Nicolai, S.; Waser, J. *Org. Lett.* **2011**, *13*, 6324.
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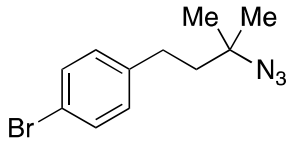
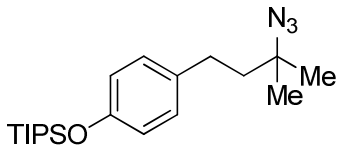
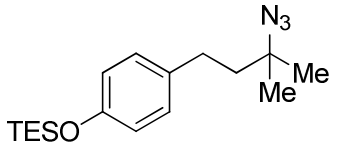
[221] Masuno, H.; Yamamoto, K.; Wang, X.; Choi, M.; Ooizumi, H.; Shinki, T.; Yamada, S. *J. Med. Chem.* **2002**, *45*, 1825.
[222] Waser, J.; Gaspar, B.; Nambu, H.; Carreira, E. M. *J. Am. Chem. Soc.* **2006**, *128*, 11693.



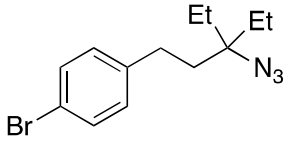
1-(3-Azido-3-methylbutyl)-4-bromobenzene **56b**. Synthesized according to the general procedure (*condition A*) after 1 h at 23 °C starting with the alcohol **43j** (122 mg, 0.500 mmol), trimethylsilyl azide (199 µL, 173 mg, 1.50 mmol) and $B(C_6F_5)_3 \bullet H_2O$ (13 mg, 0.025 mmol, 5.0 mol%). Isolated (120 mg, 90%) as a colorless oil after column chromatography (Petroleum ether). R_f = 0.39 (Petroleum ether).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.2 Hz, 2H), 7.07 (d, *J* = 8.2 Hz, 2H), 2.67-2.60 (m, 2H), 1.79-1.72 (m, 2H), 1.33 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 140.9, 131.6, 130.2, 119.8, 61.4, 43.5, 30.3, 26.2. **HRMS** (EI) for $C_{11}H_{14}BrN_3$: calcd. 267.03711; found 267.03736.



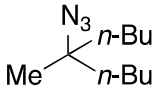
2-Azido-4-(4-triisopropilsiloxyphenyl)-2-methylbutane **56c**. Synthesized according to the general procedure (*condition A*) with benzene as a co-solvent (20% with respect to the volume of nitromethane) after 1 h at 23 °C starting with the alcohol **48** (168 mg, 0.500 mmol), trimethylsilyl azide (199 µL, 173 mg, 1.50 mmol) and $B(C_6F_5)_3 \bullet H_2O$ (13 mg, 0.025 mmol, 5.0 mol%). Isolated (161 mg, 89%) as a colorless oil after column chromatography (Petroleum ether). R_f = 0.73 (2% EtOAc in cyclohexane).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (d, 2H, *J* = 8.4 Hz), 6.83 (d, 2H, *J* = 8.4 Hz), 2.67-2.58 (m, 2H), 1.83-1.75 (m, 2H), 1.34 (s, 6H), 1.32-1.22 (m, 3H), 1.13 (d, 18H, *J* = 7.4 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 154.3, 134.2, 129.2, 119.9, 61.5, 43.7, 30.0, 26.1, 18.0, 12.8. **HRMS** (ESI) for $C_{20}H_{35}N_3OSi$: calcd. 361.25494; found 361.25697.



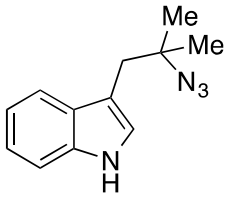
2-Azido-4-(4-triethylsiloxyphenyl)-2-methylbutane **56d**. Synthesized according to the general procedure (*condition A*) with benzene as a co-solvent (20% with respect to the volume of nitromethane) after 1 h at 23 °C starting with the alcohol **54d** (74 mg, 0.25 mmol), trimethylsilyl azide (100 µL, 87 mg, 0.75 mmol) and $B(C_6F_5)_3 \bullet H_2O$ (1.3 mg, 0.0025 mmol, 1.0 mol%). Isolated (88 mg, 69%) as a colorless oil after column chromatography (Petroleum ether). R_f = 0.25 (Petroleum ether).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (d, 2H, *J* = 8.4 Hz), 6.78 (d, 2H, *J* = 8.4 Hz), 2.66-2.57 (m, 2H), 1.82-1.73 (m, 2H), 1.33 (s, 6H), 1.01 (t, 9H, *J* = 7.9 Hz), 0.75 (q, 6H, *J* = 7.9 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 153.6, 134.5, 129.2, 120.0, 61.6, 43.7, 30.0, 26.2, 6.7, 5.1. **HRMS** (ESI) for $C_{17}H_{29}N_3OSi$: calcd. 319.20799; found 319.20959.



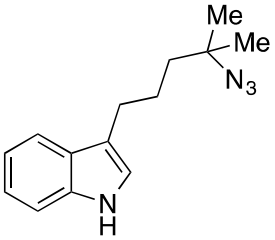
1-(3-Azido-3-ethylpentyl)-4-bromobenzene **56e**. Synthesized according to the general procedure (*condition A*) after 1 h at 23 °C starting with the alcohol **43m** (135 mg, 0.500 mmol), trimethylsilyl azide (199 µL, 173 mg, 1.50 mmol) and $B(C_6F_5)_3 \bullet H_2O$ (13 mg, 0.025 mmol, 5.0 mol%). Isolated (95 mg, 64%) as a colorless oil after column chromatography (Petroleum ether). R_f = 0.37 (Petroleum ether).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.2 Hz, 2H), 7.08 (d, *J* = 8.2 Hz, 2H), 2.64-2.54 (m, 2H), 1.78-1.72 (m, 2H), 1.63 (q, *J* = 7.3 Hz, 4H), 0.95 (t, *J* = 7.3 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 141.0, 131.6, 130.2, 119.8, 67.0, 38.0, 29.6, 28.5, 8.1. **HRMS** (EI) for $C_{13}H_{18}BrN_3$: calcd. 295.06841; found 295.07359.



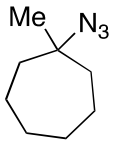
5-Azido-5-methylnonane **56f**.[149] Synthesized according to the general procedure (*condition A*) after 1 h at 23 °C starting with 5-methylnonan-5-ol **43d** (79 mg, 0.50 mmol), trimethylsilyl azide (199 µL, 173 mg, 1.50 mmol) and $B(C_6F_5)_3 \bullet H_2O$ (13 mg, 0.025 mmol, 5.0 mol%). Isolated (69 mg, 75%) as a colorless oil after column chromatography (0 to 2% EtOAc in Petroleum ether). R_f = 0.40 (Petroleum ether).
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.55-1.28 (m, 12H), 1.24 (s, 3H), 0.99-0.91 (m, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 64.2, 39.0, 26.1, 23.3, 23.0, 14.0. The analytical data are in accordance with those reported in the literature.
The use of *condition B* furnished 64 mg (70%) of the product **56f**.



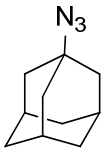
3-(2-Azido-2-methylpropyl)-1*H*-indole **56g**. Synthesized according to the general procedure (*condition A*) after 1 h at 23 °C starting with the alcohol **54g** (95 mg, 0.50 mmol), trimethylsilyl azide (199 µL, 173 mg, 1.50 mmol) and $B(C_6F_5)_3 \bullet H_2O$ (13 mg, 0.025 mmol, 5.0 mol%). Isolated (87 mg, 81%) as a brown oil after column chromatography (Petroleum ether). R_f = 0.18 (5% EtOAc in Petroleum ether).
The use of *condition B* furnished 99 mg (92%) of the product **56g**.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (br, 1H), 7.76 (d, 1H, *J* = 7.7 Hz), 7.43 (d, 1H, *J* = 7.8 Hz), 7.35-7.25 (m, 2H), 7.12 (s, 1H), 3.06 (s, 2H), 1.44 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 136.0, 128.4, 123.9, 122.0, 119.6, 119.2, 111.3, 111.2, 62.7, 37.1, 26.2. **HRMS** (ESI) for $C_{12}H_{14}N_4$: calcd. 214.12185; found 214.12365.



3-(4-Azido-4-methylpentyl)-1*H*-indole **56h**. Synthesized according to the general procedure (*condition A*) after 1 h at 23 °C starting with the alcohol **54h** (109 mg, 0.500 mmol), trimethylsilyl azide (199 µL, 173 mg, 1.50 mmol) and $B(C_6F_5)_3 \bullet H_2O$ (13 mg, 0.025 mmol, 5.0 mol%). Isolated (63 mg, 52%) as a brown oil after column chromatography (Petroleum ether). $R_f = 0.18$ (5% EtOAc in Petroleum ether).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (br, 1H), 7.71 (d, 1H, *J* = 7.8 Hz), 7.42 (d, 1H, *J* = 8.0 Hz), 7.34-7.21 (m, 2H), 7.04 (s, 1H), 2.87 (t, 2H, *J* = 7.5 Hz), 1.94-1.85 (m, 2H), 1.74-1.66 (m, 2H), 1.35 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 136.4, 127.6, 122.0, 121.3, 119.2, 118.9, 116.4, 111.2, 61.8, 41.4, 26.1, 25.4, 24.9. **HRMS** (ESI) for $C_{14}H_{18}N_4$: calcd. 242.15315; found 242.15483.

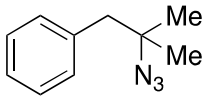


1-Azido-1-methylcycloheptane **56i**. Synthesized according to the general procedure (*condition A*) after 1 h at 23 °C starting with the alcohol **43e** (64 mg, 0.50 mmol), trimethylsilyl azide (199 µL, 173 mg, 1.50 mmol) and $B(C_6F_5)_3 \bullet H_2O$ (13 mg, 0.025 mmol, 5.0 mol%). Isolated (59 mg, 77%) as a colorless oil after column chromatography (Petroleum ether). $R_f = 0.35$ (Petroleum ether).
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.84-1.71 (m, 2H), 1.67-1.35 (m, 10H), 1.29 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 65.3, 40.2, 29.4, 27.6, 22.7. **HRMS** (ESI) for $C_8H_{15}N_3 - HN_2$: calcd. 124.11262; found 124.11285.

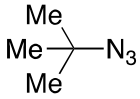


1-Adamantyl azide **56j**.[223] Synthesized according to the general procedure (*condition A*) after 1 h at 23 °C starting with 1-adamantol **31** (76 mg, 0.50 mmol), trimethylsilyl azide (199 µL, 173 mg, 1.50 mmol) and $B(C_6F_5)_3 \bullet H_2O$ (13 mg, 0.025 mmol, 5.0 mol%). Isolated (81 mg, 92%) as a colorless amorphous solid after column chromatography (Petroleum ether). R_f = 0.45 (Petroleum ether).
^{1}H NMR (400 MHz, $CDCl_3$) δ 2.15 (s, 3H), 1.80 (d, *J* = 2.6, 6H), 1.73-1.59 (m, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 59.1, 41.7, 36.0, 30.0. The analytical data are in accordance with those reported in the literature.

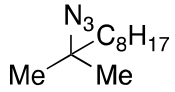
[223] Nyfeler, E.; Renaud, P. *Org. Lett.* **2008**, *10*, 985.



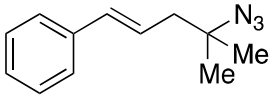
(2-Azido-2-methylpropyl)benzene **56k**.[224] Synthesized according to the general procedure (*condition A*) after 1 h at 23 °C starting with the alcohol **54k** (75 mg, 0.50 mmol), trimethylsilyl azide (199 μL, 173 mg, 1.50 mmol) and $B(C_6F_5)_3•H_2O$ (13 mg, 0.025 mmol, 5.0 mol%). Isolated (70 mg, 80%) as a colorless amorphous solid after column chromatography (Petroleum ether). R_f = 0.20 (Petroleum ether).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.26 (m, 5H), 2.83 (s, 2H), 1.33 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 136.6, 130.6, 128.4, 126.8, 61.8, 47.5, 25.9. The analytical data are in accordance with those reported in the literature.



2-Azido-2-methylpropane **56l**.[225] Synthesized according to the general procedure (*condition A*) after 1 h at 23 °C starting with *tert*-butanol (37 mg, 0.50 mmol), trimethylsilyl azide (199 μL, 173 mg, 1.50 mmol) and $B(C_6F_5)_3•H_2O$ (13 mg, 0.025 mmol, 5.0 mol%). Anisole (54 μL, 51 mg, 0.50 mmol, 1.0 equiv) was added as an internal standard and the mixture was taken up in $CDCl_3$. ^{1}H NMR of these solutions were recorded and the % yield calculated based on the ratio of the methyl resonance of anisole (δ 3.88 ppm, 3H) to the resonance corresponding to the methyl group of compound (δ 1.39, 9H). Yield of **2j** determined as 95%.
Under *condition B,* 92% of the product **56l** was detected.
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 58.9, 27.2. The analytical data are in accordance with those reported in the literature.



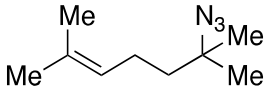
2-Azido-2-methyldecane **56m**. Synthesized according to the general procedure (*condition A*) after 1 h at 23 °C starting with the alcohol **43b** (86 mg, 0.50 mmol), trimethylsilyl azide (199 μL, 173 mg, 1.50 mmol) $B(C_6F_5)_3•H_2O$ (13 mg, 0.025 mmol, 5.0 mol%). Isolated (84 mg, 85%) as a colorless oil after column chromatography (Petroleum ether). R_f = 0.40 (Petroleum ether).
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.51-1.43 (m, 2H), 1.41-1.25 (m, 12H), 1.24 (s, 6H), 0.88 (t, *J* = 6.9, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 61.8, 41.6, 32.0, 30.0, 29.7, 29.4, 26.1, 24.4, 22.8, 14.2. **HRMS** (EI) for $C_{11}H_{23}N_3 – HN_2$: calcd. 168.17522; found 168.17607.



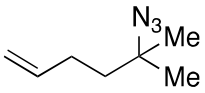
(*E*)-(4-Azido-4-methylpent-1-en-1-yl)benzene **56n**. Synthesized according to the general procedure (*condition A*) after 1 h at 0 °C starting with the alcohol **54n** (86 mg, 0.50 mmol), trimethylsilyl azide (199 μL, 173 mg, 1.50 mmol) and $B(C_6F_5)_3•H_2O$ (13 mg, 0.025 mmol,

[224] Hill, C.L.; Smegal, J.A.; Henly, T.J. *J. Org. Chem.* **1983**,*48*, 3277.
[225] Bottaro, J.C.; Penwell, P.E.; Schmitt, R.J. *Synth. Comm.* **1997**, *27*, 1465.

5.0 mol%). Isolated (46 mg, 46%) as a colorless oil after column chromatography (Petroleum ether). R_f = 0.12 (Petroleum ether).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45-7.29 (m, 5H), 6.52 (d, *J* = 15.8 Hz, 1H), 6.31-6.24 (m, 1H), 2.46 (d, *J* = 7.4 Hz, 2H), 1.37 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 137.2, 133.8, 128.6, 127.4, 126.2, 124.8, 61.8, 45.1, 25.9. **HRMS** (ESI) for $C_{12}H_{15}N_3$: calcd. 201.12660; found 201.12579.

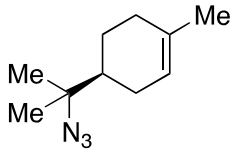


6-Azido-2,6-dimethylhept-2-ene **56o**. Synthesized according to the general procedure (*condition A*) after 1 h at 23 °C starting with the alcohol **54o** (71 mg, 0.50 mmol), trimethylsilyl azide (199 μL, 173 mg, 1.50 mmol) and $B(C_6F_5)_3$•H_2O (13 mg, 0.025 mmol, 5.0 mol%). Isolated (40 mg, 48%) as a colorless oil after column chromatography (Petroleum ether). Due to the volatility of the compound, the reaction was repeated and the yield was estimated by NMR. Anisole (54 μL, 51 mg, 0.50 mmol, 1.0 equiv) was added as an internal standard and the mixture was taken up in $CDCl_3$. ^{1}H NMR of these solutions were recorded and the % yield calculated based on the ratio of the methyl resonance of anisole (δ 3.88 ppm, 3H) to the resonance corresponding to the methylene of the target compound (δ 2.12-2.06, 2H). Yield of **56o** determined as 70%.
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.17-5.12 (m, 1H), 2.12-2.06 (m, 2H), 1.74 (s, 3H), 1.67 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 132.0, 123.7, 61.6, 41.5, 26.0, 25.7, 23.0, 17.5. **HRMS** (EI) for $C_9H_{17}N_3 - HN_2$: calcd. 138.12827; found 138.12835.

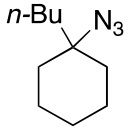


5-Azido-5-methylhex-1-ene **56p**.[226] Synthesized according to the general procedure (*condition A*) after 1 h at 23 °C starting with the alcohol **54p** (57 mg, 0.50 mmol), trimethylsilyl azide (199 μL, 173 mg, 1.50 mmol) and $B(C_6F_5)_3$•H_2O (13 mg, 0.025 mmol, 5.0 mol%). Isolated (15 mg, 26%) as a colorless oil after column chromatography (Petroleum ether). Due to the volatility of the compound, the reaction was repeated and the yield was determined by NMR. Anisole (54 μL, 51 mg, 0.50 mmol, 1.0 equiv) was added as an internal standard and the mixture was taken up in $CDCl_3$. ^{1}H NMR of these solutions were recorded and the % yield calculated based on the ratio of the methyl resonance anisole (δ 3.88 ppm, 3H) to the resonance corresponding to the methylene of compound (δ 2.20-2.15, 2H). Yield of **56p** determined as 73%.
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.92-5.82 (m, 1H), 5.11-5.01 (m, 2H), 2.20-2.15 (m, 2H), 1.65-1.61 (m, 2H), 1.33 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 138.0, 114.8, 61.5, 40.6, 28.6, 26.0. The analytical data are in accordance with those reported in the literature.

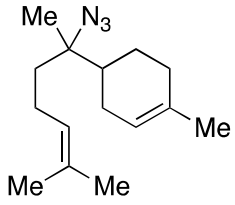
[226] Firdous, S.; Banert, K.; Auer, A. A. *Chem. Eur. J.* **2011**, *17*, 5539.



(*S*)-4-(2-Azidopropan-2-yl)-1-methylcyclohex-1-ene **56q**.[227] Synthesized according to the general procedure (*condition A*) after 1 h at 23 °C starting with the alcohol **54q** (77 mg, 0.50 mmol), trimethylsilyl azide (199 µL, 173 mg, 1.50 mmol) and $B(C_6F_5)_3$•H_2O (13 mg, 0.025 mmol, 5.0 mol%). Isolated (49 mg, 58%) as a colorless oil after column chromatography (Petroleum ether). R_f = 0.6 (Petroleum ether).
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.42 (br, 1H), 2.18-2.00 (m, 4H), 1.92-1.84 (m, 2H), 1.70 (s, 3H), 1.63-1.56 (m, 1H), 1.31 (s, 3H), 1.28 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 134.0, 120.1, 64.2, 43.4, 30.9, 26.8, 24.2, 23.9, 23.3, 23.0. The analytical data are in accordance with those reported in the literature.



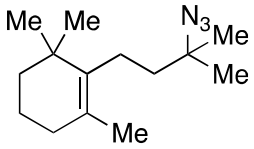
1-Azido-1-butylcyclohexane **56r.** Synthesized according to the general procedure (*condition A*) after 1 h at 23 °C starting with the alcohol **43g** (78 mg, 0.50 mmol), trimethylsilyl azide (199 µL, 173 mg, 1.50 mmol) and $B(C_6F_5)_3$•H_2O (13 mg, 0.025 mmol, 5.0 mol%). Isolated (79 mg, 87%) as a colorless oil after column chromatography (Petroleum ether). R_f = 0.38 (Petroleum ether).
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.76-1.16 (m, 16H), 0.92 (t, *J* = 6.8 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 64.2, 40.0, 34.7, 25.6, 25.5, 23.2, 22.3, 14.1. **HRMS** (EI) for $C_{10}H_{19}N_3$ – HN_2: calcd. 152.14484; found 152.14392.



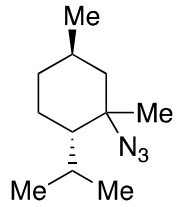
4-(2-Azido-6-methylhept-5-en-2-yl)-1-methylcyclohex-1-ene **56s**. Synthesized according to the general procedure (*condition A*) after 1 h at 23 °C starting with the alcohol **54s** (111 mg, 0.500 mmol), trimethylsilyl azide (199 µL, 173 mg, 1.50 mmol) and $B(C_6F_5)_3$•H_2O (13 mg, 0.025 mmol, 5.0 mol%). Isolated (65 mg, 53%) as a colorless oil after column chromatography (Petroleum ether). R_f = 0.56 (Petroleum ether).
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.42 (m, 1H), 5.15 (t, *J* = 6.9 Hz, 1H), 2.11-1.83 (m, 6H), 1.74 (s, 3H), 1.70 (s, 3H), 1.67 (s, 3H), 1.64-1.58 (m, 2H), 1.42-1.33 (m, 1H), 1.29 (s, 1.5H), 1.25 (s, 1.5H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 134.2, 133.8, 132.1, 123.7, 123.6, 120.4, 120.1, 66.6, 66.4, 42.1, 41.5, 37.8, 37.3, 30.9, 30.8, 26.5, 25.7, 24.0, 23.3, 23.2, 22.5, 20.1,

[227] Alarcon, M.; Cori, O.; Rojas, M. C.; Pavez, H.; Bacaloglu, R.; Bunton, C. A. *J. Phys. Org. Chem.* **1992**, 5, 83.

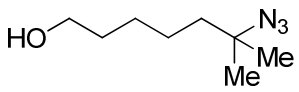
17.6 (mixture of 2 diastereoisomers, ratio 1:1). **HRMS** (ESI) for $C_{15}H_{25}N_3 - N_2$: calcd. 219.19870; found 219.19812.



2-(3-Azido-3-methylbutyl)-1,3,3-trimethylcyclohex-1-ene **56t**. Synthesized according to the general procedure (*condition A*) after 1 h at 23 °C starting with the alcohol **54t** (105 mg, 0.500 mmol), trimethylsilyl azide (199 µL, 173 mg, 1.50 mmol) and $B(C_6F_5)_3 \bullet H_2O$ (13 mg, 0.025 mmol, 5.0 mol%). Isolated (89 mg, 74%) as a colorless oil after column chromatography (Petroleum ether). R_f = 0.35 (Petroleum ether).
The use of *condition B* furnished 51 mg (42%) of the product **56t**.
^{1}H NMR (400 MHz, $CDCl_3$) δ 2.13-2.09 (m, 2H), 1.95 (t, *J* = 6.3 Hz, 2H), 1.65-1.58 (m, 7H), 1.48-1.45 (m, 2H), 1,34 (s, 6H), 1,05 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 136.2, 127.5, 61.8, 41.5, 39.8, 35.0, 32.8, 28.6, 25.8, 23.0, 19.7, 19.5. **HRMS** (EI) for $C_{14}H_{25}N_3 - HN_2$: calcd. 206.19087; found 206.18930.

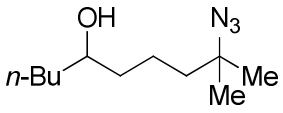


(*2S*,*5R*)-1-Azido-2-isopropyl-1,5-dimethylcyclohexane **56u**. Synthesized according to the general procedure (*condition A*) after 1 h at 23 °C starting with the alcohol **54u** (85 mg, 0.50 mmol), trimethylsilyl azide (199 µL, 173 mg, 1.50 mmol) and $B(C_6F_5)_3 \bullet H_2O$ (13 mg, 0.025 mmol, 5.0 mol%). Isolated (44 mg, 45%) as a colorless oil after column chromatography (Petroleum ether). R_f = 0.38 (Petroleum ether).
^{1}H NMR (400 MHz, $CDCl_3$) δ 2.09-2.01 (m, 1H), 1.81-1.77 (m, 2H), 1.70-1.54 (m, 2H), 1.38-1.25 (m, 4H), 1.24 (s, 3H), 1.02 (s, 1.5H), 1.01 (s, 1.5H), 0.97 (s, 1.5H), 0.95 (s, 1.5H), 0.88 (s, 1.5H), 0.86 (s, 1.5H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 134.2, 133.8, 132.1, 123.7, 123.6, 120.4, 120.1, 66.6, 66.44, 42.13, 37.8, 30.9, 30.8, 26.7, 26.5, 25.7, 24.1, 23.9, 23.3, 23.2, 22.5, 22.3, 20.16, 19.72, 17.6 (mixture of 2 diastereoisomers, ratio 7:3). **HRMS** (ESI) for $C_{11}H_{21}N_3 - HN_2$: calcd. 166.15957; found 166.16263.

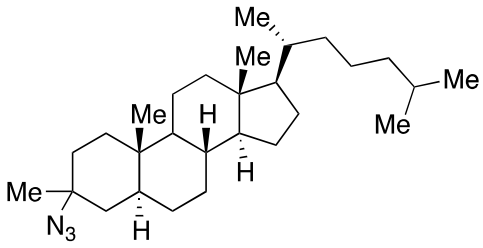


6-Azido-6-methylheptan-1-ol **56v**. Synthesized according to the general procedure (*condition A*) with benzene as a co-solvent (20% with respect to the volume of nitromethane) after 3 h at 90 °C starting with the alcohol **54v** (78 mg, 0.53 mmol), trimethylsilyl azide (278 µL, 242 mg, 2.00 mmol) and $B(C_6F_5)_3 \bullet H_2O$ (13 mg, 0.025 mmol, 5.0 mol%). After completion, the reaction was quenched with 160 µL of TFA, the volatiles of the reaction mixture were removed *in vacuo* and the residue was purified to give (58 mg, 64%) a colorless oil after column chromatography (20% EtOAc in Petroleum ether). R_f = 0.37 (20% EtOAc in Petroleum ether).

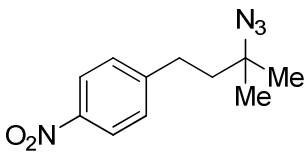
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.60 (t, 2H, *J* = 6.6 Hz), 2.25-2.08 (br, 1H), 1.60-1.50 (m, 2H), 1.50-1.42 (m, 2H), 1.39-1.29 (m, 4H), 1.22 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 62.7, 61.7, 41.5, 32.6, 26.1, 26.0, 24.1. **HRMS** (ESI) for ($C_8H_{17}N_3O$ - CH_3N_2) : calcd. 128.10754; found 128.10823.



9-Azido-9-methyldecan-5-ol **56w**. Synthesized according to the general procedure (*condition A*) with benzene as a co-solvent (20% with respect to the volume of nitromethane) after 1 h at 23 °C starting with the alcohol **54w** (94 mg, 0.50 mmol), trimethylsilyl azide (278 μL, 242 mg, 2 mmol) and $B(C_6F_5)_3$•H_2O (13 mg, 0.025 mmol, 5.0 mol%). After completion, the reaction was quenched with 160 μL of TFA, the volatiles of the reaction mixture were removed *in vacuo* and the residue was purified to give (75 mg, 70%) a colorless oil after column chromatography (5% EtOAc in Petroleum ether). R_f = 0.40 (5% EtOAc in Petroleum ether).
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.63-3.51 (m, 1H), 1.86-1.56 (br, 1H), 1.54-1.27 (m, 12H), 1.24 (s, 6H), 0.89 (t, 3H, *J* = 7.0 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 71.8, 61.8, 41.5, 37.6, 37.4, 27.9, 26.1, 26.0, 22.8, 20.5, 14.2. **HRMS** (ESI) for ($C_{11}H_{23}N_3O$ - N_3) : calcd. 171.17489; found 171.17603.



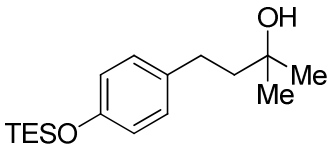
3-Azido-3-methyl-5α-cholestane **56x**. Synthesized according to the general procedure (*condition A*) after 1 h at 23 °C starting with the alcohol **54x** (80 mg, 0.20 mmol), trimethylsilyl azide (79 μL, 69 mg, 0.60 mmol) and $B(C_6F_5)_3$•H_2O (5.3 mg, 0.010 mmol, 5.0 mol%). Isolated (50 mg, 58%) as a colorless oil after column chromatography (Petroleum ether). R_f = 0.36 (Petroleum ether).
^{1}H NMR (400 MHz, $CDCl_3$) δ 2.04-1.99 (m, 1H), 1.91-1.82 (m, 1H), 1.75-1.00 (m, 32H), 0.96-0.91 (m, 9H), 0.81 (s, 3H), 0.70 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 62.2, 56.5, 56.2, 54.0, 42.6, 41.4, 40.0, 39.5, 39.4, 36.2, 35.8, 35.5, 35.4, 32.4, 31.9, 28.2, 28.0, 27.5, 24.2, 23.9, 22.8, 22.6, 21.0, 18.7, 12.1, 11.7 (signals from the major diastereoisomer; the peaks overlapping prevented definitive assignment of the diastereomeric ratio by NMR). **HRMS** (ESI) for $C_{28}H_{49}N_1 – N_2$: calcd. 399.38650; found 399.38101.



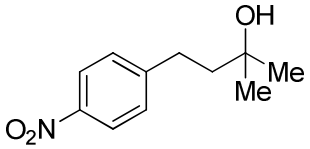
1-(3-Azido-3-methylbutyl)-4-nitrobenzene **70.** Synthesized according to the general procedure (*condition A*) after 1 h at 23 °C starting with the alcohol **69** (52 mg, 0.25 mmol),

trimethylsilyl azide (100 µL, 87 mg, 0.75 mmol) and $B(C_6F_5)_3 \bullet H_2O$ (6.7 mg, 0.013 mmol, 5.0 mol%) with no nitromethane added. Isolated (26 mg, 44%) as a colorless oil after column chromatography (3% EtOAc in Petroleum ether). R_f = 0.29 (3% EtOAc in Petroleum ether).
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, 2H, *J* = 8.5 Hz), 7.34 (d, 2H, *J* = 8.5 Hz), 2.82-2.75 (m, 2H), 1.82-1.76 (m, 2H), 1.35 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 149.8, 146.6, 129.3, 123.9, 61.3, 43.0, 30.8, 26.2. **HRMS** (EI) for $C_{11}H_{14}N_4O_2$: calcd. 234.11168; found 234.11185.

Preparation of Previously Unreported Starting Materials



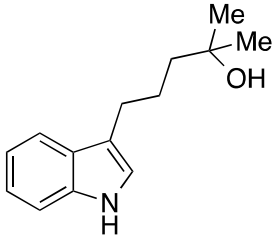
4-(4-Triethylsiloxyphenyl)-2-methyl-2-butanol **54d**.
1.1. To a magnetically stirred solution of 4-(4-hydroxyphenyl)-2-butanone (1.64 g, 10.0 mmol) in dry CH_2Cl_2 (20 mL) was added imidazole (1.36 g, 20.0 mmol) and triethylsilyl chloride sequentially (2.41 g, 16.0 mmol). The reaction mixture was allowed to stir overnight at room temperature before being diluted with CH_2Cl_2, filtered and washed with a saturated aqueous $NaHCO_3$ solution and brine. The combined organic layers were then dried over $MgSO_4$, filtered, and concentrated. The obtained material was directly used in the next step without further purification.
1.2. A solution of material from the previous step (2.87 mmol in 5 mL of ether) was added dropwise to a 3.0 M solution of methyl magnesium iodide (2.9 mL, 8.6 mmol) at 0 ºC. The solution was allowed to warm to room temperature over 2.5 hours under stirring (TLC control) and quenched with aqueous NH_4Cl, extracted with EtOAc, and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography (15% EtOAc in Petroleum ether) and pure fractions of the product were collected to give (0.47 g, 56%) of colorless oil. R_f = 0.55 (20% EtOAc in Petroleum ether).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 (d, 2H, *J* = 8.4 Hz), 6.76 (d, 2H, *J* = 8.4 Hz), 2.66-2.60 (m, 2H), 1.81-1.62 (m, 2H), 1.28 (s, 6H), 0.99 (t, 9H, *J* = 8.0 Hz), 0.73 (q, 6H, *J* = 8.0 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 153.7, 135.2, 129.2, 119.9, 71.1, 46.0, 30.0, 29.5, 6.8, 5.1. **HRMS** (ESI) for $C_{17}H_{30}O_2Si$: calcd. 294.20151; found 294.20127.



2-Methyl-4-(4-nitrophenyl)butan-2-ol **69**.[228] $TiCl_4$ (340 µL, 588 mg, 3.10 mmol) was added by syringe to about 15 mL of cooled (-78 ºC) Et_2O resulting in partial precipitation of the yellow $TiC1_4$-bisetherate. An 1.6 M ethereal solution of methyl lithium (1.9 mL, 3.1 mmol) was added slowly, which caused a color change to dark-purple. The mixture than was transferred by cannula to a solution of 4-(4-nitrophenyl)butane-2-one[229] (600 mg, 3.10 mmol)

[228] Reetz, M.T.; Kyung, S.H.; Hüllmann, M. *Tetrahedron* **1986**, *42*, 2931.
[229] Sin, I.; Kang, C. S.; Bandara, N.; Sun, X.; Zhong, Y.; Rogers, B. E.; Chong, H.-S. *Bioorg. Med. Chem.* **2014**, *22*, 2553.

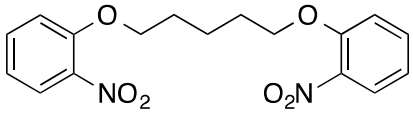
in 5 mL of Et_2O at -30 ºC. After reacting for approximately 3 hours, the cold solution was poured into cold water. The mixture was extracted with Et_2O, washed with water, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (CH_2Cl_2) to give an alcohol (197 mg, 31%, not optimized yield) as a yellow amorphous solid. $R_f = 0.24$ (CH_2Cl_2).
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, 2H, *J* = 8.6 Hz), 7.31 (d, 2H, *J* = 8.6 Hz), 2.84-2.73 (m, 2H), 1.85-1.67 (m, 3H), 1.27 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 150.9, 146.2, 129.2, 123.6, 70.6, 45.0, 30.7, 29.4. **HRMS** (EI) for $C_{11}H_{15}NO_3$: calcd. 209.10519; found 209.10302.



5-(1*H*-Indol-3-yl)-2-methylpentan-2-ol **54g**. To a solution of ethyl 4-(1*H*-indol-3-yl)butanoate (578 mg, 2.5 mmol) in dry THF (10 mL) at 0 °C under nitrogen was added dropwise a solution of methyl magnesium bromide (3.0 M in Et_2O, 2.5 mL, 7.5 mmol). The reaction mixture was allowed to stir at 0 °C for 5 min, then warmed to room temperature and stirred an additionnal 12 h. The reaction was quenched by slow addition of an aqueous solution of saturated NH_4Cl (20 mL) and the resulting mixture was extracted with Et_2O (2 x 20 mL). The organic layers were combined, washed with brine (20 mL), dried (Na_2SO_4), filtered and concentrated in *vacuo*. The residue was purified by flash chromatography on silica gel using 20 to 50% EtOAc in petroleum ether as eluant to give the alcohol (308 mg, 57%) as a brown solid. $R_f = 0.18$ (20% EtOAc in petroleum ether).
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (br, 1H), 7.68 (d, 1H, *J* = 7.8 Hz), 7.40 (d, 1H, *J* = 8.0 Hz), 7.28-7.15 (m, 2H), 7.02 (s, 1H), 2.84 (t, 2H, *J* = 7.3 Hz), 1.92-1.81 (m, 2H), 1.70-1.62 (m, 2H), 1.46 (br, 1H), 1.28 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 136.4, 127.6, 121.9, 121.2, 119.1, 119.0, 116.7, 111.1, 71.1, 43.9, 29.3, 25.6, 25.0. **HRMS** (ESI) for $C_{14}H_{19}NO$: calcd. 217.14666 ; found 217.14815.

Reaction with Bisnitro Compound 71

Condition C. To a 10 mL reaction tube containing **43i** (41 mg, 0.25 mmol, 1 equiv) in CH_2Cl_2 (125 µL, 2.0 M) was added trimethylsilyl azide (99 µL, 86 mg, 0.75 mmol, 3 equiv), followed by 2-nitroanisole (38 mg, 0.25 mmol, 100 mol%) or **71** (43 mg, 0.125 mmol, 50 mol%) and $B(C_6F_5)_3$•H_2O (1.3 mg, 2.0 µmol, 1.0 mol%). The vial was capped and the mixture allowed to stir for 4 h at 23 °C and the reaction was monitored by GC-MS. 66% yield of **56a** for detected in case of **71** and 17% in case of 2-nitroanisole, respectively.

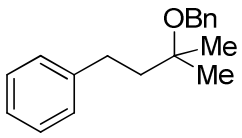


1,5-bis(2-Nitrophenoxy)pentane **71**. A 50 mL round bottom flask equipped with reflux condenser was charged with 2-nitrophenol (2.78 g, 20.0 mmol), dry DMF (20 mL) and anhydrous K_2CO_3 (3.04 g, 20.0 mmol). 1,5-dibromopentane (2.30 g, 10.0 mmol) was introduced and the mixture was heated to 150 °C for 24 h. After cooling to room temperature,

the resulting mixture was pourred into chilled water (100 mL) to afford crude 1,5-bis(2-nitrophenoxy)pentane, which was washed several times with water and recrystallized from ethanol to give a brown powder (2.37 g, 68%).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.56 (ddd, *J* = 8.5, 1.2, 1.2 Hz, 2H), 7.13 (dd, *J* = 8.5, 1.2 Hz, 2H), 7.05 (ddd, *J* = 8.2, 1.2, 1.2 Hz, 2H) 4.19 (t, *J* = 6.2 Hz, 4H), 2.02-1.92 (m, 4H), 1.82-1.72 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 152.4, 140.0, 134.1, 125.5, 120.1, 114.5, 69.4, 28.5, 22.5. **HRMS** (ESMS) for $C_{17}H_{18}N_2O_6$ + Na : calcd. 369.1063 ; found 369.1057.

Reaction of Tertiary Aliphatic Benzyl Ether 72

To a 10 mL reaction tube containing the compound **72** (64 mg, 0.25 mmol), *n*-dodecane (the internal standard, 17.0 µL, 12.8 mg, 75.0 µmol) and nitromethane (125 µL, 2.00 M) was added trimethylsilyl azide (100 µL, 86.5 mg, 0.750 mmol), followed by $B(C_6F_5)_3 \cdot H_2O$ (6.4 mg, 0.013 mmol, 5.0 mol%). The vial was capped quickly and the mixture allowed to stir at 23 ^oC. Aliquot was taken after 1 h of reaction time, diluted with EtOAc to 10^{-4} M and analysed by GC-MS. The yield of product formed was determined as 61% by integrating the peak corresponding to azide product relative to the peak corresponding to the internal standard (response factor is equal to 1.14). The equivalent amount of TMSOBn was detected on the same chromatogram and the identity of the signal was confirmed by comparison to an authentic sample.

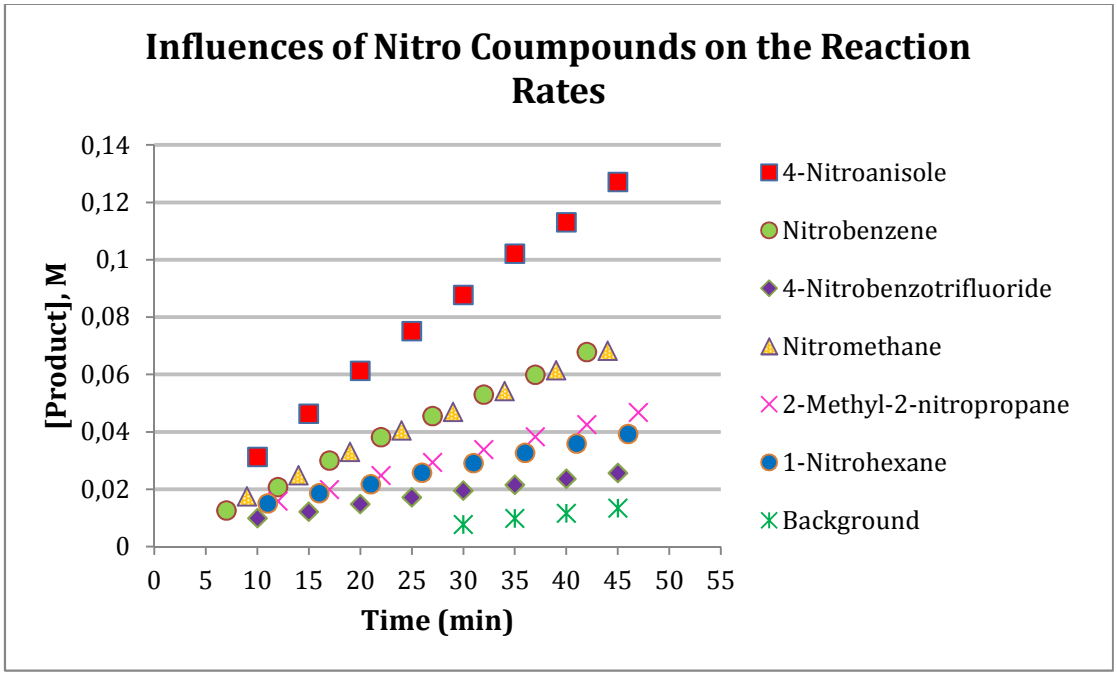


Benzyl 1,1-dimethyl-3-phenylpropyl ether **72**.[230] To a suspension of NaH (60 % dispersion in mineral oil, 0.60 g, 15 mmol) in DMF (10 ml) was added an alcohol **1e** (1.64 g, 10.0 mmol) in DMF (2.0 ml) at 0 °C and stirred for 30 min. Benzyl bromide (1.43 ml, 2.05 g, 12.0 mmol) was added at 0 °C and the mixture was stirred at room temperature overnight. After completion of the reaction, water was added at 0 °C and the mixture was extracted with ether. The organic layers were washed with brine, dried over Na_2SO_4, filtered and evaporated in vacuo. The residue was purified by column chromatography (5% EtOAc in Petroleum Ether) to give an ether (440 mg, 17%, not optimised yeild) as a colorless oil. R_f = 0.66 (5 % EtOAc in Petroleum ether)
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44-7.17 (m, 10H), 4.50 (s, 2H), 2.80-2.73 (m, 2H), 1.96-1.88 (m, 2H), 1.36 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 143.0, 140.0, 128.5, 128.5, 128.4, 127.4, 127.3, 125.8, 75.1, 63.8, 42.6, 30.5, 25.9. The analytical data are in accordance with those reported in the literature.

[230] Yamada, K.; Fujita, H.; Kunishima, M. *Org. Lett.* **2012**, 14, 5026.

Kinetic Experiments

Initial rate experiments.
Silyl ether **55a** (118 mg, 0.500 mmol), tris(pentafluorophenyl)borane hydrate (2.6 mg, 0.0050 mmol), the appropriate nitro compound (0.50 mmol) and *n*-dodecane (the internal standard, 34.0 μL, 25.5 mg, 0.150 mmol) were weighed in a 10 mL reaction tube with a stirring bar. Benzene (216 μL) was added, followed by trimethylsilyl azide (132 μL, 1.00 mmol). The resulting mixture was stirred at room temperature and the reaction was monitored by GC-MS. Aliquots were taken every 5 minutes over the period of 45-50 minutes and diluted with isopropanol to 10^{-4} M before analysis. The time at which the first point was taken varied slightly from one experiment to another. The concentration of product formed was determined by integrating the peak corresponding to azide product relative to the peak corresponding to the internal standard (response factor is equal to 1.14) assuming that reaction volume is equal to 0.500 mL (silyl ether + *n*-dodecane + trimethylsilyl azide + benzene).



Nitro compound	Time, min	[Product], M
4-Nitroanisole	10	0,0312
	15	0,0462
	20	0,0612
	25	0,0750
	30	0,0876
	35	0,1021
	40	0,1129
	45	0,1270

Nitro compound	Time, min	[Product], M
Nitrobenzene	7	0,0126
	12	0,0207
	17	0,0300
	22	0,0381

	27	0,0455
	32	0,0529
	37	0,0598
	42	0,0677

Nitro compound	Time, min	[Product], M
4-Nitrobenzotrifluoride	10	0,0098
	15	0,0121
	20	0,0148
	25	0,0171
	30	0,0194
	35	0,0215
	40	0,0236
	45	0,0256

Nitro compound	Time, min	[Product], M
Nitromethane	9	0,0174
	14	0,0248
	19	0,0330
	24	0,0405
	29	0,0469
	34	0,0542
	39	0,0614
	44	0,0682

Nitro compound	Time, min	[Product], M
2-Methyl-2-nitropropane	12	0,0158
	17	0,0198
	22	0,0247
	27	0,0293
	32	0,0337
	37	0,0382
	42	0,0424
	47	0,0467

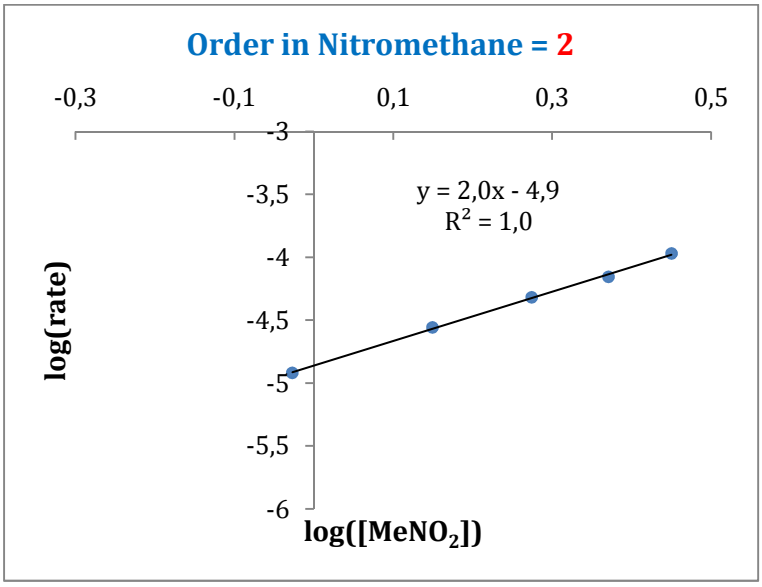
Nitro compound	Time, min	[Product], M
1-Nitrohexane	11	0,0150
	16	0,0185
	21	0,0216
	26	0,0257
	31	0,0291
	36	0,0326
	41	0,0358
	46	0,0392

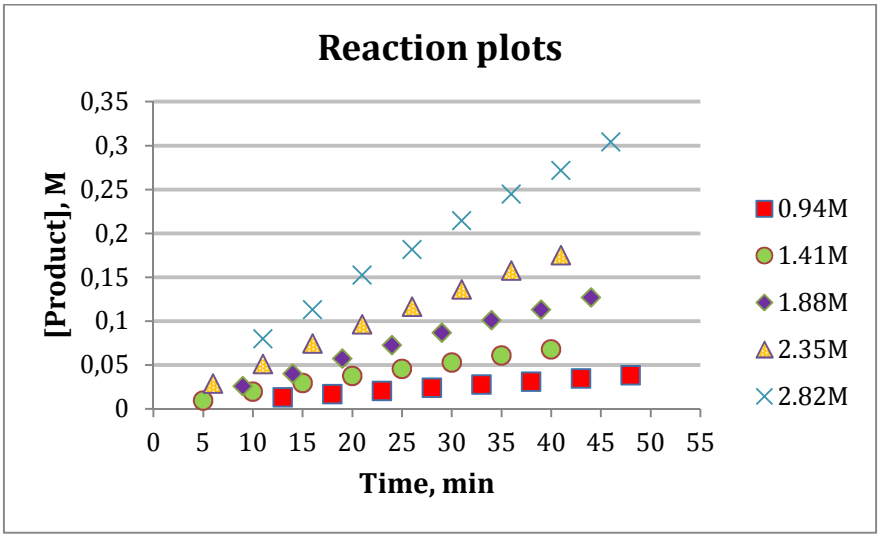
Nitro compound	Time, min	[Product], M
None	30	0,0076
	35	0,0097
	40	0,0115

	45	0,0133

Order in nitromethane

α,α-Dimethylbenzenepropanol **43i** (82 mg, 0.50 mmol), tris(pentafluorophenyl)borane hydrate (2.6 mg, 0.0050 mmol), nitromethane (0.500 mmol, 1.00 mmol, 1.50 mmol, 2.00 mmol, 2.50 mmol) and *n*-dodecane (the internal standard, 34.0 μL, 25.5 mg, 0.150 mmol) were weighed in a 10 mL reaction tube with a stirring bar. Benzene was added and trimethylsilyl azide (199 μL, 173 mg, 1.50 mmol). The amount of benzene added (189 μL, 176 μL, 162 μL, 148 μL, 135 μL, respectively) corresponds to 0.532 mL minus the amount of liquid components used. The resulting mixture was stirred at room temperature and the reaction was monitored by GC-MS. Aliquots were taken every 5 minutes over a period of 45-50 minutes and diluted with isopropanol to 10^{-4} M before analysis. The time at which the first point was taken varied slightly from one experiment to another. The concentration of product formed was determined by integrating the peak corresponding to azide product relative to the peak corresponding to the internal standard (response factor is equal to 1.14).





[Nitromethane], M	Time, min	[Product], M	V_0, M/sec
0.94	13	0,0128	1,20E-05
	18	0,0166	
	23	0,0201	
	28	0,0237	
	33	0,0274	
	38	0,0309	
	43	0,0344	
	48	0,0381	

[Nitromethane], M	Time, min	[Product], M	V_0, M/sec
1.41	5	0,0094	2,76E-05
	10	0,0196	
	15	0,0292	
	20	0,0372	
	25	0,0455	
	30	0,0528	
	35	0,0607	
	40	0,0675	

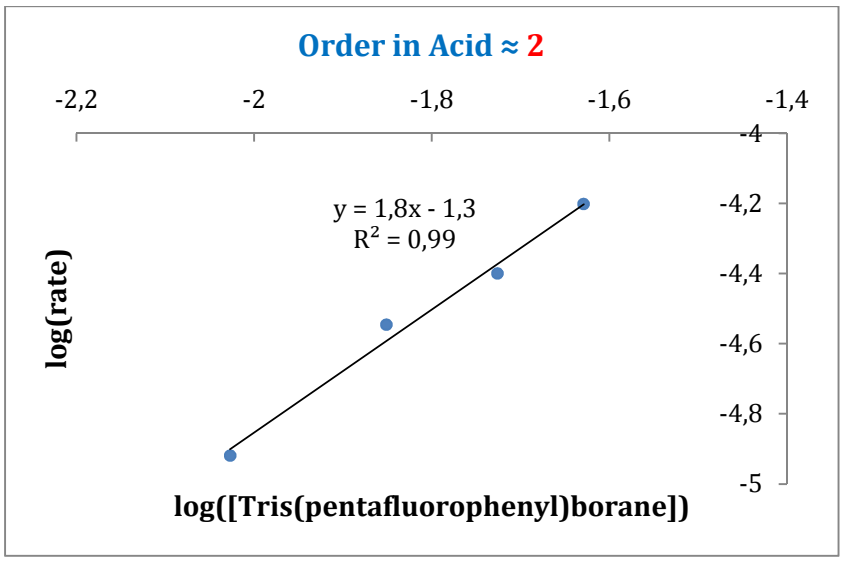
[Nitromethane], M	Time, min	[Product], M	V_0, M/sec
1.88	9	0,0258	4,80E-05
	14	0,0399	
	19	0,0572	
	24	0,0724	
	29	0,0865	
	34	0,1008	
	39	0,1129	
	44	0,1266	

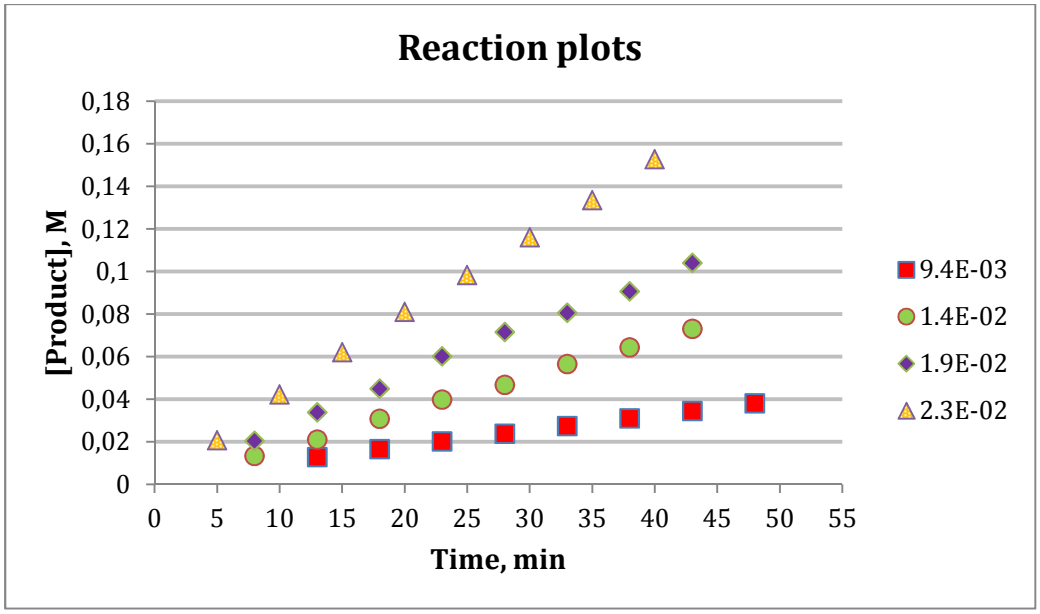
[Nitromethane], M	Time, min	[Product], M	V_0, M/sec
2.35	6	0,0285	6,97E-05
	11	0,0510	
	16	0,0742	
	21	0,0962	
	26	0,1162	
	31	0,1359	
	36	0,1574	
	41	0,1749	

[Nitromethane], M	Time, min	[Product], M	V_0, M/sec
2.82	11	0,0798	1,07E-04
	16	0,1127	
	21	0,1523	
	26	0,1813	
	31	0,2144	
	36	0,2447	
	41	0,2716	
	46	0,3042	

Order in acid

α,α-Dimethylbenzenepropanol **43i** (82 mg, 0.50 mmol), tris(pentafluorophenyl)borane hydrate (5.00 μmol, 7.50 μmol, 10.0 μmol, 12.5 μmol), nitromethane (27.0 μL, 30.5 mg 0.500 mmol) and *n*-dodecane (the internal standard, 34.0 μL, 25.5 mg, 0.150 mmol) were weighed in a 10 mL reaction tube with a stirring bar. Benzene (189 μL) was added, followed by trimethylsilyl azide (199 μL, 173 mg, 1.50 mmol). The resulting mixture was stirred at room temperature and the reaction was monitored by GC-MS. Aliquots were taken every 5 minutes over the period of 45-50 minutes and diluted with isopropanol to concentration 10^{-4} M before analysis. The time at which the first point was taken varied slightly from one experiment to another. The concentration of product formed was determined by integrating the peak corresponding to azide product relative to the peak corresponding to the internal standard (response factor is equal to 1.14) assuming that the reaction volume is equal to 0.532 mL (the total volume of liquid components).





[Tris(pentafluorophenyl)borane], M	Time, min	[Product], M	V_0, M/sec
9.4E-03	13	0,0128	1,20E-05
	18	0,0166	
	23	0,0201	
	28	0,0237	
	33	0,0274	
	38	0,0309	
	43	0,0344	
	48	0,0381	

[Tris(pentafluorophenyl)borane], M	Time, min	[Product], M	V_0, M/sec
1.4E-02	8	0,0133	2,84E-05
	13	0,0210	
	18	0,0308	
	23	0,0399	
	28	0,0468	
	33	0,0566	
	38	0,0643	
	43	0,0730	

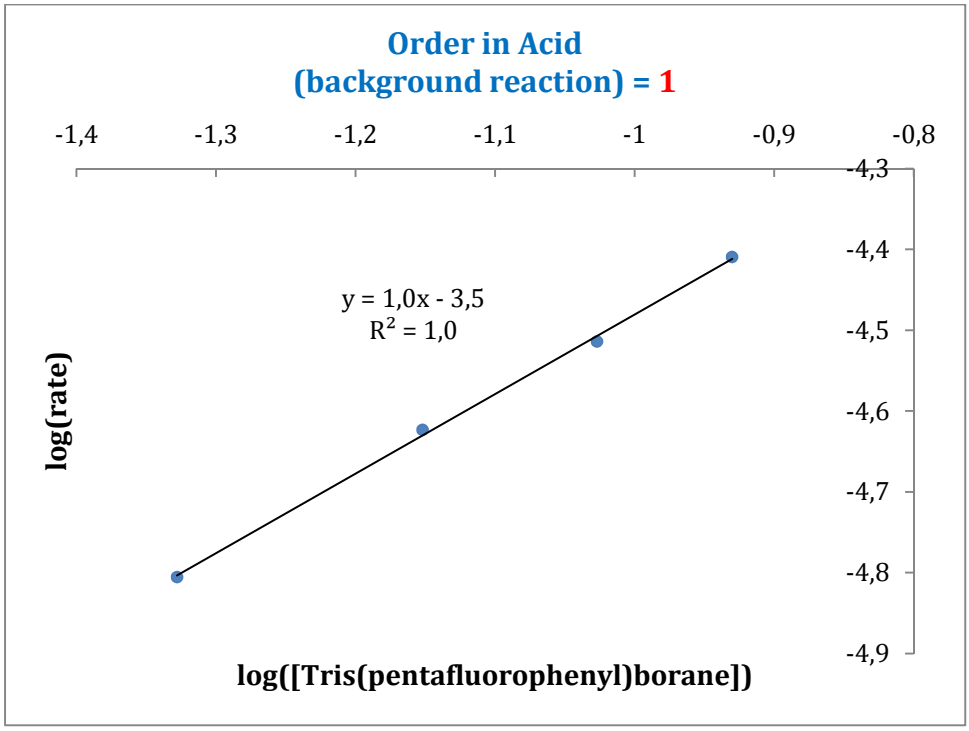
[Tris(pentafluorophenyl)borane], M	Time, min	[Product], M	V_0, M/sec
1.9E-02	8	0,0204	3,98E-05
	13	0,0338	
	18	0,0449	
	23	0,0601	
	28	0,0715	
	33	0,0806	
	38	0,0906	
	43	0,1040	

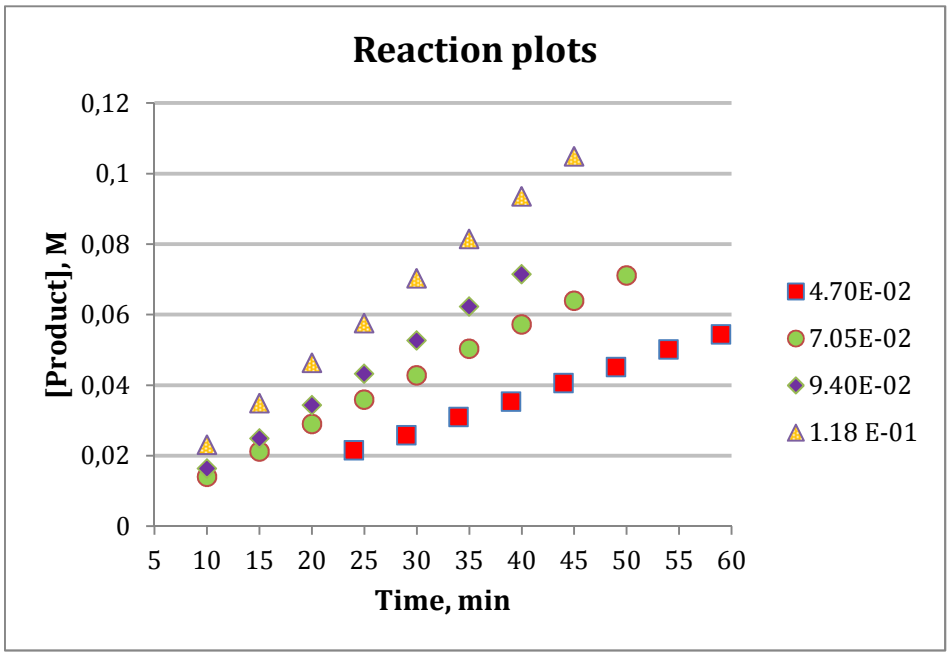
[Tris(pentafluorophenyl)borane], M	Time, min	[Product], M	V_0, M/sec
2.3E-02	5	0,0208	6,28E-05
	10	0,0423	
	15	0,0621	
	20	0,0811	
	25	0,0984	
	30	0,1161	
	35	0,1336	
	40	0,1527	

Order in acid (background reaction)

α,α-Dimethylbenzenepropanol **43i** (82 mg, 0.50 mmol), tris(pentafluorophenyl)borane hydrate (25.0 μmol, 37.5 μmol, 50.0 μmol, 62.5 μmol) and *n*-dodecane (the internal standard, 34.0 μL, 25.5 mg, 0.150 mmol) were weighed in a 10 mL reaction tube with a stirring bar. Benzene (216 μL) was added, followed by trimethylsilyl azide (199 μL, 173 mg, 1.50 mmol). The resulting mixture was stirred at room temperature and the reaction was monitored by GC-MS. Aliquots were taken every 5 minutes over the period of 60 minutes and diluted with isopropanol to 10^{-4} M before analysis. The time at which the first point was taken varied

slightly from one experiment to another. The concentration of product formed was determined by integrating the peak corresponding to azide product relative to the peak corresponding to the internal standard (response factor is equal to 1.14) assuming that the reaction volume is equal to 0.532 mL (the total volume of liquid components).





[Tris(pentafluorophenyl)borane], M	Time, min	[Product], M	V_0, M/sec
4.7E-02	24	0,0216	1.56E-05
	29	0,0259	
	34	0,0310	
	39	0,0354	
	44	0,0407	

	49	0,0452	
	54	0,0502	
	59	0,0545	

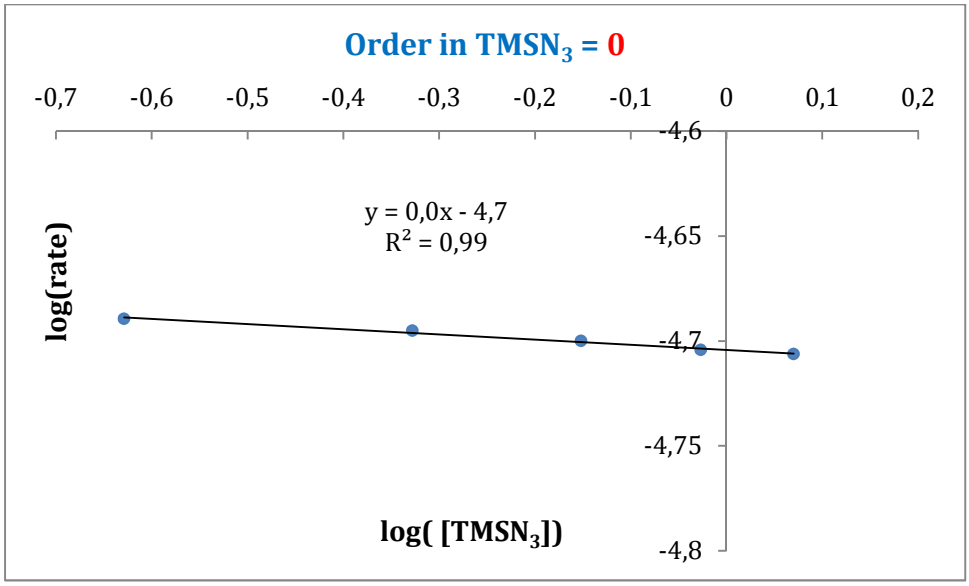
[Tris(pentafluorophenyl)borane], M	Time, min	[Product], M	V_0, M/sec
7.1E-02	10	0,0141	2.38E-05
	15	0,0212	
	20	0,029	
	25	0,0359	
	30	0,0428	
	35	0,0504	
	40	0,0573	
	45	0,0640	
	50	0,0712	

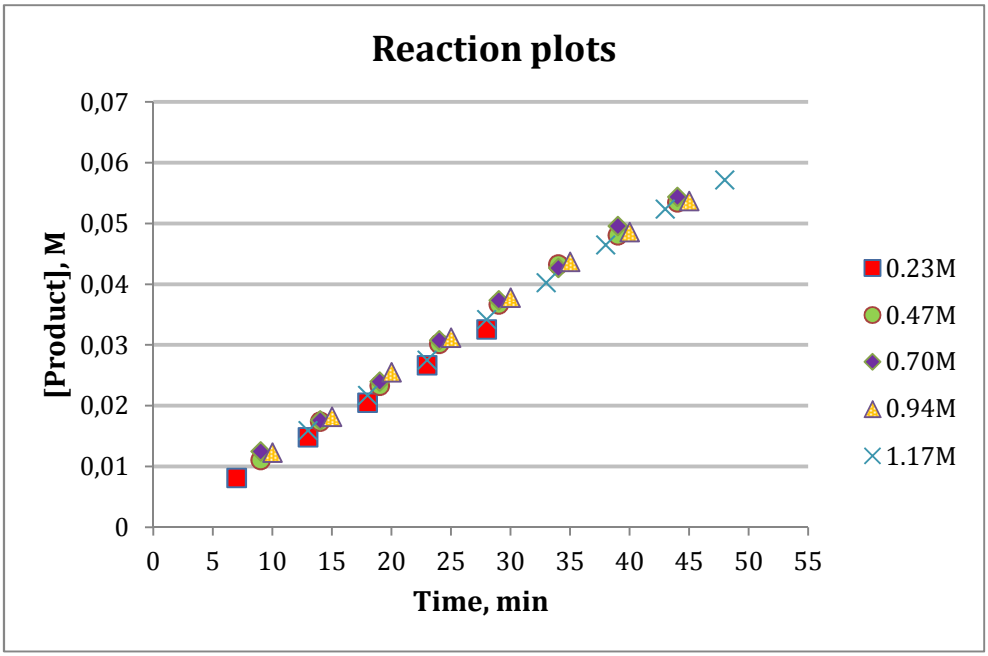
[Tris(pentafluorophenyl)borane], M	Time, min	[Product], M	V_0, M/sec
9.4E-02	10	0,0164	3.06E-05
	15	0,0250	
	20	0,0344	
	25	0,0433	
	30	0,0527	
	35	0,0624	
	40	0,0715	

[Tris(pentafluorophenyl)borane], M	Time, min	[Product], M	V_0, M/sec
1.2E-01	10	0,0231	3.89E-05
	15	0,0349	
	20	0,0464	
	25	0,0576	
	30	0,0703	
	35	0,0815	
	40	0,0936	
	45	0,1049	

Order in trimethylsilyl azide

Silyl ether **55a** (59 μL, 59 mg, 0.25 mmol), tris(pentafluorophenyl)borane hydrate (1.3 mg, 0.0025 mmol), nitromethane (81.0 μL, 91.6 mg, 1.50 mmol) and *n*-dodecane (the internal standard, 17.0 μL, 12.7 mg, 75.0 μmol) were weighed in a 10 mL reaction tube with a stirring bar. Benzene was added followed by trimethylsilyl azide (0.125 mmol, 0.250 mmol, 0.375 mmol, 0.500 mmol, 0.625 mmol). The amount of benzene added (358 μL, 342 μL, 326 μL, 309 μL, 293 μL, respectively) corresponds to 0.532 mL minus the amount of liquid components used. The resulting mixture was stirred at room temperature and the reaction was monitored by GC-MS. Aliquots were taken every 5 minutes over the period of 45-50 minutes and diluted with isopropanol to 10^{-4} M before analysis. The time at which the first point was taken varied slightly from one experiment to another. The concentration of product formed was determined by integrating the peak corresponding to azide product relative to the peak corresponding to the internal standard (response factor is equal to 1.14).





[Trimethylsilyl azide], M	Time, min	[Product], M	V_0, M/sec
0.23	7	0,0081	2,04E-05
	13	0,0148	
	18	0,0205	
	23	0,0267	
	28	0,0326	

[Trimethylsilyl azide], M	Time, min	[Product], M	V_0, M/sec
0.47	9	0,0111	2,02E-05
	14	0,0174	
	19	0,0233	
	24	0,0302	
	29	0,0367	
	34	0,0433	

	39	0,0481	
	44	0,0535	

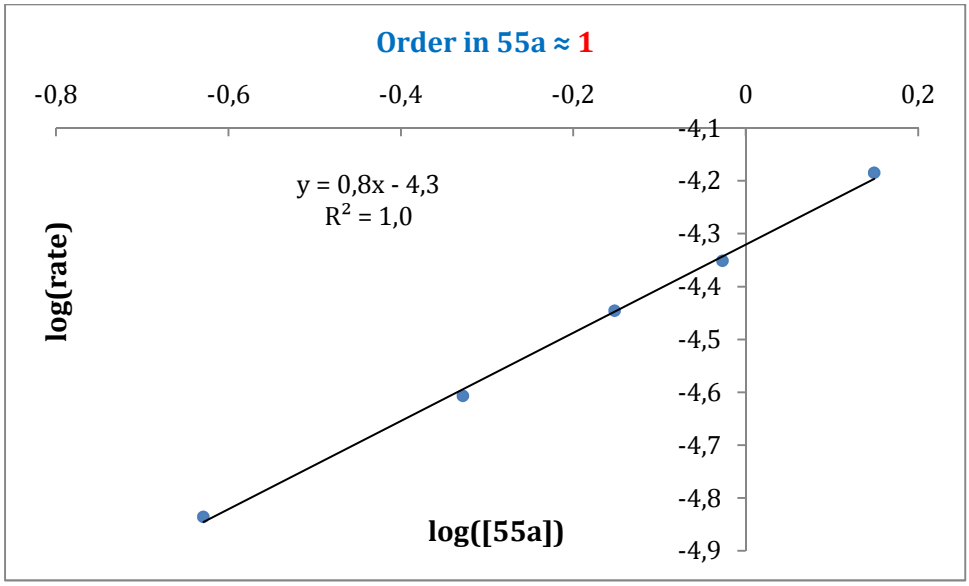
[Trimethylsilyl azide], M	Time, min	[Product], M	V_0, M/sec
0.70	9	0,0125	2,00E-05
	14	0,0176	
	19	0,0240	
	24	0,0308	
	29	0,0374	
	34	0,0427	
	39	0,0496	
	44	0,0544	

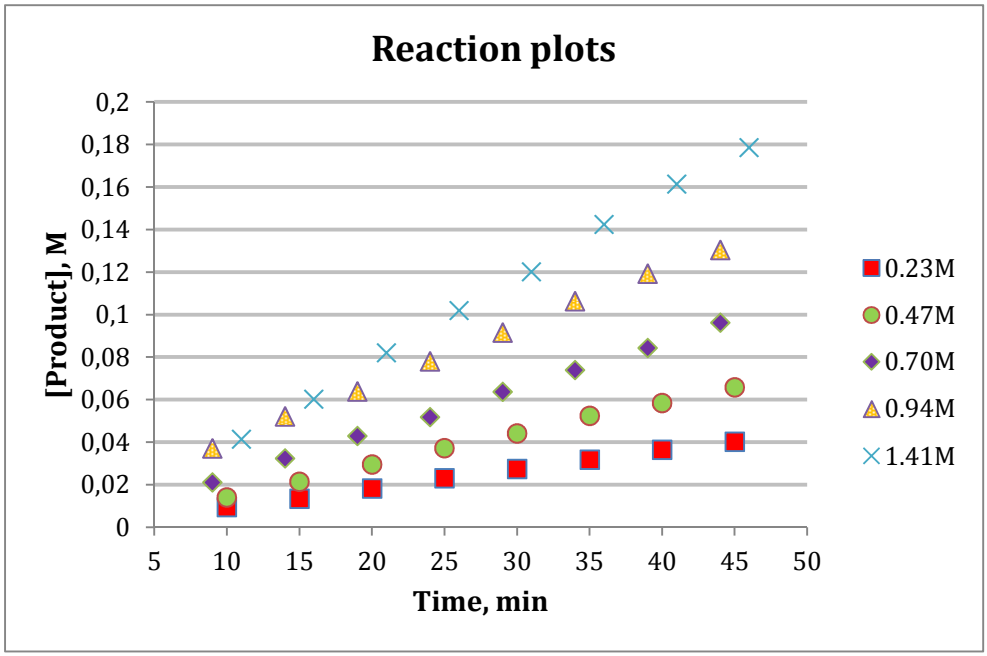
[Trimethylsilyl azide], M	Time, min	[Product], M	V_0, M/sec
0.94	10	0,0123	1,98E-05
	15	0,0182	
	20	0,0255	
	25	0,0312	
	30	0,0378	
	35	0,0437	
	40	0,0486	
	45	0,0537	

[Trimethylsilyl azide], M	Time, min	[Product], M	V_0, M/sec
1.17	13	0,0159	1,97E-05
	18	0,0217	
	23	0,0275	
	28	0,0342	
	33	0,0403	
	38	0,0465	
	43	0,0524	
	48	0,0572	

Order in 55a

Silyl ether **55a** (0.125 mmol, 0.250 mmol, 0.375 mmol, 0.500 mmol, 0.750 mmol), tris(pentafluorophenyl)borane hydrate (2.6 mg, 0.0050 mmol), nitromethane (54 μL, 61 mg, 1.0 mmol) and *n*-dodecane (the internal standard, 34.0 μL, 25.5 mg, 0.150 mmol) were weighed in a 10 mL reaction tube with a stirring bar. Benzene was added followed by trimethylsilyl azide (132 μL, 115 mg, 1.00 mmol). The amount of benzene added (282 μL, 253 μL, 224 μL, 194 μL, 135 μL, respectively) corresponds to 0.532 mL minus the amount of liquid components used. The resulting mixture was stirred at room temperature and the reaction was monitored by GC-MS. Aliquots were taken every 5 minutes over the period of 40-50 minutes and diluted with isopropanol to 10^{-4} M before analysis. The time at which the first point was taken varied slightly from one experiment to another. The concentration of product formed was determined by integrating the peak corresponding to azide product relative to the peak corresponding to the internal standard (response factor is equal to 1.14).





[Silyl ether], M	Time, min	[Product], M	V_0, M/sec
0.23	10	0,0095	1,46E-05
	15	0,0134	
	20	0,0183	
	25	0,0231	
	30	0,0274	
	35	0,0318	
	40	0,0364	
	45	0,0402	

[Silyl ether], M	Time, min	[Product], M	V_0, M/sec
0.47	10	0,0141	2,47E-05
	15	0,0214	
	20	0,0296	

	25	0,0372	
	30	0,0442	
	35	0,0524	
	40	0,0585	
	45	0,0659	

[Silyl ether], M	Time, min	[Product], M	V_0, M/sec
0.70	9	0,0211	3,58E-05
	14	0,0324	
	19	0,0430	
	24	0,0519	
	29	0,0637	
	34	0,0740	
	39	0,0844	
	44	0,0962	

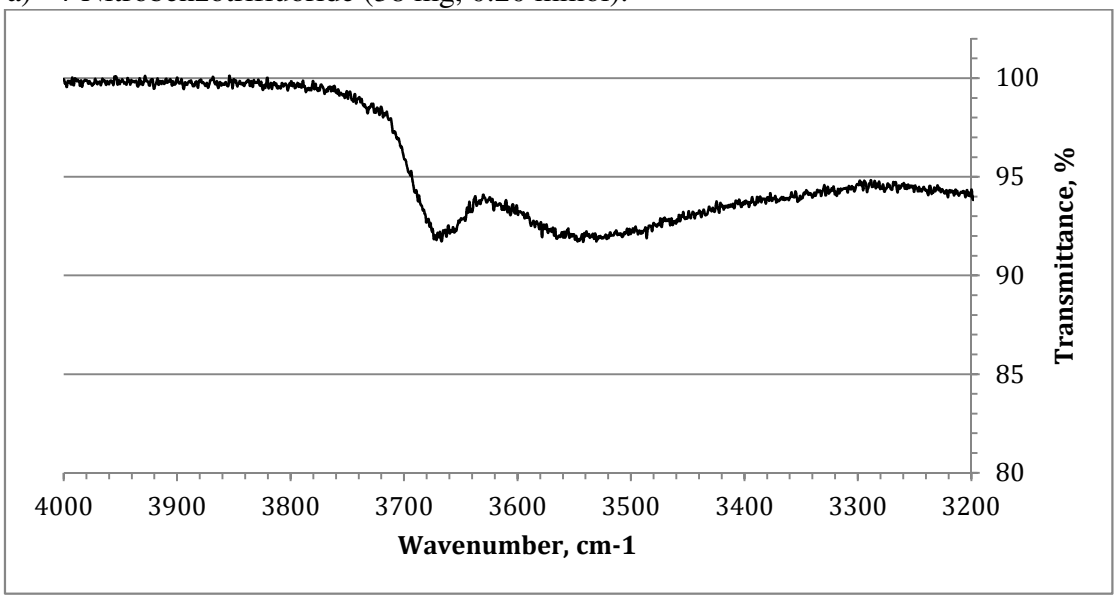
[Silyl ether], M	Time, min	[Product], M	V_0, M/sec
0.94	9	0,0370	4,45E-05
	14	0,0521	
	19	0,0638	
	24	0,0781	
	29	0,0916	
	34	0,1064	
	39	0,1193	
	44	0,1305	

[Silyl ether], M	Time, min	[Product], M	V_0, M/sec
1.41	11	0,0414	6,53E-05
	16	0,0602	
	21	0,0821	
	26	0,1020	
	31	0,1202	
	36	0,1425	
	41	0,1615	
	46	0,1786	

IR Experiments

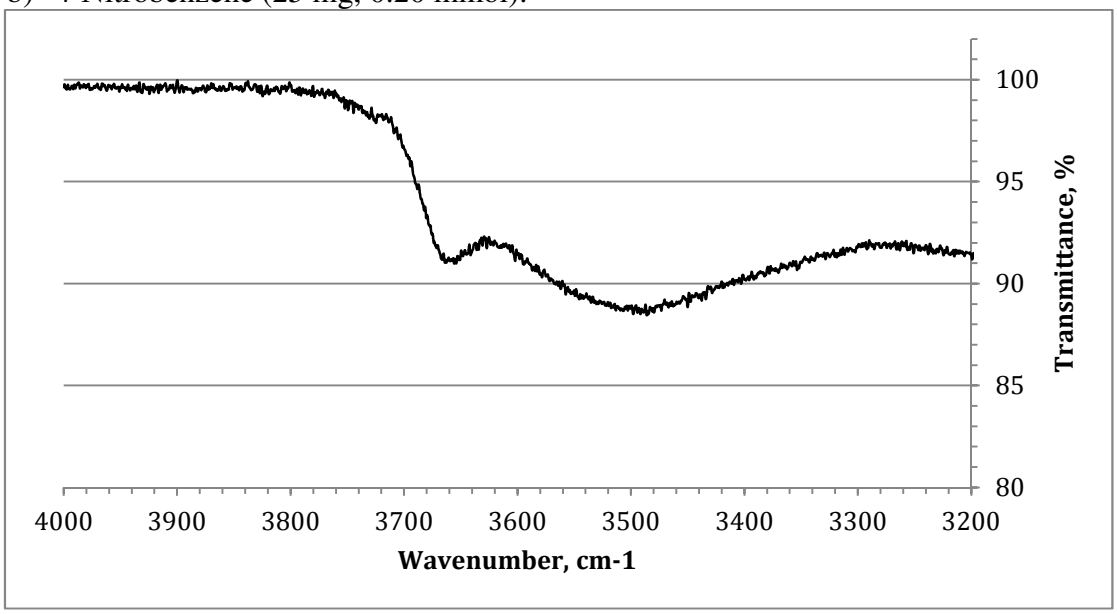
Effect of nitro compouds on the OH stretch:
The nitro compound (a-c) (0.20 mmol) and tris(pentafluorophenyl)borane hydrate (53 mg, 0.10 mmol) were mixed in a 2 ml vial and the content was dissolved in dichloromethane (0.10 mL). The resulting homogeneous solution was dropped on the surface for the measurements, waited untill dichloromethane was evaporated and IR spectrum was recorded.

a) 4-Nitrobenzotrifluoride (38 mg, 0.20 mmol):



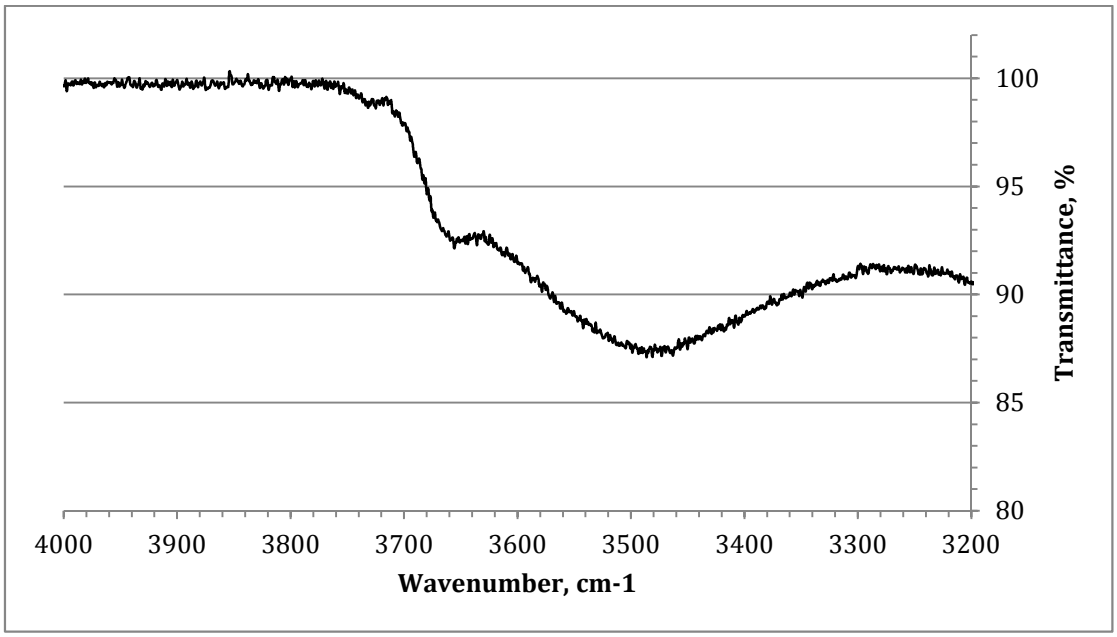
λ_{max} (cm^{-1}): 3665; 3523.

b) 4-Nitrobenzene (25 mg, 0.20 mmol):



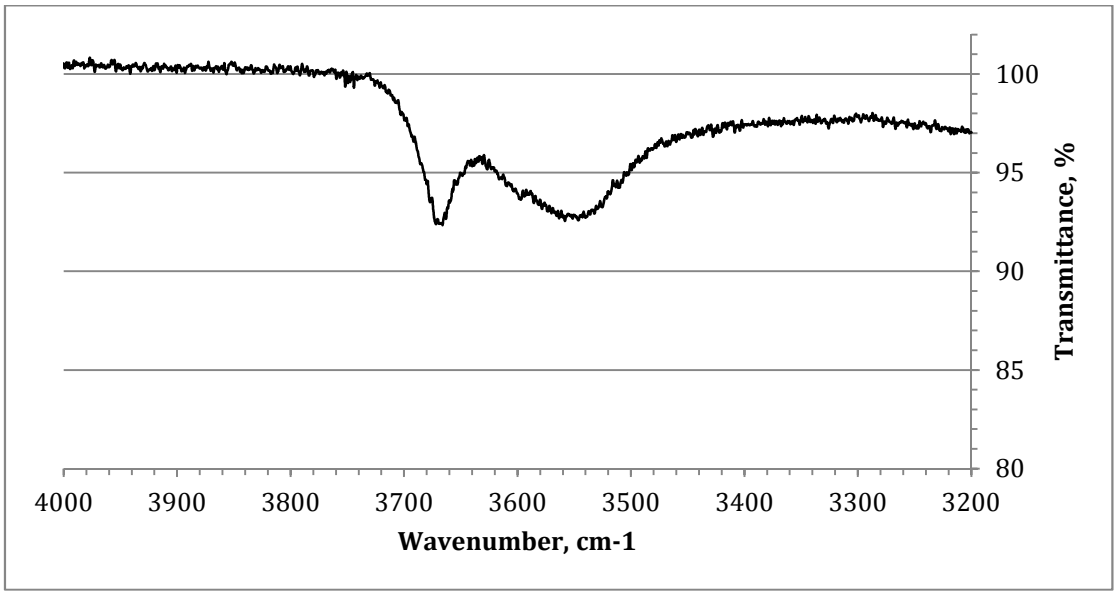
λ_{max}(cm^{-1}): 3659; 3480.

c) 4-Nitroanisole (31 mg, 0.2 mmol):



λ_{max} (cm^{-1}): 3648; 3465.

OH stretch in toluene:
In a 2 ml vial tris(pentafluorophenyl)borane (53 mg, 0.10 mmol) was mixed with a minimum amount of toluene (40 μL) to obtain homogeneous solution. The resulting mixture was dropped on the surface for the measurements and IR spectrum was recorded.

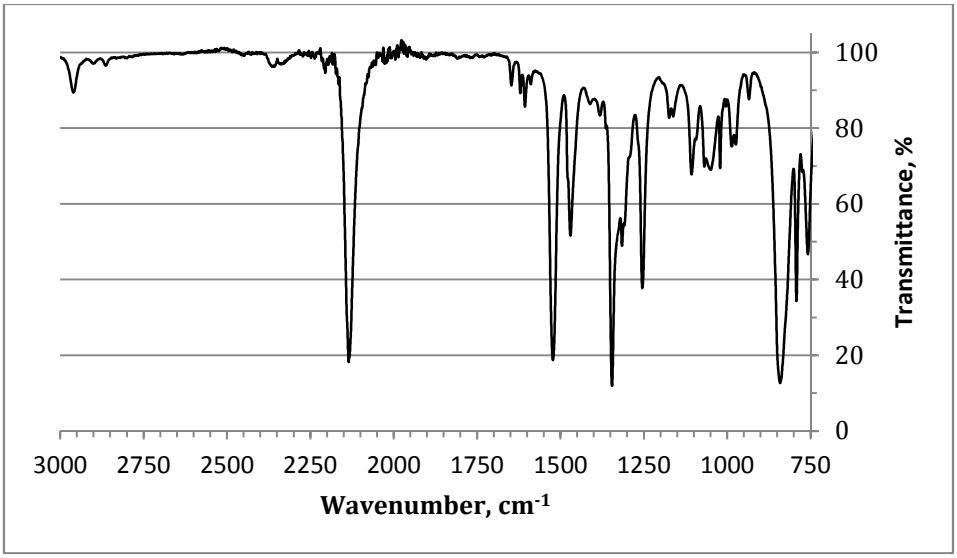


λ_{max} (cm^{-1}): 3667; 3546.

Influence of nitro compounds on the activation of $TMSN_3$:

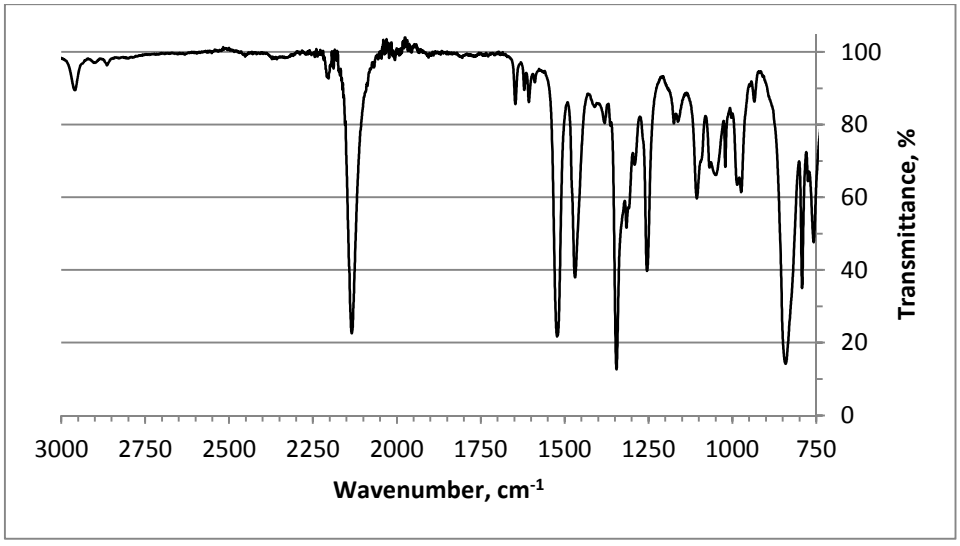
Tris(pentafluorophenyl)borane (5.0, 10, 20 mmol) and the appropriate solvent were weighed in a 2 mL vial in quantities, according to the experiments below (a-e). Trimethylsilyl azide (139 μL, 121 mg, 1.00 mmol) was added to the mixture the last and IR spectrum of the resulted solution was recorder.

a) Mixture of nitrobenzene (103 μL, 123 mg, 1.00 mmol), tris(pentafluorophenyl)borane (26 mg, 50 μmol) and trimethylsilyl azide (139 μL, 121 mg, 1.00 mmol).



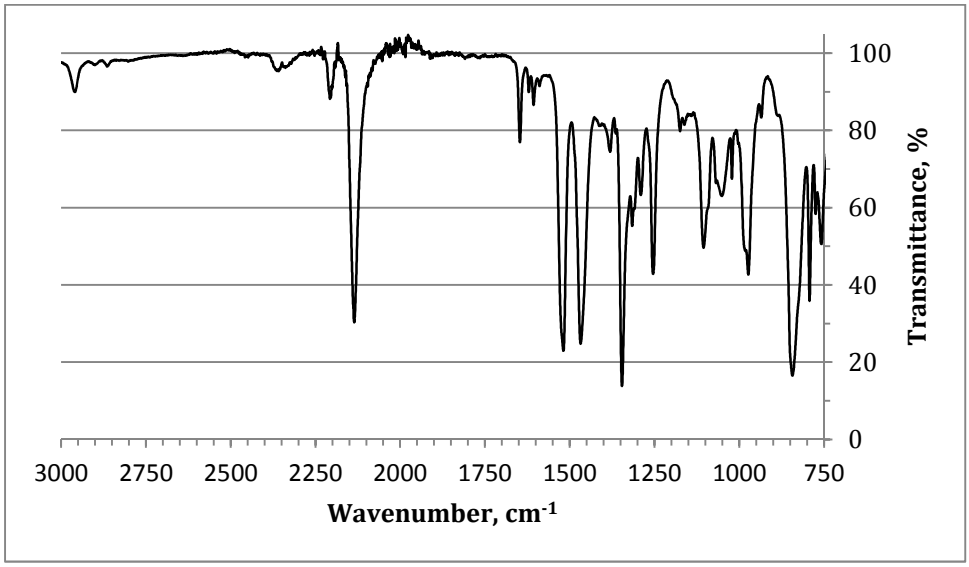
λ_{max} (cm^{-1}): 2207 (new), 2136 (azide N=N), 1522 (nitro N-O), 1345 (nitro N-O).

b) Mixture of nitrobenzene (103 μL, 123 mg, 1.00 mmol), tris(pentafluorophenyl)borane (53.0 mg, 100 μmol) and trimethylsilyl azide (139 μL, 121 mg, 1.00 mmol).



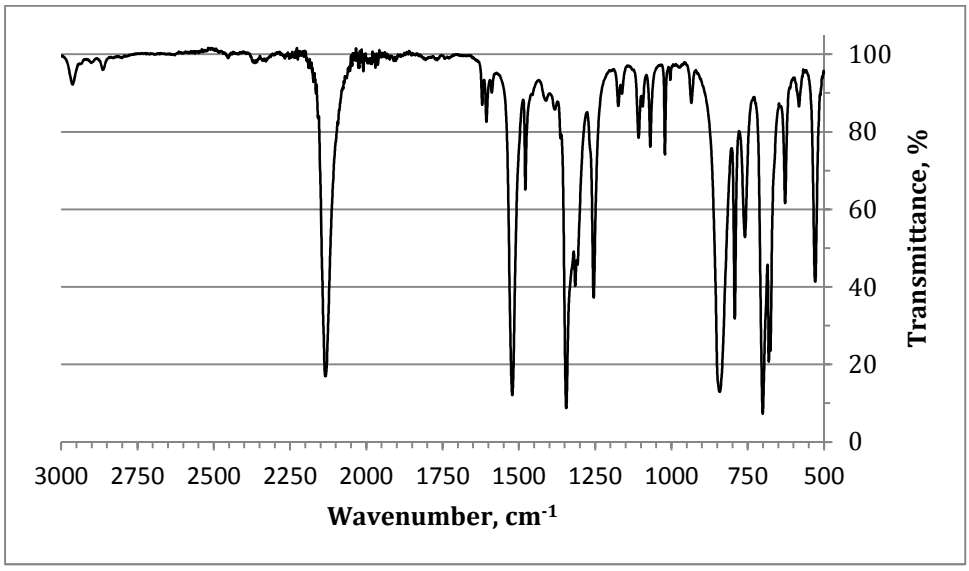
λ_{max} (cm^{-1}): 2207 (new), 2136 (azide N=N), 1521 (nitro N-O), 1345 (nitro N-O).

c) Mixture of nitrobenzene (103 μL, 123 mg, 1.00 mmol), tris(pentafluorophenyl)borane (106 mg, 200 μmol) and trimethylsilyl azide (139 μL, 121 mg, 1.00 mmol).



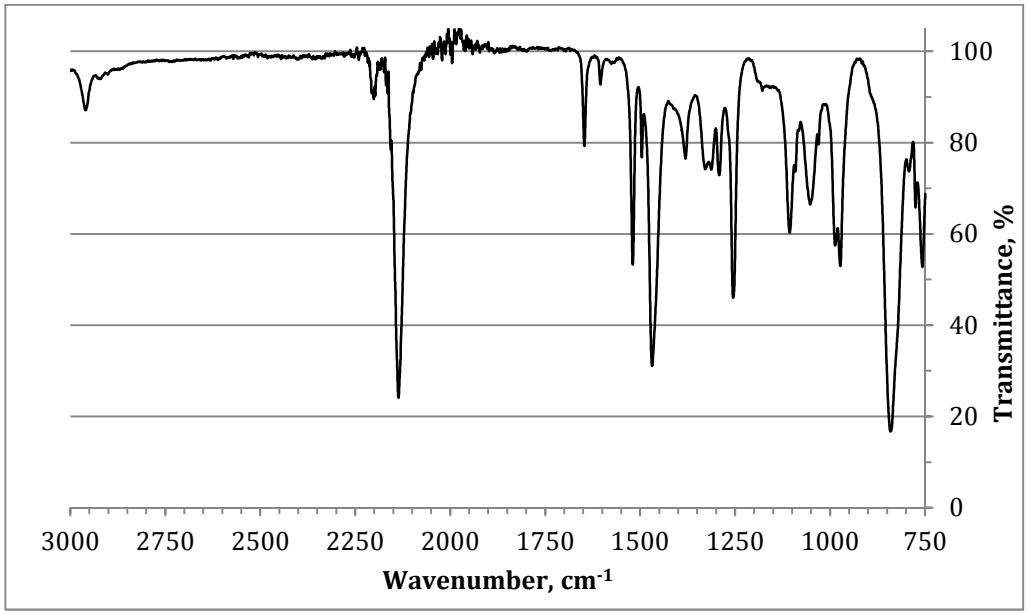
λ_{max} (cm^{-1}): 2207 (new), 2136 (azide N=N), 1520 (nitro N-O), 1345 (nitro N-O).

d) Mixture of nitrobenzene (103 μL, 123 mg, 1.00 mmol) and trimethylsilyl azide (139 μL, 121 mg, 1.00 mmol).



λ_{max} (cm^{-1}): 2136 (azide N=N), 1522 (nitro N-O), 1345 (nitro N-O).

e) Mixtue of toluene (106 μL, 1.00 mmol), tris(pentafluorophenyl)borane (106 mg, 200 μmol) and trimethylsilyl azide (139 μL, 121 mg, 1.00 mmol).



λ_{max} (cm^{-1}): 2200 (new), 2136 (azide N=N).

Rate law

In context of **Scheme 4.12**. *Plausible catalytic cycle for nitro-assisted Brønsted acid-catalyzed azidation:*

Given that the rate-determining step of the catalytic cycle is proposed to be silyl transfer from (**B**) to (**C**), the rate law can be expressed as follows:

$$rate = K_{Si}[\boldsymbol{B}][\boldsymbol{C}]$$

where, since the assembly of (**B**) is proposed to be saturated in $TMSN_3$, [**B**] can be expressed as:

$$[\boldsymbol{B}] = K_{eq2}[\boldsymbol{A}] = K_{eq1}K_{eq2}[RNO_2]^2[B(C_6F_5)_3 \bullet H_2O]^2$$

Thus,

$$rate = K_{Si}K_{eq1}K_{eq2}[RNO_2]^2[B(C_6F_5)_3 \bullet H_2O]^2[\boldsymbol{C}]$$

In context of **Scheme 4.14**. *Additional mechanistic considerations for a slower competing secondary pathway*

Given that the rate-determining step of the catalytic cycle is proposed to be silyl ether ionization, the rate law can be expressed as follows:

$$rate = K_{Si}[\boldsymbol{B}]$$

where, [**B**] can be expressed as:

$$[\boldsymbol{B}] = K_{eq2}[\boldsymbol{A}][\boldsymbol{C}] = K_{eq1}K_{eq2}[RNO_2]^2[B(C_6F_5)_3 \bullet H_2O]^2[\boldsymbol{C}]$$

Thus,

$$rate = K_{Si}K_{e1}K_{eq2}[RNO_2]^2[B(C_6F_5)_3 \bullet H_2O]^2[\boldsymbol{C}]$$

EXPERIMENTAL SECTION – CHAPTER 5

General information.

All defluorination reactions were performed in 2 mL disposable vials under an air atmosphere. All reactions to prepare starting materials were performed in air-dried flasks under nitrogen atmosphere, unless otherwise noted. Purification of reaction products was carried out by flash column chromatography using Merck silica gel (40-63 μm) or by Kugelrohr distillation using standard technique. Analytical thin layer chromatography (TLC) was performed on aluminum sheets pre-coated with silica gel 60 F254 (E. Merck), cut to size. Visualization was accomplished with UV light followed by dipping in a potassium permanganate, *p*-anisaldehyde and/or Seebach's staining solutions and heating.

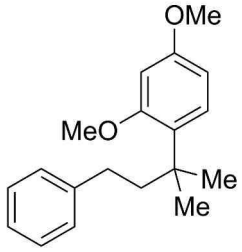
^{1}H NMR spectra were recorded on a Bruker Avance400 (400 MHz) spectrometer at ambient temperature unless otherwise noted and are reported in ppm using solvent as the internal standard ($CDCl_3$ at 7.26 ppm, C_6D_6 at 7.16 ppm, CD_3NO_2 at 4.33 ppm). Data are reported as: multiplicity (ap = apparent, br = broad, s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, sx = sextet, sp = septet, oct = octet, non = nonet, m = multiplet), integration and coupling constant(s) in Hz. ^{13}C NMR spectra were recorded on a Bruker Avance400 (100 MHz) spectrometer. Chemical shifts are reported in ppm from tetramethylsilane, with the residual solvent resonance employed as the internal standard ($CDCl_3$ at 77.0 ppm or C_6D_6 at 128.06 ppm). ^{19}F NMR spectra were recorded on a Bruker Avance400 (376 MHz) spectrometer and reported in ppm referred to CF_3COOH (-76.55 ppm) used as the external standard.

Melting points were measured using a *BÜCHI* Melting Point B-540 instrument. GCMS analysis was conducted on a GC System 7820A (G4320) connected to a MSD block 5977E (G7036A) using *Agilent* High Resolution Gas Chromatography Column: PN 19091S – 433UI, HP – 5MS UI, 30m×0.250mm, 0.25 Micron, SN USD 489634H.

Materials. Unless otherwise noted, all commercial materials were purchased from *Sigma-Aldrich* and used without further purification. The substrates 3-chloro-3-methyl-1-phenylbutane **76**,231 3-bromo-3-methyl-1-phenylbutane **82**,[231] 3-methoxy-3-methyl-1-phenylbutane **83**,[232] were prepared following a literature procedure. Tris(pentafluorophenyl)borane $B(C_6F_5)_3$ was purchased from *Alfa Aesar* and used under air, without any precaution to exclude moisture or air.

Isolation of Friedel-Crafts Product 79

To a 2 mL disposable vial containing 3-fluoro-3-methyl-1-phenylbutane **73** (42 mg, 0.25 mmol, 1 equiv) in nitromethane (0.25 mL, 1.0 M) was added 1,3-dimethoxybenzene (163 μL, 173 mg, 1.25 mmol, 5 equiv), followed by $B(C_6F_5)_3 \bullet H_2O$ (1.3 mg, 2.5 μmol, 1.0 mol%). The vial was capped and the mixture allowed to stir for 1 h at room temperature. After that time, the reaction mixture was filtered through a short bed of Celite and the solvent was removed under reduced pressure. The residue was purified by Kugelrohr distillation to deliver **79** (64 mg, 90% yield) in the form of a colorless oil.



3-(2,4-Dimethoxyphenyl)-3-methyl-1-phenylbutane **79. ^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.30-7.25 (m, 2H), 7.23-7.10 (m, 4H), 6.53 (d, *J* = 2.5 Hz, 1H), 6.50 (dd, *J* = 8.4 Hz, 2.5 Hz, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 2.34-2.26 (m, 2H), 2.19-2.12 (m, 2H), 1.43 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.5, 159.2, 144.0, 128.8, 128.4, 128.3, 128.2, 125.4, 103.4, 99.6, 55.4, 55.1, 43.3, 37.9, 32.2, 28.8. **HRMS** (ESMS) for $C_{19}H_{24}O_2$ + H: calcd. 285.1855; found 285.1849.

General Procedure for Alkylation of Arenes with 73

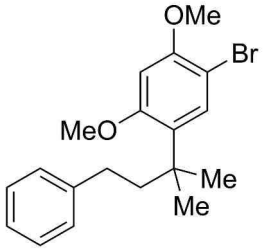
Condition A. To a 2 mL disposable vial containing 3-fluoro-3-methyl-1-phenylbutane **73** (42 mg, 0.25 mmol, 1 equiv) in nitromethane (0.25 mL, 1.0 M) was added the arene nucleophile (0.75 mmol, 3 equiv), followed by $B(C_6F_5)_3 \bullet H_2O$ (1.3 mg, 2.5 μmol, 1.0 mol%). The vial was capped and the mixture allowed to stir for 1 h at 23 ^oC. After completion, the reaction mixture was directly purified by flash chromatography on SiO_2.

Condition B. To a 2 mL disposable vial containing 3-fluoro-3-methyl-1-phenylbutane **1a** (84 mg, 0.50 mmol, 1 equiv) in nitromethane (0.50 mL, 1.0 M) was added the arene nucleophile (1.50 mmol, 3 equiv), followed by $B(C_6F_5)_3 \bullet H_2O$ (2.6 mg, 5.0 μmol, 1.0 mol%). The vial was

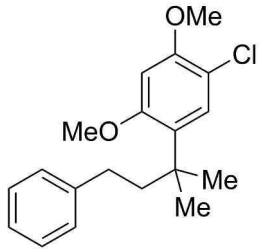
[231] Someya, H.; Yorimitsu, H.; Oshima, K. *Tetrahedron* **2010**, *66*, 5993.
[232] Dinnocenzo, J. P.; Zuilhof, H.; Lieberman, D. R.; Simpson, T. R.; Mckechney, M. W. *J. Am. Chem. Soc.* **1997**, *119*, 994.

capped and the mixture allowed to stir for 1 h at indicated temperature. After completion, the reaction mixture was filtered through a short bed of Celite and the solvent was removed under reduced pressure. The residue was purified by Kugelrohr distillation.

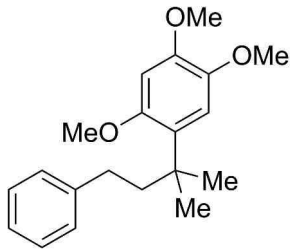
Spectral Data for all Alkylation Products (Nucleophile Scope):



3-(5-Bromo-2,4-dimethoxyphenyl)-3-methyl-1-phenylbutane **84a.** Synthesized according to the *general procedure B* at room temperature using 1-bromo-2,4-dimethoxybenzene (326 mg, 1.50 mmol). Isolated (137 mg, 75%) as a colorless oil that turns into a waxy solid after Kugelrohr distillation.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (s, 1H), 7.28-7.21 (m, 2H), 7.15 (t, *J* = 7.4 Hz, 1H), 7.11-7.07 (m, 2H), 6.49 (s, 1H), 3.92 (s, 3H), 3.86 (s, 3H), 2.30-2.25 (m, 2H), 2.14-2.08 (m, 2H), 1.39 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 158.7, 154.9, 143.6, 132.0, 130.2, 128.4, 128.3, 125.5, 101.5, 97.5, 56.5, 55.5, 43.0, 38.0, 32.1, 28.6. **HRMS** (ES) for $C_{19}H_{23}BrO_2$+H: calcd. 363.0960; found 363.0954. m.p. = 71-73 °C.

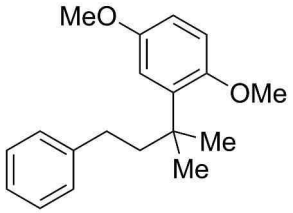


3-(5-Chloro-2,4-dimethoxyphenyl)-3-methyl-1-phenylbutane **84b**. Synthesized according to the *general procedure B* at room temperature using 1-chloro-2,4-dimethoxybenzene (259 mg, 1.50 mmol). Isolated (124 mg, 78%) as a colorless oil after Kugelrohr distillation.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26-7.20 (m, 3H), 7.13 (t, *J* = 7.3 Hz, 1H), 7.09-7.05 (m, 2H), 6.50 (s, 3H), 3.92 (s, 3H), 3.85 (s, 3H), 2.29-2.24 (m, 2H), 2.13-2.07 (m, 2H), 1.37 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 158.0, 153.9, 143.6, 129.7, 129.2, 128.4, 128.3, 125.5, 113.0, 97.7, 56.4, 55.6, 43.0, 38.0, 32.1, 28.6. **HRMS** (ES) for $C_{19}H_{23}ClO_2$: calcd. 318.1387; found 318.1381.

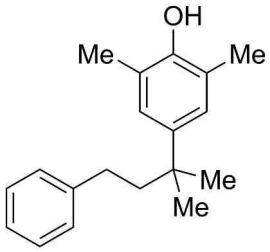


3-(2,4,5-Trimethoxyphenyl)-3-methyl-1-phenylbutane **84c** Synthesized according to the *general procedure B* at room temperature using 1,2,4-trimethoxybenzene (252 mg, 1.50 mmol). Isolated (132 mg, 84%) as a colorless oil after Kugelrohr distillation.

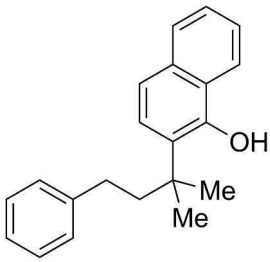
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28-7.22 (m, 2H), 7.18-7.09 (m, 3H), 6.89 (s, 1H), 6.57 (s, 1H), 3.92 (s, 3H), 3.89 (s, 3H), 3.84 (s, 3H), 2.35-2.29 (m, 2H), 2.17-2.11 (m, 2H), 1.43 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 152.8, 147.8, 143.8, 142.3, 128.4, 128.2, 128.0, 125.4, 113.4, 98.6, 57.1, 56.2, 56.0, 43.3, 38.1, 32.1, 28.7. **HRMS** (ES) for $C_{20}H_{26}O_3$: calcd. 314.1882; found 314.1876.



3-(2,5-Dimethoxyphenyl)-3-methyl-1-phenylbutane **84d.** Synthesized according to the *general procedure B* at room temperature using 2,6-dimethylphenol (346 mg, 2.50 mmol) and 500 μL of the nitromethane/1,1,1,3,3,3-hexafluoro-2-propanol solution as a solvent (1 to 1 volume ratio). Isolated (80 mg, 56%) as a colorless oil after Kugelrohr distillation.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27-7.21 (m, 2H), 7.17-7.09 (m, 3H), 6.91 (d, *J* = 3.1 Hz, 1H), 6.83 (d, *J* = 8.8 Hz, 1H), 6.73 (dd, *J* = 8.8 Hz, 3.1 Hz, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 2.33-2.27 (m, 2H), 2.19-2.14 (m, 2H), 1.41 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 153.4, 153.0, 143.8, 137.8, 128.4, 128.3, 125.4, 115.7, 112.1, 110.0, 55.7, 55.6, 43.1, 38.6, 32.1, 28.5. **HRMS** (ES) for $C_{19}H_{24}O_2$: calcd. 284.1776; found 284.1771.

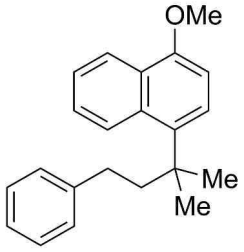


3-(3,5-Dimethyl-4-hydroxyphenyl)-3-methyl-1-phenylbutane **84e.** Synthesized according to the *general procedure B* at room temperature using 2,6-dimethylphenol (183 mg, 1.50 mmol). Isolated (127 mg, 95%) as a colorless oil after Kugelrohr distillation.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26-7.21 (m, 2H), 7.17-7.07 (m, 3H), 6.98 (s, 2H), 4.49-4.41 (br, 1H), 2.40-2.34 (m, 2H), 2.26 (s, 6H), 1.91-1.84 (m, 2H), 1.33 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 150.1, 143.5, 141.0, 128.4, 126.4, 125.6, 122.5, 46.8, 37.3, 31.5, 29.3, 16.4. **HRMS** (ESMS) for $C_{19}H_{24}O$: calcd. 268.1827; found 268.1822.

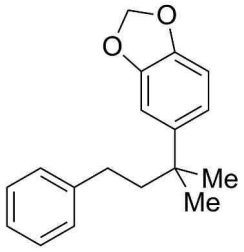


3-(4-Hydroxynaphthyl)-3-methyl-1-phenylbutane **84f** Synthesized according to the *general procedure A* using 1-naphthol (108 mg, 0.750 mmol). Isolated (63 mg, 87%) as a yellow oil after column chromatography (15% Et_2O in Petroleum ether). R_f = 0.62 (20% Et_2O in

Petroleum ether). The product degraded after several days at -20 °C. The presence of minor impurities prevented definitive descrimination between *ortho* and *para* regioisomeric structures by 2D NMR analysis. However, the *ortho* substitution pattern was assigned by analogy with literature ^{13}C data for 1-methyl-naphth-4-ol[233] and 2-methyl-naphthalen-1-ol.[234]
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.0 Hz, 1H), 7.91 (d, *J* = 8.0 Hz, 1H), 7.61-7.52 (m, 4H), 7.31 (t, *J* = 7.2 Hz, 2H), 7.25-7.17 (m, 3H), 5.64-5.52 (br, 1H), 2.50-2.43 (m, 2H), 2.39-2.31 (m, 2H), 1.67 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 149.0, 143.3, 133.4, 128.4, 128.3, 128.0, 127.8, 126.5, 125.6, 125.5, 125.0, 120.3, 119.7, 44.2, 38.3, 32.1, 29.1. **HRMS** (ESMS) for $C_{21}H_{22}O$ - H: calcd. 289.1592; found 289.1587.



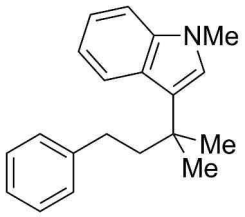
3-(4-Methoxynaphthyl)-3-methyl-1-phenylbutane **84g.** Synthesized according to the <u>*general procedure A*</u> using 1-methoxynaphthalene (109 μL, 119 mg, 0.750 mmol). Isolated (33 mg, 43%) of a yellow oil after column chromatography (Petroleum ether). R_f = 0.15 (Petroleum ether). The presence of minor impurities prevented definitive descrimination between *ortho* and *para* regioisomeric structures by 2D NMR analysis. The *para* substitution pattern was assigned by contrasting with **84f** and in accordance with literature ^{13}C data for 1-methoxy-4-methyl-naphthalene.[235]
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (dd, *J* = 8.1 Hz, 1.5 Hz, 1H), 8.42 (dd, *J* = 8.1 Hz, 1.8 Hz, 1H), 7.56-7.47 (m, 2H), 7.42 (d, *J* = 8.3 Hz, 1H), 7.23-7.18 (m, 2H), 7.12 (t, *J* = 7.2 Hz, 1H), 7.03-6.97 (m, 2H), 6.78 (d, *J* = 8.3 Hz, 1H), 4.02 (s, 3H), 2.41-2.36 (m, 2H), 2.29-2.22 (m, 2H), 1.65 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 154.3, 143.3, 135.8, 132.8, 128.4, 128.3, 127.0, 126.1, 125.6, 125.5, 124.8, 124.4, 123.2, 103.0, 55.5, 45.2, 39.3, 32.0, 30.8. **HRMS** (ES) for $C_{22}H_{24}O$: calcd. 304.1827; found 304.1822.



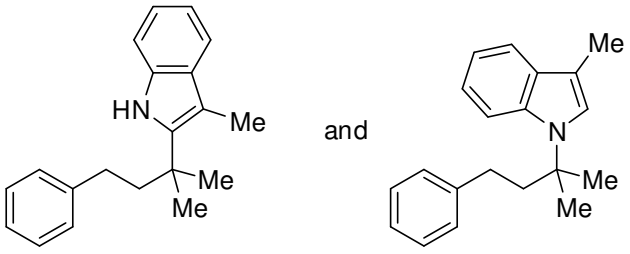
5-(2-methyl-4-phenylbutan-2-yl)benzo[d][1,3]dioxole **84h**. Synthesized according to the <u>*general procedure A*</u> using 1,3-benzodioxole (86 μL, 92 mg, 0.75 mmol) and 250 μL of the nitromethane/1,1,1,3,3,3-hexafluoro-2-propanol solution as a solvent (1 to 1 volume ratio). Isolated (40 mg, 60%) as a colorless oil (92% of the desired regioisomer together with the minor regioisomer and bisalkylation product) after column chromatography (Petroleum ether). R_f = 0.12 (Petroleum ether).

[233] Odedra, A.; Wu, C.-J.; Pratap, T. B.; Huang, C.-W.; Ran, Y.-F.; Liu. R.-S. *J. Am. Chem. Soc.* **2005**, *127*, 3406.
[234] Allen, A.; Le Marquand, P.; Burton, R.; Villeneuve, K.; Tam. W. *J. Org. Chem.* **2007**, *72*, 7849.
[235] Xing, L.; Wang, X.; Cheng, C.; Zhu, R.; Liu, B.; Hu. Y. *Tetrahedron* **2007**, *63*, 9382.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.23 (m, 2.18H, mixture), 7.20-7.09 (m, 3.14H. mixture); 6.93 (d, *J* = 1.9 Hz, 0.92H, major); 6.86 (dd, *J* = 8.2 Hz, 1.9 Hz, 0.92H, major), 6.84-6.75 (m, 1.15H, mixture), 5.96 (s, 1.85H, major), 5.93 (s, 0.15, mixture), 2.46-2.31 (m, 2.20H, mixture), 2.11-2.03 (m, 0.22H, mixture), 1.95-1.86 (m, 2.20H, mixture), 1.43 (s, 0.41H, minor), 1.36 (s, 5.70, mixture), 1.29 (s, 0.41, minor); **^{13}C NMR** (100 MHz, $CDCl_3$) major regioisomer δ 147.8, 145.4, 143.4, 143.2, 128.4, 128.3, 125.7, 118.8, 107.9, 106.9, 100.9, 47.0, 38.0, 31.5, 29.4. **HRMS** (ESMS) for $C_{18}H_{20}O_2$: calcd. 268.1463; found 268.1458.



3-(1-Methyl-1*H*-indol-3-yl)-3-methyl-1-phenylbutane **84i.** Synthesized according to the <u>*general procedure B*</u> at 90 °C using 1-methylindole (187 μL, 197 mg, 1.50 mmol). Isolated (115 mg, 83%) as a colorless oil after Kugelrohr distillation.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.1 Hz, 1H), 7.33 (d, *J* = 8.1 Hz, 1H), 7.26-7.19 (m, 3H), 7.16-7.06 (m, 4H), 6.83 (s, 1H), 3.77 (s, 3H), 2.44-2.38 (m, 2H), 2.18-2.12 (m, 2H), 1.49 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 143.6, 138.0, 128.5, 128.3, 126.5, 125.7, 125.5, 123.2, 121.3, 121.2, 118.5, 109.5, 45.2, 35.2, 32.7, 31.9, 29.1. **HRMS** (ESMS) for $C_{20}H_{23}N$: calcd. 277.1830; found 277.1825.

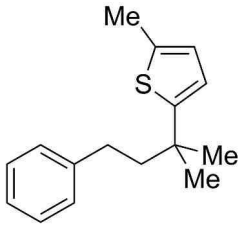


84j$_a$ **84j$_b$**

3-(3-Methyl-1*H*-indol-2-yl)-3-methyl-1-phenylbutane **84j$_a$**
3-(3-methyl-1H-indol-1-yl)-3-methyl-1-phenylbutane **84j$_b$**.
Synthesized according to the <u>*general procedure B*</u> at 90 °C using 3-methylindole (197 mg, 1.50 mmol). By Kugelrohr distillation, the fraction containing the nucleophile was distilled off and the following fraction containing the desired product was collected. The obtained colorless oil was additionally subjected to column chromatography purification (4% Et_2O in Petroleum ether) to give 9 mg of *N*-alkylated product (R_f = 0.30, 4% Et_2O in Petroleum ether) and 97 mg of *C*-alkylated product (R_f = 0.15, 4% Et_2O in Petroleum ether) both in the form of a colorless oil. Total yield 108 mg, 76%.
*C2-Alkylated product **84j$_a$**;major regioisomer present in quantities greater than 90% (GCMS control)*
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15-6.87 (m, 10H), 2.62-2.40 (m, 5H), 2.27-2.11 (m, 2H), 1.69-1.56 (m, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) major regioisomer δ 142.8, 139.9, 134.1, 130.6, 128.5, 128.4, 125.8, 121.1, 119.1, 118.0, 110.3, 106.0, 45.2, 36.5, 31.7, 28.1, 10.4. **HRMS** (ESMS) for $C_{20}H_{23}N$: calcd. 277.1830; found 277.1825.

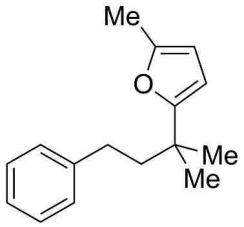
N-Alkylated product ***84j$_b$***

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65-7.58 (m, 2H), 7.23-7.11 (m, 5H), 7.08 (s, 1H), 7.00 (d, *J* = 7.4 Hz, 2H), 2.41-2.33 (m, 5H), 2.29-2.22 (m, 2H), 1.76 (s, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 142.1, 135.4, 130.5, 128.5, 128.4, 125.9, 124.0, 121.0, 119.3, 118.4, 113.0, 109.2, 58.2, 43.3, 30.5, 28.6, 9.8. **HRMS** (ESMS) for $C_{20}H_{23}N$: calcd. 277.1830; found 277.1825.



3-Methyl-3-(5-methylthienyl)-1-phenylbutane **84k.** Synthesized according to the <u>*general procedure A*</u> using 2-methylthiophene (73 μL, 74 mg, 0.75 mmol). Isolated (51 mg, 83%) as a colorless oil (85:15 mixture of regioisomers) after column chromatography (Petroleum ether). R_f = 0.50 (Petroleum ether).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.27 (m, 2H), 7.24-7.16 (m, 3H), 7.00 (s, 0.15H), 6.77 (d, *J* = 6.1 Hz, 0.14H), 6.67 (d, *J* = 3.4 Hz, 0.85H), 6.64-6.60 (m, 0.85H), 2.57-2.45 (m, 5H), 2.00-1.90 (m, 2H), 1.45 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) major regioisomer δ 153.2, 143.1, 137.2, 128.5, 128.4, 125.7, 124.5, 122.1, 47.9, 37.8, 31.5, 30.2, 15.5. **HRMS** (ESMS) for $C_{16}H_{20}S$+H: calcd. 245.1364; found 245.1358.



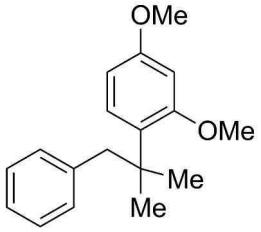
3-Methyl-3-(5-methylfuryl)-1-phenylbutane **84l.** Synthesized according to the <u>*general procedure A*</u> using 2-methylfuran (68 μL, 62 mg, 0.75 mmol) and 250 μL of the nitromethane/1,1,1,3,3,3-hexafluoro-2-propanol solution as solvent (1 to 1 v/v). Isolated 18 mg (32%) as a colorless oil after column chromatography (Petroleum ether). R_f = 0.42 (Petroleum ether).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.24 (m, 2H), 7.19-7.13 (m, 3H), 5.90 (d, *J* = 3.0 Hz, 1H), 5.88-5.84 (dt, *J* = 3.0 Hz, 1.0 Hz, 1H), 2.48-2.42 (m, 2H), 2.28 (d, *J* = 1.0 Hz, 3H), 1.92-1.86 (m, 2H), 1.31 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 161.0, 150.3, 143.3, 128.5, 128.4, 125.7, 105.6, 104.1, 44.3, 36.0, 31.5, 27.1, 13.7. **HRMS** (ESMS) for $C_{16}H_{20}O$: calcd. 228.1514; found 228.1509.

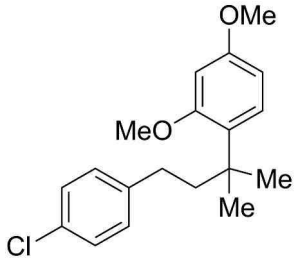
General Procedure for Alkylation of 1,3-Dimethoxybenzene

<u>*Condition C.*</u> To a 2 mL disposable vial containing tertiary aliphatic fluoride (0.50 mmol, 1 equiv), 1,3-dimethoxybenzene (196 μL, 207 mg, 1.50 mmol, 3 equiv) in nitromethane (0.50 mL, 1.0 M) was added $B(C_6F_5)_3$•H_2O (2.6 mg, 5.0 μmol, 1.0 mol%) under the stirring. The mixture was allowed to stir for 1 h at room temperature. After completion, the reaction mixture was filtered through a short bed of Celite and the solvent was removed under reduced pressure. The residue was purified by Kugelrohr distillation.

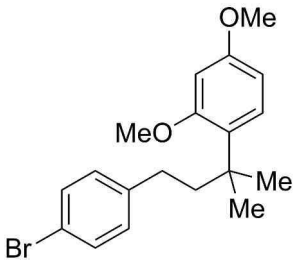
Spectral Data for all Alkylation Products (Substrate Scope)



2-(2,4-Dimethoxyphenyl)-2-methyl-1-phenylpropane **81a.** Synthesized according to the general procedure C using 2-fluoro-2-methyl-1-phenylpropane **80a** (76 mg, 0.50 mmol). Isolated (103 mg, 76%) as a yellow oil after Kugelrohr distillation.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19-7.14 (m, 3H), 6.95-6.89 (m, 3H), 6.60 (d, J = 2.5 Hz, 1H), 6.39 (dd, J = 8.5 Hz, 2.5 Hz, 1H), 3.96 (s, 3H), 3.84 (s, 3H), 3.18 (s, 2H), 1.40 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.3, 159.2, 140.3, 130.4, 128.7, 128.3, 127.4, 125.6, 103.4, 99.6, 55.3, 55.1, 46.4, 38.7, 28.4. **HRMS** (ESMS) for $C_{18}H_{22}O_2$+H: calcd. 271.1698; found 271.1693.

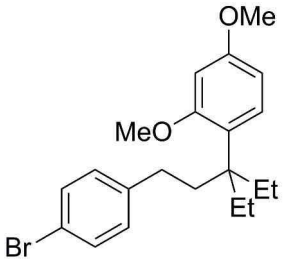


1-(4-Chlorophenyl)-3-(2,4-dimethoxyphenyl)-3-methylbutane **81b.** Synthesized according to the *general procedure C* using 1-(4-chlorophenyl)-3-fluoro-3-methylbutane **80d** (100 mg, 0.500 mmol). Isolated (121 mg, 76%) as a yellow oil after Kugelrohr distillation.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26-7.18 (m, 3H), 7.04 (d, *J* = 8.3 Hz, 2H), 6.54 (d, *J* = 2.4 Hz, 1H), 6.50 (dd, 8.4 Hz, 2.4 Hz, 1H), 3.86 (s, 6H), 2.32-2.25 (m, 2H), 2.19-2.11 (m, 2H), 1.44 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.4, 159.3, 142.3, 131.0, 129.7, 128.4, 128.3, 128.2, 103.5, 99.5, 55.3, 55.0, 43.1, 37.9, 31.5, 28.8. **HRMS** (ESMS) for $C_{19}H_{23}ClO_2$: calcd. 318.1387; found 318.1381.

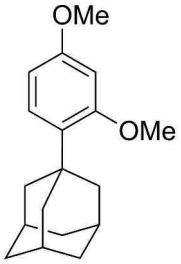


1-(4-Bromophenyl)-3-(2,4-dimethoxyphenyl)-3-methylbutane **81c.** Synthesized according to the *general procedure C* using 1-(4-bromophenyl)-2-fluoro-2-methylbutane **80c** (123 mg, 0.500 mmol). Isolated (148 mg, 81%) as a colorless oil after Kugelrohr distillation.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, *J* = 8.4 Hz, 2H), 7.19 (d, *J* = 8.5 Hz, 1H), 6.98 (d, *J* = 8.4 Hz, 2H), 6.52 (d, *J* = 2.5 Hz, 1H), 6.49 (dd, *J* = 8.5 Hz, 2.5 Hz, 1H), 3.84 (s, 6H), 2.28-2.12 (m, 2H), 2.16-2.09 (m, 2H), 1.42 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.4, 159.3,

142.8, 131.2, 130.2, 128.4, 128.2, 119.0, 103.5, 99.5, 55.3, 55.0, 43.1, 37.9, 31.6, 28.8. **HRMS** (ESMS) for $C_{19}H_{23}BrO_2$: calcd. 362.0881; found 362.0876.

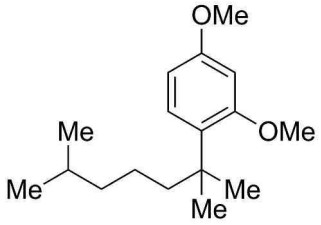


1-(4-Bromophenyl)-3-ethyl-3-(2,4-dimethoxyphenyl)-pentane **81d.** Synthesized according to the *general procedure C* using 1-(4-bromophenyl)-3-ethyl-3-fluoropentane **80d** (137 mg, 0.500 mmol). Isolated (148 mg, 76%) as a colorless oil after Kugelrohr distillation.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.3 Hz, 2H), 7.11 (d, *J* = 8.6 Hz, 1H), 6.96 (d, *J* = 8.3 Hz, 2H), 6.48 (d, *J* = 2.6 Hz, 1H), 6.45 (dd, *J* = 8.6 Hz, 2.6 Hz, 1H), 3.81 (s, 3H), 3.79 (s, 3H), 2.23-2.17 (m, 2H), 2.07-2.01 (m, 2H), 1.95-1.85 (m, 2H), 1.82-1.72 (m, 2H), 0.70 (t, *J* = 7.4 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.5, 159.1, 143.1, 131.3, 130.2, 129.7, 126.6, 119.1, 103.4, 99.6, 55.3, 55.1, 43.9, 36.9, 30.6, 26.6, 8.5. **HRMS** (ESMS) for $C_{21}H_{27}BrO_2$: calcd. 390.1194; found 390.1189.

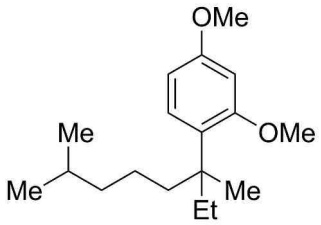


1-(2,4-Dimethoxy)-adamantane **81e.** Synthesized according to the *general procedure C* using 1-adamantylfluoride **80e** (77.1 mg, 0.500 mmol). The nucleophile fraction was distilled off by Kugelrohr distillation and the residue was purified by column chromatography (2% Et_2O in Petroleum ether) to give a white solid (95 mg, 70%). R_f = 0.38 (4% Et_2O in Petroleum ether).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (d, *J* = 8.6 Hz, 1H), 6.50 (d, *J* = 2.6 Hz, 1H), 6.47 (dd, *J* = 8.6 Hz, 2.6 Hz, 1H), 3.84 (s, 3H), 3.82 (s, 3H), 2.12-2.07 (m, 9H), 1.80 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.8, 158.8, 131.4, 126.9, 103.5, 99.8, 55.3, 55.0, 41.0, 37.3, 36.5, 29.3. The analytical data are in accordance with those reported in the literature.[236] m.p. = 102-103 °C.

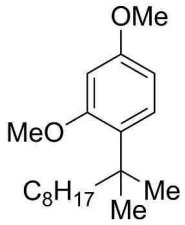
[236] Delgado-Abad, T.; Martínez-Ferrer, J.; Caballero, A.; Olmos, A.; Mello, R.; González-Núñez, M. E.; Pérez, P. J.; Asensio, G. *Angew. Chem. Int. Ed.* **2013**, *52*, 13298.



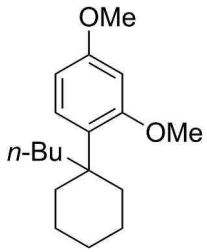
2-(2,4-Dimethoxyphenyl)-2,6-dimethylheptane **81f.** Synthesized according to the *general procedure C* using 2-fluoro-2,6-dimethylheptane **80f** (73.2 mg, 0.500 mmol). Isolated (95 mg, 72%) as a yellow oil after Kugelrohr distillation.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (d, *J* = 8.5 Hz, 1H), 6.49 (d, *J* = 2.6 Hz, 1H), 6.45 (dd, *J* = 8.5 Hz, 2.6 Hz, 1H), 3.83 (s, 3H), 3.82 (s, 3H), 1.81-1.74 (m, 2H), 1.51 (hep, *J* = 6.6 Hz, 1H), 1.35 (s, 6H), 1.15-1.09 (m, 2H), 1.06-0.98 (m, 2H), 0.83 (d, *J* = 6.6 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.5, 159.0, 129.6, 128.1, 103.3, 99.6, 55.3, 55.0, 41.3, 39.9, 37.7, 28.7, 27.8, 23.0, 22.8. **HRMS** (ESMS) for $C_{17}H_{28}O_2$+H: calcd. 265.2168; found 265.2162.



3-(2,4-Dimethoxyphenyl)-3,7-dimethyloctane **81j.** Synthesized according to the *general procedure C* using 3-fluoro-3,7-dimethyloctane **80j** (80.2 mg, 0.500 mmol). Isolated (111 mg, 80%) in form of a yellow oil as a mixture of regioisomers (87:13) after Kugelrohr distillation.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (d, *J* = 8.5 Hz, 0.13H), 7.06 (d, *J* = 8.5 Hz, 0.86H), 6.53-6.39 (m, 2H), 3.83-3.77 (m, 6H), 2.16-1.99 (m, 1.78H), 1.87-1.66 (m, 0.22H), 1.54-0.81 (m, 16.47H), 0.64 (t, *J* = 7.6 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) major regioisomer δ 159.5, 158.9, 129.4, 127.7, 103.2, 99.4, 55.2, 55.1, 41.5, 40.6, 40.0, 33.0, 27.8, 24.8, 22.9, 22.7, 9.2. **HRMS** (ESMS) for $C_{18}H_{30}O_2$+H: calcd. 279.2324; found 279.2319.

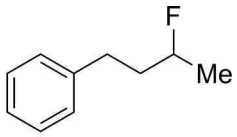


2-(2,4-Dimethoxyphenyl)-2-methyldecane **81h.** Synthesized according to the *general procedure C* using 2-fluoro-2-methyldecane **80h** (87 mg, 0.50 mmol). Isolated (119 mg, 81%) as a yellow oil after Kugelrohr distillation.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (d, *J* = 8.5 Hz, 1H), 6.50 (d, *J* = 2.5 Hz, 1H), 6.45 (dd, *J* = 8.5 Hz, 2.5 Hz, 1H), 3.83 (s, 6H), 1.84-1.76 (m, 2H), 1.36 (s, 6H), 1.32-1.19 (m, 10H), 1.06-0.98 (m, 2H), 0.92 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.5, 159.0, 129.6, 128.1, 103.3, 99.6, 55.3, 55.0, 41.1, 37.7, 32.1, 30.6, 29.7, 29.5, 28.7, 25.3, 22.8, 14.3. **HRMS** (ESMS) for $C_{19}H_{32}O_2$+H: calcd. 293.2481; found 293.2475.

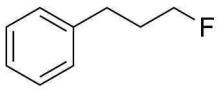


1-Butyl-(2,4-dimethoxyphenyl)-cyclohexane **81i.** Synthesized according to the *general procedure C* using 1-butyl-fluorocyclohexane **80i** (79.2 mg, 0.500 mmol). Isolated (88 mg, 64%) as a colorless oil after Kugelrohr distillation.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (d, *J* = 8.4 Hz, 1H), 6.49-6.42 (m, 2H), 3.81 (s, 3H), 3.77 (s, 3H), 2.18-2.07 (m, 2H), 1.77-1.62 (m, 4H), 1.59-1.51 (m, 2H), 1.47-1.37 (m, 4H), 1.16 (ap. sx, *J* = 7.4 Hz, 2H), 0.90-0.82 (m, 2H), 0.79 (t, *J* = 7.4 Hz, 3H);**^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.9, 158.7, 129.9, 127.7, 103.4, 99.8, 55.3, 55.2, 41.4, 37.8, 36.1, 27.1, 26.5, 23.6, 22.8, 14.2. **HRMS** (ESMS) for $C_{18}H_{28}O_2$+H: calcd. 277.2168; found 277.2162.

Procedures for Preparation of Substrates for Selectivity Study



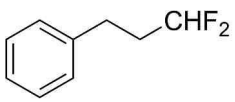
2-Fluoro-4-phenylbutane **82**. To a solution of 4-phenyl-2-butanol (774 μL, 751 mg, 5.00 mmol) in dry THF (50 mL) at -78 °C, was added (diethylamino)sulfur trifluoride (991 μL, 1.21 g, 7.50 mmol, 1.50 equiv). The mixture was slowly warmed to room temperature and stirred for 2 h. The reaction was diluted with EtOAc, washed with saturated aqueous sodium chloride solution, dried over sodium sulfate, filtered and evaporated. The residue was purified by silica gel chromatography (Petroleum ether) to afford product (406 mg, 53% yield) as a colorless oil. R_f = 0.39 (Petroleum ether).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.19 (m, 5H), 4.82-4.60 (m, 1H), 2.91-2.69 (m, 2H), 2.11-1.78 (m, 2H), 1.40 (dd, *J* = 24.1 Hz, 6.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 141.6, 128.6, 126.1, 90.1 (d, *J* = 165.1 Hz), 38.8 (d, *J* = 20.9 Hz), 31.5 (d, *J* = 4.8 Hz), 21.1 (d, *J* = 22.6 Hz); **^{19}F NMR** (376 MHz, $CDCl_3$; CF_3COOH – ext. std.) δ -173.9 – -174.4 (m). The analytical data are in accordance with those reported in the literature.[237]



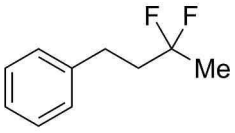
1-Fluoro-3-phenylpropane **83**. Synthesized in analogy with the procedure for preparation of 2-fluoro-4-phenylbutane **82** starting with 3-phenyl-1-propanol (681 μL, 681 mg, 5.00 mmol). Crude product was purified by silica gel chromatography (Petroleum ether) to afford a colorless oil (319 mg, 46% yield). R_f = 0.40 (Petroleum ether).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47-7.23 (m, 5H), 4.65-4.47 (dt, *J* = 47.3 Hz, 6.0 Hz, 2H), 2.91-2.87 (t, *J* = 7.4, 2H), 2.20-2.04 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 141.2, 128.6, 128.5, 126.1, 83.1 (d, *J* = 164.9 Hz), 32.2 (d, *J* = 19.8 Hz), 31.4 (d, *J* = 5.4 Hz); **^{19}F NMR**

[237] L'heureux, A.; Beaulieu, F.; Bennett, C.; Bill, D. R.; Clayton, S.; LaFlamme, F.; Mirmehrabi, M.; Tadayon, S.; Tovell, D.; Couturier, M. *J. Org. Chem.* **2010**, *75*, 3401.

(376 MHz, $CDCl_3$; CF_3COOH – ext. std.) δ -218.8 (tt, *J* = 48.0 Hz, 23.1 Hz). The analytical data are in accordance with those reported in the literature.[237]



1,1-Difluoro-3-phenylpropane **84**. Synthesized in analogy with the procedure reported by Daub and co-workers.[238] Hydrocinnamaldehyde (658 μL, 671 mg, 5.00 mmol) was dissolved in anhydrous dichloromethane (5 mL) in an oven-dried flask under dry nitrogen. This solution was cooled to 0 °C and (diethylamino)sulfur trifluoride (991 μL, 1.21 g, 7.50 mmol, 1.50 equiv) was added via syringe over a 1 min period. The reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction was diluted with CH_2Cl_2, washed with saturated aqueous sodium chloride solution, dried over sodium sulfate, filtered and evaporated. The residue was purified by silica gel chromatography (Petroleum ether) to afford product (197 mg, 25% yield) as a colorless oil. R_f = 0.32 (Petroleum ether).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.19 (m, 5H), 5.83 (tt, *J* = 56.7 Hz, 4.4 Hz, 1H), 2.82 (t, *J* = 7.9 Hz, 2H), 2.26-2.09 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 140.1, 128.8, 128.4, 126.5, 116.8 (t, *J* = 239.2 Hz), 35.8 (t, *J* = 21.5 Hz), 28.5 (t, *J* = 6.1 Hz); **^{19}F NMR** (376 MHz, $CDCl_3$; CF_3COOH – ext. std.) δ -115.9 (dt, *J* =56.7 Hz, 17.2 Hz). The analytical data are in accordance with those reported in the literature.[239]



3,3-Difluoro-1-phenylbutane **85**. Synthesized in analogy with the procedure for preparation of 1,1-difluoro-3-phenylpropane **84** starting with 4-phenyl-2-butanone (748 μL, 741 mg, 5.00 mmol). Crude product was purified by silica gel chromatography (Petroleum ether) to afford a colorless oil (221 mg, 26% yield). R_f = 0.30 (Petroleum ether).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.19 (m, 5H), 2.89-2.81 (m, 2H), 2.27-2.11 (m, 2H), 1.66 (t, *J* = 18.4 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 140.8, 128.7, 128.4, 126.4, 123.9 (t, *J* = 238.3 Hz), 40.0 (t, *J* = 25.4 Hz), 29.0 (t, *J* = 4.9 Hz), 23.6 (t, *J* = 27.9 Hz); **^{19}F NMR** (376 MHz, $CDCl_3$; CF_3COOH – ext. std.) δ -90.1 (qt, *J* =18.4 Hz, 16.2 Hz). **HRMS** (EI) for $C_{10}H_{12}F_2$: calcd. 170.0907; found 170.0902.

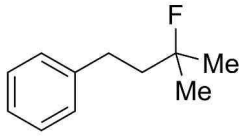
Procedures for preparation of tertiary aliphatic fluorides 73, 80a-j

Condition D. To a solution of alcohol (5.0 mmol) in dry THF (30 mL) at -78 °C, was added (diethylamino)sulfur trifluoride (1.32 mL, 1.61 g, 10.0 mmol, 2.00 equiv). The mixture was slowly warmed to room temperature and stirred for 2 h. The reaction was diluted with Et_2O, washed with precooled saturated aqueous sodium chloride solution, dried over sodium sulfate, filtered and evaporated on the rotary evaporator (< 20 °C). The residue was purified by silica gel chromatography (Petroleum ether) to afford the product.
Condition E. To a solution of alcohol (9.75 mmol) in dry CH_2Cl_2 (30 mL) at -78 °C, was added (diethylamino)sulfur trifluoride (2.60 mL, 3.14 g, 19.5 mmol, 2.00 equiv). The mixture

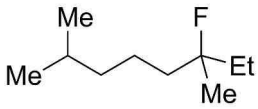
[238] Daub, G. W.; Zuckermann, R. N.; Johnson, W. S. *J. Org. Chem.* **1985**, *50* (10), 1599–1602.
[239] Beaulieu, F.; Beauregard, L.-P.; Courchesne, G.; Couturier, M.; LaFlamme, F.; L'Heureux, A. *Org. Lett.* **2009**, *11*, 5050.

was slowly warmed to room temperature and stirred for 2 h. The reaction was diluted with CH_2Cl_2, washed with saturated aqueous sodium chloride solution, dried over sodium sulfate, filtered and evaporated on the rotary evaporator (< 20 °C). The residue was purified by silica gel chromatography (Petroleum ether) to afford the product.

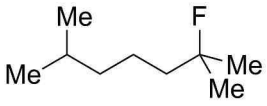
Spectral Data for all Tertiary Aliphatic Fluorides



3-Fluoro-3-methyl-1-phenylbutane **73**. Synthesized according to the *procedure E* starting with *α*,*α*-dimethylbenzenepropanol **43i** (1.65 mL, 1.60 g, 9.75 mmol). Isolated (1.34 g, 83%) as a colorless oil after column chromatography (Petroleum ether). R_f = 0.26 (Petroleum ether).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.16 (m, 5H), 2.77-2.69 (m, 2H), 2.00-1.87 (m, 2H), 1.42 (d, *J* = 21.4 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 142.2, 128.6, 128.4, 126.0, 95.4 (d, *J* = 165.8 Hz), 43.5 (d, *J* = 23.0 Hz), 30.4 (d, *J* = 5.3 Hz), 26.8 (d, *J* = 25.1 Hz); **^{19}F NMR** (376 MHz, $CDCl_3$; CF_3COOH – ext. std.) δ -137.6 (ap. non, *J* = 20.9 Hz). The analytical data are in accordance with those reported in the literature.[240]

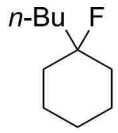


3-Fluoro-3,7-dimethyloctane **80j**. Synthesized according to the *procedure E* starting with 3,7-dimethyl-3-octanol (1.86 mL, 1.54 g, 9.75 mmol). Isolated (565 mg, 36%) as a colorless oil after column chromatography (Petroleum ether). R_f = 0.58 (Petroleum ether).
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.68-1.50 (m, 5H), 1.39-1.32 (m, 2H), 1.28 (d, *J* = 21.9 Hz, 3H), 1.21-1.14 (m, 2H), 0.92 (t, *J* = 7.6 Hz, 3H), 0.88 (d, *J* = 6.7 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 97.9, 39.5, 39.4 (d, *J* = 23.0 Hz), 32.4 (d, *J* = 23.2 Hz), 28.1, 23.9 (d, *J* = 25.0 Hz), 22.7, 21.5 (d, *J* = 5.9 Hz), 8.1 (d, *J* = 6.8 Hz); **^{19}F NMR** (376 MHz, $CDCl_3$; CF_3COOH – ext. std.) δ -144.3 (ap. oct, *J* = 20.9 Hz). **HRMS** (EI) for $C_{10}H_{21}F$ – HF: calcd. 140.1565; found 140.1559.

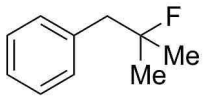


2-Fluoro-2,6-dimethylheptane **80f**. Synthesized according to the *procedure E* starting with 2,6-dimethyl-2-heptanol (937 mg, 6.50 mmol). Isolated (253 mg, 36%) as a colorless oil after column chromatography (Petroleum ether). R_f = 0.63 (Petroleum ether).
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.63-1.50 (m, 3H), 1.42-1.27 (m, 8H), 1.22-1.14 (m, 2H), 0.88 (d, *J* = 6.7 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 95.9, 41.8 (d, *J* = 22.3 Hz), 39.4, 28.1, 26.8 (d, *J* = 24.3 Hz), 22.7, 21.9 (d, *J* = 5.3 Hz); **^{19}F NMR** (376 MHz,$CDCl_3$; CF_3COOH – ext. std.) δ -144.3 (ap. non, *J* = 20.7 Hz). **HRMS** (EI) for $C_9H_{19}F$ – HF: calcd. 126.1409; found 126.1404.

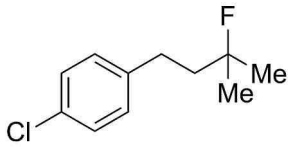
[240] Hirano, K.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2004**, *6*, 4873.



1-Butyl-fluorocyclohexane **80i**. Synthesized according to the *procedure E* starting with 1-butylcyclohexanol **43g** (938 mg, 6.00 mmol). Isolated (470 mg, 50%) as a colorless oil after column chromatography (Petroleum ether). R_f = 0.66 (Petroleum ether).
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.84-1.74 (m, 2H), 1.65-1.20 (m, 14H), 0.90 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 96.2 (d, *J* = 169.7 Hz), 40.2 (d, *J* = 23.2 Hz), 35.2 (d, *J* = 22.9 Hz), 25.6, 25.2 (d, *J* = 4.6 Hz), 23.3, 22.2 (d, *J* = 3.2 Hz), 14.2; **^{19}F NMR** (376 MHz, $CDCl_3$; CF_3COOH – ext. std.) δ -153.9 (br). **HRMS** (EI) for $C_{10}H_{19}F$ – HF: calcd. 138.1409; found 138.1404.

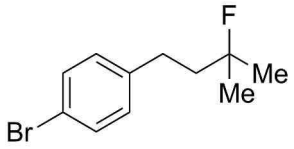


2-Fluoro-2-methyl-1-phenylpropane **80a**. Synthesized according to the *procedure E* starting with 2-methyl-1-phenyl-2-propanol **54k** (976 mg, 6.50 mmol). Isolated (625 mg, 63%) as a colorless oil after column chromatography (Petroleum ether). R_f = 0.32 (Petroleum ether).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.21 (m, 5H), 2.93 (d, *J* = 20.5 Hz, 2H), 1.35 (t, *J* = 21.4 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 137.1 (d, *J* = 4.1 Hz), 130.5, 128.2, 126.7, 95.3 (d, *J* = 168.3 Hz), 47.8 (d, *J* = 23.3 Hz), 26.8 (d, *J* = 24.5 Hz); **^{19}F NMR** (376 MHz, $CDCl_3$; CF_3COOH – ext. std.) δ -136.6 to -137.3 (m). The analytical data are in accordance with those reported in the literature.[241]

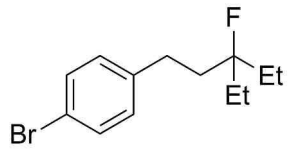


1-(4-Chlorophenyl)-3-fluoro-3-methylbutane **80b**. Synthesized according to the *procedure E* starting with 4-(4-chlorophenyl)-2-methyl-2-butanol **43k** (1.29 g, 6.50 mmol). Isolated (970 mg, 74%) as a colorless oil after column chromatography (Petroleum ether). R_f = 0.20 (Petroleum ether).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.4 Hz, 2H), 7.16 (d, *J* = 8.4 Hz, 2H), 2.77- 2.69 (m, 2H), 1.98-1.86 (m, 2H), 1.44 (d, *J* = 21.3 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 140.6, 131.7, 129.8, 128.7, 95.2 (d, *J* = 166.5 Hz), 43.3 (d, *J* = 23.0 Hz), 29.7 (d, *J* = 5.3 Hz), 26.8 (d, *J* = 24.8 Hz); **^{19}F NMR** (376 MHz, $CDCl_3$; CF_3COOH – ext. std.) δ -138.0 (ap. non, *J* = 20.9 Hz). **HRMS** (EI) for $C_{11}H_{14}ClF$: calcd. 200.0768; found 200.0763.

[241] Umemoto, T.; Singh, R. P.; Xu, Y.; Saito, N. *J. Am. Chem. Soc.* **2010**, *132*, 18199.



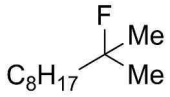
1-(4-Bromophenyl)-3-fluoro-3-methylbutane **80c**. Synthesized according to the *general procedure E* starting with 4-(4-bromophenyl)-2-methyl-2-butanol **43j** (544 mg, 2.23 mmol). Isolated (494 mg, 90%) as a yellowish oil after column chromatography (Petroleum ether). R_f = 0.32 (Petroleum ether).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.3 Hz, 2H), 7.08 (d, *J* = 8.3 Hz, 2H), 2.72- 2.65 (m, 2H), 1.95-1.84 (m, 2H), 1.41 (d, *J* = 21.4 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 141.3, 131.6, 130.2, 119.7, 95.2 (d, *J* = 165.4 Hz), 43.2 (d, *J* = 23.0 Hz), 29.8 (d, *J* = 5.0 Hz), 26.8 (d, *J* = 25.1 Hz);**^{19}F NMR** (376 MHz, $CDCl_3$; CF_3COOH – ext. std.) δ -138.0 (ap. non, *J* = 20.5 Hz). **HRMS** (EI) for $C_{11}H_{14}BrF$: calcd. 244.0263; found 244.0259.



1-(4-Bromophenyl)-3-ethyl-3-fluoropentane **80d**. Synthesized according to the *procedure E* starting with 1-(4-bromophenyl)-3-ethylpentan-3-ol **43m** (1.09 g, 4.00 mmol). Isolated (918 mg, 84%) as a yellow oil after column chromatography (Petroleum ether). R_f = 0.28 (Petroleum ether).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.4 Hz, 2H), 7.08 (d, *J* = 8.4 Hz, 2H), 2.66-2.60 (m, 2H), 1.91-1.81 (m, 2H), 1.76-1.64 (m, 4H), 0.94 (t, *J* = 7.6 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 141.4, 131.6, 130.2, 119.7, 99.2 (d, *J* = 170.5 Hz), 38.3 (d, *J* = 23.1 Hz), 29.2 (d, *J* = 5.8 Hz), 23.9 (d, *J* = 29.0 Hz), 7.8 (d, *J* = 7.3 Hz);**^{19}F NMR** (376 MHz, $CDCl_3$; CF_3COOH – ext. std.) δ -153.4 (ap. sp, *J* = 19.3 Hz). **HRMS** (EI) for $C_{13}H_{18}BrF$: calcd. 272.0576; found 272.0571.

1-Fluoroadamantane **80e.** Synthesized according to the *procedure E* starting with 1-adamantanol **31** (761 mg, 5.00 mmol). Isolated (635 mg, 82%) as a white solid after column chromatography (Petroleum ether). R_f = 0.33 (Petroleum ether).
^{1}H NMR (400 MHz, $CDCl_3$) δ 2.23 (s, 3H), 1.93-1.84 (m, 6H), 1.68-1.57 (m, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 92.5 (d, *J* = 183.5 Hz), 42.9 (d, *J* = 16.9 Hz), 36.0 (d, *J* = 2.2 Hz), 31.6 (d, *J* = 9.8 Hz); **^{19}F NMR** (376 MHz, $CDCl_3$; CF_3COOH – ext. std.) δ -128.3 to -128.5 (m). mp = 205-207 ^{o}C. The analytical data are in accordance with those reported in the literature.[242]

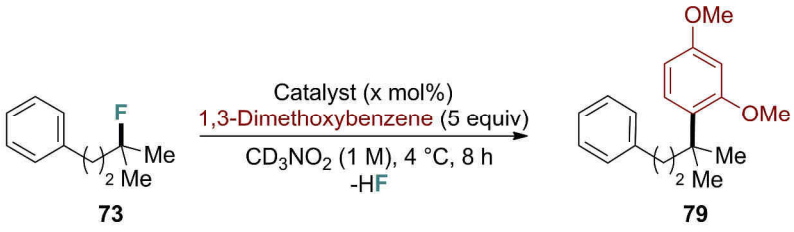
[242] Aoyama, M.; Fukuhara, T.; Hara, S. *J. Org. Chem.* **2008**, *73*, 4186.



2-Fluoro-2-methyldecane **80h**. Synthesized according to the *procedure E* starting with 2-methyldecan-2-ol **43b** (424 mg, 2.45 mmol). Isolated (353 mg, 83%) as a colorless oil after column chromatography (Petroleum ether). R_f = 0.28 (Petroleum ether).
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.64-1.53 (m, 2H), 1.41-1.21 (m, 18H), 0.88 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 96.0 (d, *J* = 164.5 Hz), 41.7 (d, *J* = 22.6 Hz), 32.0, 30.2, 29.7, 29.4, 26.8 (d, *J* = 25.3 Hz), 24.1 (d, *J* = 5.4 Hz), 22.8, 14.2; **^{19}F NMR** (376 MHz, $CDCl_3$; CF_3COOH – ext. std.) δ -135.8 (ap. nont, *J* = 21.6 Hz, 2.9 Hz). **HRMS** (EI) for $C_{11}H_{23}F$ – HF: calcd. 154.1722; found 154.1716.

4-(1-Fluoro-1-methylethyl)-1-methyl-cyclohexene **40j**. Synthesized according to the *procedure A* starting with α-terpineol (829 µL, 771 mg, 5.00 mmol). Isolated (260 mg, 33%) as a colorless oil after column chromatography (Petroleum ether). R_f = 0.43 (Petroleum ether).
^{1}H NMR (400 MHz, C_6D_6) δ 5.37-5.30 (br, 1H), 2.00-1.62 (m, 7H), 1.60 (s, 3H), 1.13 (dd, *J* = 21.4 Hz, 2.3 Hz, 6H); **^{13}C NMR** (100 MHz, C_6D_6) δ 133.7, 120.7, 96.7(d, *J* = 168.2 Hz), 43.9 (d, *J* = 22.2 Hz), 30.9, 27.0 (d, *J* = 6.9 Hz), 25.0 (d, *J* = 25.4 Hz), 24.1 (d, *J* = 4.7 Hz), 23.8 (d, *J* = 25.3 Hz), 23.6. **^{19}F NMR** (376 MHz, $CDCl_3$; CF_3COOH – ext. std.) δ -140.8 (spd, *J* = 22.5 Hz, 11.5 Hz). The analytical data are in accordance with those reported in the literature.[243]

Time-Dependent NMR Experiments



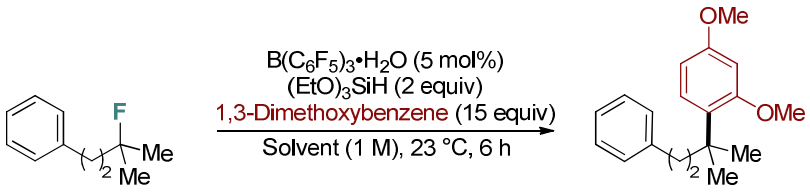
An oven dried NMR tube was charged with 3-fluoro-3-methyl-1-phenylbutane **73** (42 mg, 0.25 mmol, 1 equiv), nitromethane-d^3 (0.25 mL, 1.0 M) and 1,3-dimethoxybenzene (163 µL, 173 mg, 1.25 mmol, 5.00 equiv). The tube was precooled to 0 °C and the catalyst was added at this temperature. The sample was introduced into the NMR spectrometer at 4 °C and the reaction was monitored at that temperature.
Spectra were recorded every 10 min for 8 hours. Each spectrum was then analyzed to calculate the conversion of the starting material into the Friedel-Crafts products. The disappearance of a multiplet of the starting material (2.90-2.76 ppm, 2H) was monitored, along with the appearance of a multiplet for the desired compound (2.40-2.33 ppm, 2H).

[243] Lee, E.; Yandulov, D. V. *J. Fluor. Chem.* **2009**, *130*, 474.

Integrating both signals, a conversion percentage was calculated for each spectrum and plotted against time. The results are presented below.

Catalyst	*Loading, mg*	*Mol %*
$B(C_6F_5)_3•H_2O$	1.3	1.0
$B(C_6F_5)_3•H_2O$	13.3	10.0
TfOH	0.4	1.0
HF (48% in H_2O)	0.1	1.0

Study on the Activity of $B(C_6F_5)_3•H_2O$



73 **79**

An oven dried NMR tube was charged with 3-fluoro-3-methyl-1-phenylbutane **73** (33 mg, 0.20 mmol, 1.0 equiv), 1,3-dimethoxybenzene (391 μL, 415 mg, 3.00 mmol, 15.0 equiv), fresh C_6D_6 (0.1 mL), nitromethane (0.2 mL or not added), fluorobenzene (18.8 μL, 19.2 mg, 200 μmol, 1 equiv) and triethoxysilane (74 μL, 66 mg, 0.40 mmol, 2.00 equiv). The tube was capped and mixed by shaking. Tris(pentafluorophenyl)borane hydrate was added and the sample was introduced into the NMR spectrometer. The consumption of **73** was monitored for approximately a 6 hour period by ^{19}F NMR. Each spectrum was then analyzed separately by means of the relative integration of the nonet of **73** (-138.6 ppm, J = 20.9 Hz) against the internal standard peak (m, -113.1-113.3 ppm).

Marian DRYZHAKOV

Nitro-Assisted Brønsted Acid Catalysis: Activation of C(sp^3)–O and C(sp^3)–F Bonds

Résumé

Les alcools sont des partenaires électrophiles attractifs pour des réactions de substitution nucléophile puisque l'eau est le seul sous-produit de la réaction en présence de nucléophiles protiques. Malgré le fait que la réaction soit fortement intéressante, la portée des transformations catalytique reste limitée à une combinaison spécifique alcool/nucléophile, ce qui rend l'emploi d'un ensemble général de conditions catalytiques fortement élusif. Cette thèse décrit le développement d'un système général de catalyse doux pour l'activation d'une large gamme d'alcools π-activés ainsi que d'alcools aliphatiques abordant ainsi les limitations clés dans le domaine. $B(C_6F_6)_3$•H_2O, un acide de Brønsted fort quand il est combiné avec le nitrométhane, a été découvert comme étant un système catalytique idéal pour la substitution chimiosélective d'alcools en présence de fonctionnalités et de groupements protecteurs sensibles aux conditions acides sans le compromis typique entre vitesse de réaction, réactivité substrat/nucléophile et quantité de catalyseur. Plus particulièrement, un effet co-catalytique de composés nitro est décrit pour la réaction d'azidation des alcools aliphatiques tertiaires en employant $B(C_6F_6)_3$•H_2O, permettant, pour la première fois, un turnover catalytique. Sur la base des investigations cinétiques, électroniques et spectroscopiques qui ont été menées, des agrégats de composés nitro et d'acides liés par des intéractions hydrogènes sont proposé comme étant l'espèce catalytiques responsables de la cinétique de la catalyse observée. L'utilité des nouvelles conditions catalytiques a été étendue au-delà de l'activation d'alcool et appliquée au clivage des liaisons fortes C-F dans les réactions de Friedel-Crafts défluorinatives de fluorures aliphatiques tertiaires.

Mots clés: activation d'alcool, catalyse par un acide de Brønsted, composés nitro, fluorures aliphatiques tertiaires

Abstract

Alcohols are attractive electrophilic partners for nucleophilic substitution reactions as water is the only by-product in a reaction with protic nucleophiles. Despite being a highly desirable reaction, the scope of useful catalytic transformations remains limited to specific alcohol-nucleophile pairs and a general set of catalytic conditions remains elusive. This thesis describes the development of a general and mild catalyst system for the activation of a broad range of π-activated and aliphatic alcohols to address key limitations in the field. $B(C_6F_6)_3$•H_2O, a strong Brønsted acid, when combined with nitromethane has been found as a widely useful catalyst system for chemoselective alcohol substitution in the presence of acid sensitive functionalities and protecting groups without the typical compromises in reaction rates, substrate/nucleophile scope and catalyst loading. In particular, a co-catalytic effect of nitro compounds is described for the $B(C_6F_6)_3$•H_2O catalyzed azidation of tertiary aliphatic alcohols, enabling catalyst turnover for the first time. On the basis of kinetic, electronic, and spectroscopic investigations, higher order hydrogen-bonded aggregates of nitro compounds and acids are proposed as kinetically competent Brønsted acid catalysts at the origin of the enhanced reactivity. The utility of the new catalytic conditions has been extended beyond alcohol activation and applied to the cleavage of strong C–F bonds in defluorinative Friedel-Crafts reactions of tertiary aliphatic fluorides.

Key words: alcohol activation, Brønsted acid catalysis, nitro compounds, tertiary aliphatic fluorides