N-HALO ORGANIC COMPOUNDS AS CATALYSTS OR REAGENTS FOR COMPREHENSIVE TRANSFORMATION OF ALCOHOLS

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Doctoral Dissertation
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Doktorska disertacija

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Abstract

A group of organic molecules bearing an active *N*-halogen bond: *N*-halosuccinimides, 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis-tetrafluoroborate (*Selectfluor™ F-TEDA-BF_4)* and *N*-fluorobenzenesulfonimide (*Accufluor™ NFSi*) was introduced, tested and applied as new, efficient, non-metal and non-acidic catalysts for comprehensive direct transformation of organic compounds, bearing the hydroxyl functional group. The type of transformation, thus forming new C-C or C-heteroatom bonds in starting alcohol material, was found to depend on the presence and structure of different organic molecules acting as sources of corresponding nucleophile species. The reactions were selectively and efficiently performed under solvent-free reaction conditions, under high substrate reaction conditions or in aqueous media, thus contributing to green chemical profiles of these transformations.

Benzyl alcohols in the presence of substoichiometric amounts of named *N*-halo compounds, under solvent-free reaction conditions, gave symmetric ethers, while the presence of other alcohols (alkyl and primary benzyl alcohol) as nucleophile sources under high concentration reaction conditions resulted in the formation of the corresponding ethers. The named substrates, under solvent-free reaction conditions, in the presence of equimolar amounts of electron rich compounds, such as: phenyl substituted alkenes, heteroatom benzo-cyclenes, 1,3-dicarbonyl compounds or tertiary benzyl alcohols, bearing a vicinal hydrogen atom, efficiently and selectively resulted in the formation of the products bearing a new C-C bond, while in the presence of equimolar amounts of acetonitrile or anilines, the formation of products bearing a new C-N bond were observed. Comprehensive types of trimethyl substituted silanes were further used as sources of different nucleophiles, and the *N*-halo compounds catalyzed formation of halogenated, etherificated, isothiocyanated or silylated derivatives of simple alcohols were observed.

A new method for direct transformation of phenyl substituted tertiary alcohols, bearing a vicinal hydrogen atom, to vicinal halohydrins, halomethoxy derivatives or haloalkenes using equimolar amounts of *N*-halosuccinimides were discovered and tested on 1,1-diphenylethanol and 2-phenyl-2-propanol. The type of transformation and its selectivity was found to depend on the structure of alcohol and the structure of the nucleophile source (water, MeOH or AcOH).

Keywords: nucleophilic substitution, solvent-free reaction conditions, alcohols, C-C or C-heteroatom bond formation, *N*-halo compounds, vicinal halohydrins, green chemistry.

Povzetek

Odkrila in testirala sem katalitsko učinkovitost *N*-halo derivatov organskih molekul: *N*-halosukcinimida, 1-klorometil-4-fluoro-1,4-diazoniabiciklo[2.2.2]oktan bis-tetrafluoroborata (*Selectfluor™ F-TEDA-BF_4)* in *N*-fluorobenzensulfonimida (*Accufluor™ NFSi*) in jih nato uporabila kot nov tip učinkovitih nekovinskih in nevtralnih katalizatorjev za številne direktne pretvorbe organskih spojin, ki vsebujejo hidroksilno funkcionalno skupino. Ugotovila sem, da je vrsta pretvorbe, kjer pride do nastanka nove vezi ogljik-ogljik ali ogljik-heteroatom, odvisna od strukture izhodnega alkohola in vrste ter izvora prisotnega nukleofila. Pri razvoju reakcijskih pogojev omenjenih transformacij sem poskušala slediti principom zelene kemije z izvajanjem reakcij pod pogoji brez uporabe topil oz. pod pogoji visokih koncentracij reaktantov ter z uporabo vode kot reakcijskega medija.

Ugotovila sem, da se benzilni alkoholi ob prisotnosti katalitskih količin omenjenih N-halo spojin pod reakcijskimi pogoji brez uporabe topil pretvorijo v simetrične etre. Pod pogoji visoke koncentracije reaktantov poteka ob prisotnosti alkilnih alkoholov etrenje do ustreznih benzil alkil etrov. Ekvivalentne količine elektronsko bogatih organskih spojin, tj. fenil substituiranih alkenov, aktiviranih aromatov, 1,3-dikarbonilnih derivatov ali terciarnih benzilnih alkoholov z vsaj enim vodikovim atomom na vicinalnem položaju, vodijo transformacijo do derivatizacije benzilnega mesta preko nove ogljik-ogljik vezi. Do prav tako učinkovite derivatizacije benzilnega mesta preko nove vezi ogljik-dušik pa pride tudi ob prisotnosti ekvimolarnih količin acetonitrila ali anilinov. Da bi obseg derivatizacij še bolj razširila, sem nato kot vir nukleofilov uporabila trimetilsilil substituirane spojine in tako dosegla učinkovito originalno sintetsko pot do benzil halogenidov, etrov ter izotiocianatov, v nekaterih primerih pa do trimetilsililoksi benzilnih analogov študiranih benzilnih alkoholov.

Odkrila sem novo metodo za direktno transformacijo terciarnih benzilnih alkoholov z vsaj enim vodikovim atomom na vicinalnem položaju do vicinalnih halohidrinov, vicinalnih halometoksi analogov ali haloalkenov z uporabo ekvimolarnih količin N-halosukcinimidov. Metodo sem testirala na primeru dveh alkoholov, 1,1-difeniletanola in 2-fenil-2-propanola, ter ugotovila, da je vrsta in selektivnost transformacije odvisna od strukture alkohola in izvora kisikovega nukleofila (voda, metanol ali ocetna kislina).

Ključne besede: zelena kemija, reakcijski pogoji brez uporabe topil, alkoholi, *N*-halo organske spojine, tvorba ogljik-ogljik in ogljik-heteroatom vezi, vicinalni halohidrini.

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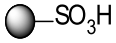
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Abbreviations

Accufluor™NFSi	. . .	*N*-fluorobenzenesulfonimide
AcOH	. . .	Acetic acid
BF_3•OEt_2	. . .	Boron trifluoride-diethyl ether
BMPM	. . .	Bis(methoxyphenyl) methyl
cat.	. . .	catalyst
CC	. . .	Column chromatography
$CDCl_3$	. . .	Chloroform
$CFCl_3$	. . .	Trichlorofluoromethane
CSA	. . .	Camphorsulfonic acid
Cy	. . .	Cyclohexyl
DBSA	. . .	Dodecylbenzenesulfonic acid
DCE	. . .	1,2-Dichloroethane
DCM	. . .	Dichloromethane
DNBSA	. . .	2,4-Dinitrobenzenesulfonic acid
2,4-DNPH	. . .	2,4-Dinitrophenylhydrazine
DPM	. . .	Diphenylmethyl
dppm	. . .	Bis(diphenylphosphino)methane
EMIOTf	. . .	*N*-ethyl-*N*-methyl imidazolium trifluoromethanesulfonate
equiv.	. . .	equivalent
Et	. . .	Ethyl
EtOAc	. . .	Ethyl acetate
EtOH	. . .	Ethanol
FC	. . .	Flash chromatography
HCRC	. . .	High concentration reaction condition in our case “is defined as concentration when less than 0.2 mL of solvent/mmol of substrate and reagent was used”
HFIP	. . .	1,1,1,3,3,3-Hexafluoroisopropanol
HMDS	. . .	Hexamethyldisilazane
HR-MS	. . .	High-resolution Mass Spectrometry
*i*PrOH	. . .	Isopropanol
lit.	. . .	literature
MCB	. . .	Monochlorobenzene
Me	. . .	Methyl
MeCN	. . .	Acetonitrile
MeOH	. . .	Methanol
2-MeTHF	. . .	2-Methyltetrahydrofuran
mmol	. . .	milimol
Na-mont	. . .	Sodium montmorillonite
NBS	. . .	*N*-bromosuccinimide
NCS	. . .	*N*-chlorosuccinimide
NIS	. . .	*N*-iodosuccinimide
NMR	. . .	Nuclear magnetic resonance
NXS	. . .	*N*-halosuccinimide
PFPAT	. . .	Pentafluorophenyl ammonium triflate
Ph	. . .	Phenyl
PMA	. . .	Phosphomolybdic acid
PTSA or TsOH	. . .	*p*-Toluenesulfonic acid or tosylic acid

PWA	. . .	12-Phosphotungstic acid
r.t.	. . .	room temperature
SDS	. . .	Sodium dodecyl sulfate
Selectfluor™ F-TEDA-BF_4	. . .	1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis-tetrafluoroborate
SFRC	. . .	Solvent-free reaction condition is defined as reaction conditions where no additional solvent was used as reaction media
	. . .	Polymer-bound *p*-toluensulfonic acid
SiO_2	. . .	Silicon dioxide, silica gel
Solkane™ 365	. . .	1,1,1,3,3 Pentafluorobutane
SSA	. . .	Silica sulfuric acid
TEAX	. . .	Tetraethylammonium halide
TeaMs	. . .	Triethylamino-methane sulfonic acid
TFA	. . .	Trifluoroacetic acid
TFE	. . .	2,2,2-Trifluoroethanol
TfOH	. . .	Trifluoromethanesulfonic acid or triflic acid
TLC	. . .	Thin-layer chromatography
TMS	. . .	Tetramethylsilane
TMSOTf	. . .	Trimethylsilyl trifluoromethanesulfonate
TMSX	. . .	Trimethylsilyl halide
TMSBr	. . .	Bromotrimethylsilane
TMSCl	. . .	Chlorotrimethylsilane
TMSCN	. . .	Cyanotrimethylsilane
UV	. . .	Ultraviolet

Chapter 1

Introduction

The development of protocols for the transformation of organic compounds following the principles of green chemistry [1] is currently one of the main trends in organic synthesis. In accordance with the principle of atom economy, efficient catalytic methodologies, suitability of a safer reaction media (water, ionic liquids, fluorous liquids etc.) or solvent-free reaction conditions (SFRC) instead of the volatile of organic solvents, low energy consumption and low waste leaving behind is a major challenge in organic chemistry.

Hydroxyl functional groups are one of the most abundant functional groups in organic compounds; thus, hydroxyl transformations under green reaction conditions represent a considerable challenge and have attracted the interest of organic chemists.

Nucleophilic substitution of alcohols is an important and attractive process used in the synthesis of organic compounds, which offers a potential impact on the environment, producing water as a by-product of the reaction.

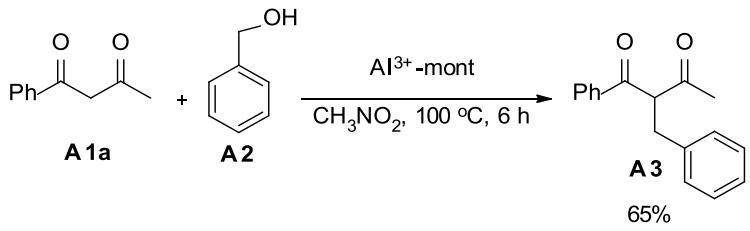
In order to manipulate a particular transformation of the hydroxyl moiety, often their activation is necessary. Numerous related methodologies have been elaborated using a substoichiometric amount of Brønsted acids, Lewis acids, molecular iodine or other promoters. The following chapters include recent trends and developments reported in the literature involving mainly nucleophilic S_N1- type reactions.

1.1 Catalytic activation of alcohols

1.1.1 Brønsted acid-catalyzed approaches

Bhanage developed a new method for the synthesis of substituted alkenes from alcohols and styrenes using ionic liquid *N*-methyl-2-pyrrolidine hydrogen sulphate $[NMP]^+HSO_4^-$ which acts as a catalyst, as well as a solvent. Reactions were successful only with secondary benzyl alcohols [2].

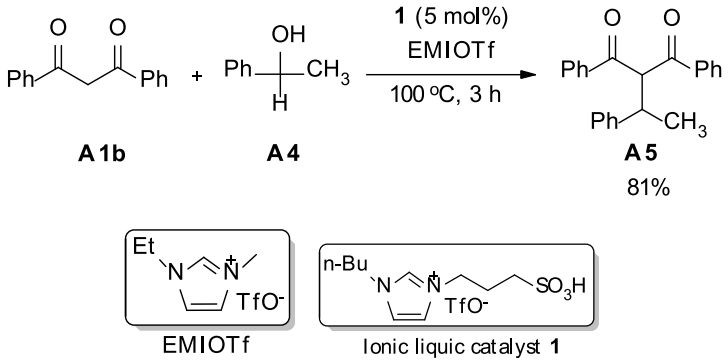
Kaneda developed an environmentally benign synthetic approach to nucleophilic substitution reactions of alcohols catalyzed by proton- and metal-exchanged montmorillonites (H- and M^{n+}-mont). Anilines, amides, indoles 1,3-dicarbonyl compounds and allylsilane acted as a nucleophile for the H-mont-catalyzed substitutions of alcohols, for the formation of various C-N and C-C bonds. Especially, an Al^{3+}-mont expressed high catalytic activity for the α-benzylation of 1,3-dicarbonyl compounds with primary alcohols (Scheme A1) [3].



Scheme A1: α-alkylation of benzoylacetone **A1a** with benzylalcohol **A2**.

Later on, Sanz reported benzylation of 1, 3-dicarbonyl compounds catalyzed by triflic acid (TfOH, 5 mol%) and *p*-toluene-sulfonic acid (PTS, 5 mol%) using undried solvents. In the absence of catalyst, no reaction took place, while in the absence of the nucleophile, substituted alkenes generated through a formal dimerization reaction were obtained [4].

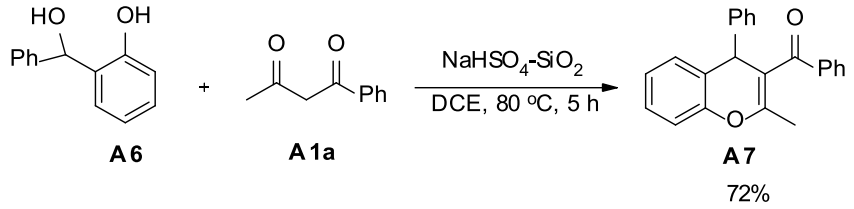
12-Phosphotungstic acid (PWA) as an efficient, eco-friendly and air- and moisture-stable catalyst was developed by Wang for the direct substitution of benzylic and allylic alcohols with ß-dicarbonyl compounds [5]. Various types of ß-diketones were reacted with 1-phenylethanol under the optimized conditions (i.e. 50 mg $MgSO_4$, 5 mg PWA in $MeNO_2$, 20 °C) providing a corresponding alkylated product in excellent yields. In 2009, Funabiki's group developed the direct benzylation/allylation/propargylation of 1,3-dicarbonyl compounds catalyzed by ionic Brønsted acid (5 mol%) with various alcohols in an ionic liquid [*N*-ethyl-*N*-methyl imidazolium trifluoromethanesulfonate (EMIOTf)] producing the corresponding product in good to excellent (Scheme A2) [6].



Scheme A2: Reaction of 1-phenylethanol **A4** with dibenzoylmethane **A1b**.

Moreover, tandem benzylation-cyclization-dehydration of 1,3-dicarbonyl compounds to produce functionalized 4*H*-chromenes was also described. The catalyst can be used up to three times without any significant loss of activity.

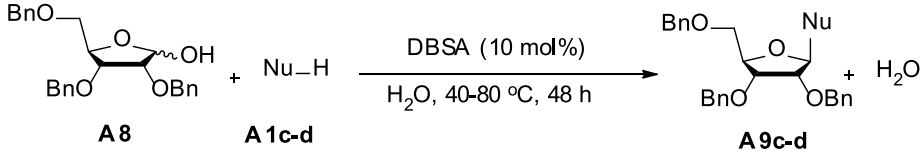
A simple and efficient method for the synthesis of 4*H*-chromenes from o-hydroxybenzylic alcohols and dicarbonyl compounds in the presence of sodium bisulfate on silicagel was developed [7]. Various diketones/ketoesters/ketoamides could be used in the synthesis of the 4*H*-chromenes (Scheme A3).



Scheme A3: Reaction of 2-(hydroxy(phenyl)methyl)phenol **A6** with benzoylacetone **A1a** catalyzed by $NaHSO_4$-SiO_2.

$Fe(HSO_4)_3$ catalyzed *C*-alkylation of a variety of ß-dicarbonyl compounds (acyclic and cyclic ß-diketones, ß-keto esters and ß-diester) using benzylic and allylic alcohols as electrophiles in 1,2-dichloroethane [8]. The catalyst can be recovered and reused up to five times.

Using dodecylbenzenesulfonic acid (DBSA) as the surfactant-type Brønsted acid catalyst in water for the dehydrative nucleophile substitution of benzyl alcohols with various arenes/heteroarenes was reported by Kobayashi [9]. Common Brønsted acids, such as AcOH, TfOH, TFA and TsOH, were not effective. The developed method could be applied to the stereoselective C-glycosylation of 1-hydroxy sugars **A8** in water (Scheme A4).



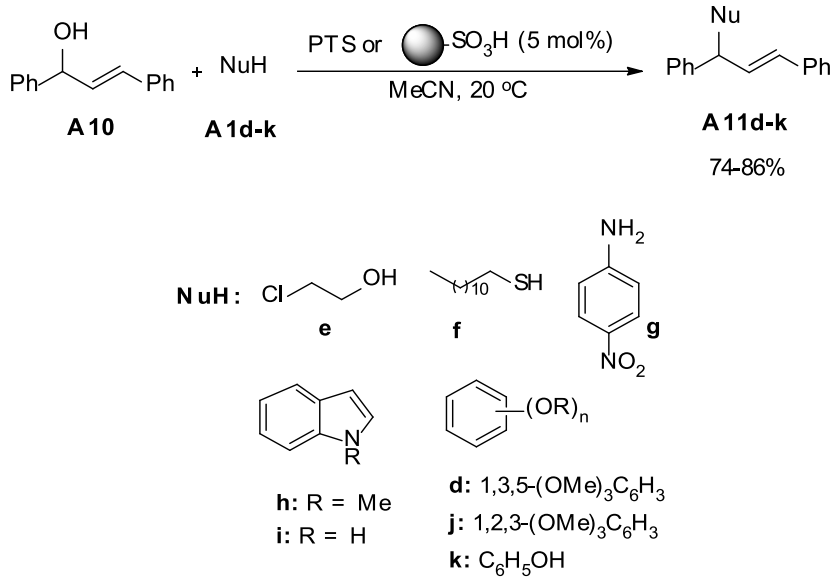
Nu: **c**= 1,2-dimethylindole, 40 °C, 61%

Nu: **d**= 1,3,5-trimethoxybenzene, 80 °C, 62%

Scheme A4: Dehydrative nucleophilic substitutions of alcohol **A8** in water catalyzed by DBSA.

A convenient and efficient method for C-C bond formation was developed by direct dehydrative coupling of alcohols or alkenes with alcohols using a series of alkenesulfonic acid group-functionalized ionic liquids (SO_3H-functionalized IL) without additives. The protocol provides for synthesizing polysubstituted olefins in good to excellent yield [10].

Sanz reported the direct nucleophilic substitution of the allylic and benzylic alcohols with different nucleophiles using *p*-toluene-sulfonic acid monohydrate (PTS) or polymer-bound *p*-toluenesulfonic acid (5 mol%) where water was the only side product (Scheme A5) [11].



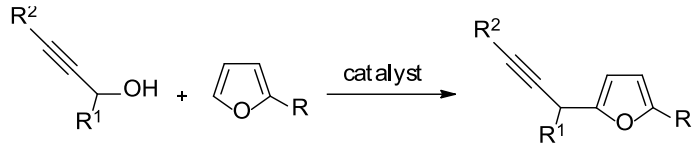
Scheme A5: Substitution reactions of alcohol **A10** with different nucleophiles catalyzed by PTS.

McCubbin reported functionalization of electron rich aromatic and heteroaromatic ring with a variety of benzylic alcohols in the presence of pentafluorophenylboronic acid as a stable and recoverable catalyst [12].

Direct nucleophilic substitutions of the propargylic alcohols with a large variety of carbon- and heteroatom-centred nucleophiles were reported by the Sanz's group [13]. After screening of various acids (5 mol%), Lewis acids, such as $InCl_3$, $AlCl_3$ and $CeCl_3$, were shown to catalyse the reaction between alkynol and ethanol as nucleophile in MeCN, at 80 °C, producing the corresponding product in > 95%, 80% and 34% yields in 1-36 h. The same reaction was catalyzed by PTS or CSA and the corresponding products were obtained in quantitative yields. Moreover, dilute HCl (10 mol%) also catalyzed this reaction in excellent yield. Later on, Sanz's group also performed a direct alkylation reaction between indoles and tertiary propargylic alcohols catalyzed by PTSA (5 mol%), in MeCN, at room temperature [14].

Alkylation of furans by benzyl, allyl, and propargyl alcohols [13,15] in the presence of Brønsted acids as a catalyst has been reviewed [16] and selected results are shown in (Table A1).

Table A1: Catalytic alkylation of furan **A1l-m** catalyzed by Brønsted acid.

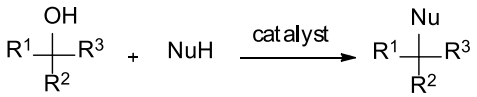


A12a-b **A1l-m** **A13l-m**

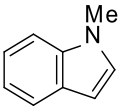
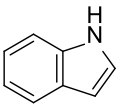
Alcohol	R	Catalyst	Reaction conditions solvent/T	Yield (%)	Ref.
R^1=3-$MeOC_6H_4$, R^2=Ph	H	*p*-TSA	MeCN/80 °C	76	[13]
R^1=R^2=Ph	Me	$C_6F_5B(OH)_2$	CH_2Cl_2/r.t.	41	[15]

The catalytic nucleophilic substitution of tertiary alcohols [9,12,17] using carbon- or heteroatom-based nucleophiles in the presence of Brønsted acid has been reviewed [18] and selected results are shown in (Table A2).

Table A2: Nucleophilic substitution of tertiary alcohols **A14a-b** catalyzed by Brønsted acid.



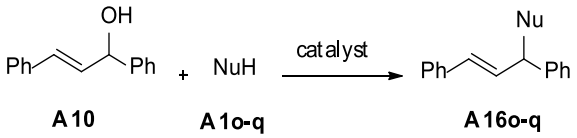
A14a-b **A1h-n** **A15h-n**

Alcohol	NuH	Catalyst	Reaction conditions solvent/T/t	Yield (%)	Ref.
R^1=R^2=R^3=Ph		DBSA	H_2O/80 °C/24 h	96	[9]
R^1=R^2=R^3=Ph		$C_6F_5B(OH)_2$	DCE/reflux/16 h	99	[12]
R^1=HF_2C, R^2=H, R^3=Ph	MeCN	H_2SO_4	reflux/70-80 °C	55	[17]

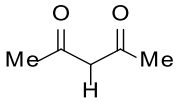
Zheng's group [19] developed the method for direct nucleophilic substitution of propargylic alcohols with various nucleophiles using Amberlite IR-120H resin as the catalyst.

The direct nucleophilic substitution of allylic alcohols [20-22] through S_N1-type reactions in the presence of Brønsted acid as a catalyst has been reviewed [23] and selected results are shown in (Table A3).

Table A3: Nucleophilic substitution of allylic alcohols **A10** catalyzed by Brønsted acid.

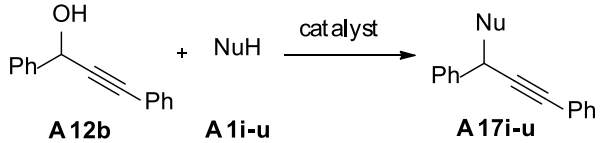


A10 **A1o-q** **A16o-q**

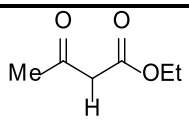
	NuH	Catalyst	Reaction conditions solvent/T/t	Yield (%)	Ref.
o:		TfOH	$BrCH_2CH_2Br$/60 °C	87	[20]
p:	TMSCN	Sn or Ti-Monts	DCM/rt/0.1 h	98 or 94	[21]
q:		H_2SO_4	$MeNO_2$/101 °C/5 min.	87	[22]

The direct nucleophilic S_N1-type reactions of alcohols [24,25] in the presence of Brønsted acid as a catalyst have been reviewed [26] and selected results are shown in (Table A4).

Table A4: Nucleophilic substitution of alcohol **A12b** catalyzed by Brønsted acid.

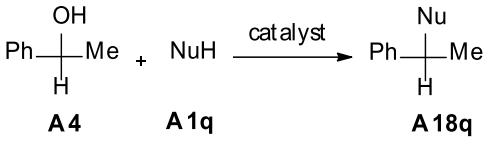


A12b **A1i-u** **A17i-u**

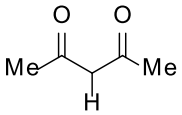
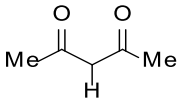
	NuH	Catalyst	Reaction conditions solvent/T/t	Yield (%)	Ref.
r:		PTSA	MeCN/rt/8 h	54	[24]
k,s,t,u,i:	Phenol, anisole, *o*-cresol, 2-naphtol, 1*H*-indole	PMA-SiO_2	SFRC/rt/0.5-3.5 h	90-96	[25]

Recent approaches for direct dehydrative coupling strategies to form C-C bond in the presence of Brønsted acid as a catalyst have been reviewed [27] and selected resulsts are shown in (Table A5).

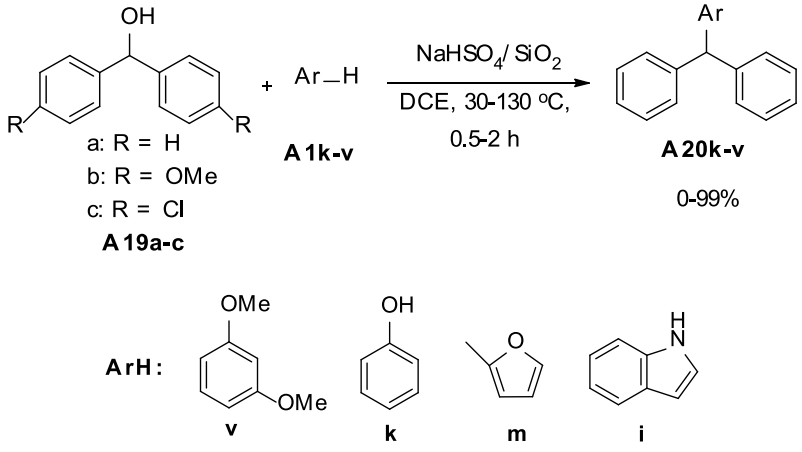
Table A5: Nucleophilic substitution of alcohol **A4** catalyzed by Brønsted acid.



A4 **A1q** **A18q**

NuH	Catalyst	Reaction conditions solvent/T/t	Yield (%)	Ref.
	$TfOH\text{-}SiO_2$	SFRC or $MeNO_2$/70 °C/5 h	90	[28]
	$HClO_4$	toluene/70 °C/17 h	88	[29]

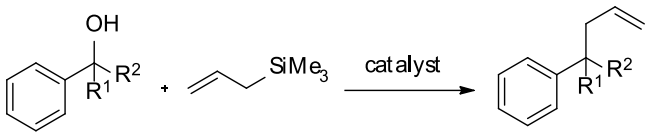
The use of sodium hydrogen sulfate supported on silica allows alkylation of aromatics with alcohols [30]. After screening of various acid catalysts at 80 °C for 2 h it was found that silica sulfuric acid (SSA) catalyzed the reaction between diphenylmethanol and benzene in 83% yield. When the reaction was performed in the presence of $NaHSO_4$ no reaction was observed. Moreover, gel-supported acids PPA/SiO_2 and SA/SiO_2 slightly supported the reaction and the corresponding products were obtained in low yields (13-22%), $ZnCl_2/SiO_2$ gave the corresponding product in 70% yield. In the case when Lewis and Brønsted acids ($AlCl_3$, $FeCl_3$, and H_2SO_4) were used, the corresponding products were obtained in 32-76% yields. Different aromatic compounds were treated with benzhydrol catalyzed by $NaHSO_4/SiO_2$ (Scheme A6). The catalyst can be recycled and reused eight times without losing the catalytic activity.



Scheme A6: Alkylation of aromatics from alcohols in the presence of $NaHSO_4/SiO_2$ as the catalyst.

Direct allylation of alcohols [11,13,31,32] using allyltrimethylsilane for C-C bond formation in the presence of Brønsted acid as a catalyst has been reviewed [33] and selected results are shown in (Table A6).

Table A6: Allylation of alcohols using allyltrimethysilane **A1w** catalyzed by Brønsted acid.



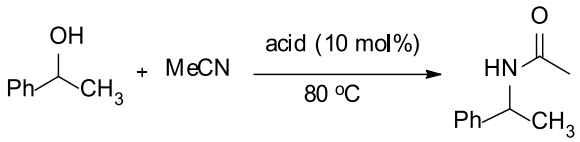
A21a-c A1w A22w

	Alcohol	Catalyst	Reaction conditions solvent/T/t	Yield (%)	Ref.
a:	R^1=H, R^2=CCPh	PTS	MeCN/20-80 °C	73-80	[13,31]
b:	R^1=H, R^2=Ph	PMA	DCM/rt/30 min.	90	[32]
c:	R^1=H, R^2=CH=CHPh	PTS or 	MeCN/20 °C	90	[11]

The Ritter reaction is a very efficient and widely used protocol for the formation of amides. Remarkable progress has been made and developments in the Ritter reaction in the presence of Brønsted acid as a catalyst were reviewed in 2012 [34]. In 2006, Hu, reported the Ritter reaction of tertiary α-CF_2H carbinols with acetonitrile in the presence of 98% concentrated H_2SO_4 to provide corresponding amides in high yields [17].

Sanz [35] reported a method for amidation of secondary alcohols in high yields using a Brønsted acid-catalyst (Table A7).

Table A7: Catalyst screening for the Ritter reaction of 1-phenylethanol **A4** in acetonitrile **A1n**.



A4 A1n A23n

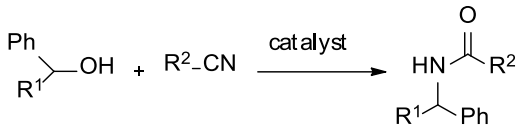
Acid	Amount (mol%)	t (h)	Yield (%)
PTS	10	48	84
TfOH	10	12	85
H_2SO_4	10	15	82
DNBSA	10	12	85
DNBSA	5	24	75

The amidation of 1-phenylethanol was performed using different Brønsted acids as catalysts (10 mol%) such as PTS, 2,4-dinitrobenzenesulfonic acid (DNBSA), TfOH and H_2SO_4 in acetonitrile. The only difference between these acids was the reaction time required for conversion of the starting material. Due to its high activity and easiness of handling, DNBSA was used as a catalyst for this reaction. When the substoichiometric amount of DNBSA was decreased from 10 mol% to 5 mol%, the reaction time was increased from 12 h to 24 h for the formation of the main product.

Brønsted-acidic imidazolium ionic liquid [BMIM(SO_3H)][OTf], as a convenient and recyclable catalyst, was reported by Laali for the high yield synthesis of variety of amides under mild conditions via the Ritter reaction of alcohols with nitriles [36]. Moreover, using $NOPF_6$ immobilized in [BMIM][PF6] ionic liquid for the Ritter reaction of bromides with nitriles and for the synthesis of adamant amides from adamantane and nitriles was also reported.

Recent developments in the Ritter reaction of alcohols [37-41] and nitriles catalyzed by Brønsted acid have been reviewed [42] and some of the results are shown in (Table A8).

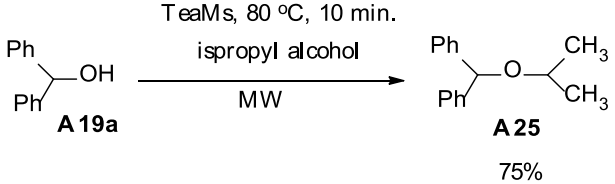
Table A8: Ritter reaction of alcohols **A4-A19a** and nitriles **A1n-nb** catalyzed by Brønsted acid.



A4-A19a **A1n-nb** **A24n-nb**

Alcohol		R^2	Catalyst	Reaction conditions solvent/T/t	Yield (%)	Ref.
R^1=Me	**na:**	Ph	Nanocat.-Fe-OSO_3H	SFRC 90 °C/5 h	84	[37]
R^1=Ph		Me	$CoFe_2O_4$@SiO_2-DASA	SFRC 80 °C/4 h	90	[38]
R^1=Ph	**nb:**	CH_2=CH-CH_2	$NaHSO_4/SiO_2$	DCE 80 °C/8 h or MCB 30 °C/0.5 h	87 or 84	[39]
R^1=Me		Me	PFPAT	SFRC 90 °C/2 h	95	[40]
R^1=Me		Me	TfOH/SDS	H_2O 200 °C/5 h	82	[41]

Moreover, unsymmetrical ethers were prepared from different alcohols in the presence of sodium bisulfite ($NaHSO_3$, 0.3-1 mol%) as the catalyst [43]. Gowda performed an efficient synthesis of *tert*-butyl ethers from alcohols using methyl *tert*-butyl ethers as a tert-butyl source and solvent, in the presence of H_2SO_4 [44]. Synthesis of several diphenylmethyl ethers and thioethers was achieved using a combination of microwave irradiation and protic ionic liquids (pIL), namely triethylamino-methane sulfonic acid (TeaMs) as a co-solvent and catalyst in an organic solvent (Scheme A7) [45].



A19a **A25**

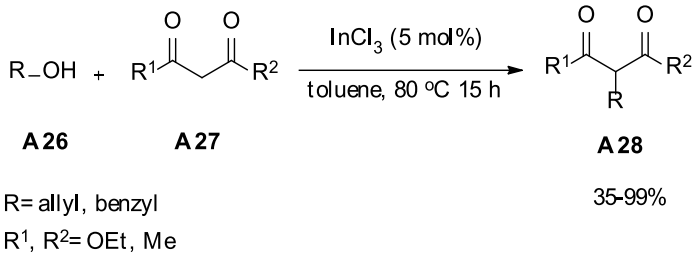
75%

Scheme A7: Formation of diphenylmethyl ether **A25** using protic ionic liquids.

Benzyl ethers were obtained from primary benzylic alcohols using hydrophobic phosphonium ionic liquids containing the trihexyl(tetradecyl)phosphonium cation paired with six different anions under microwave irradiation [46].

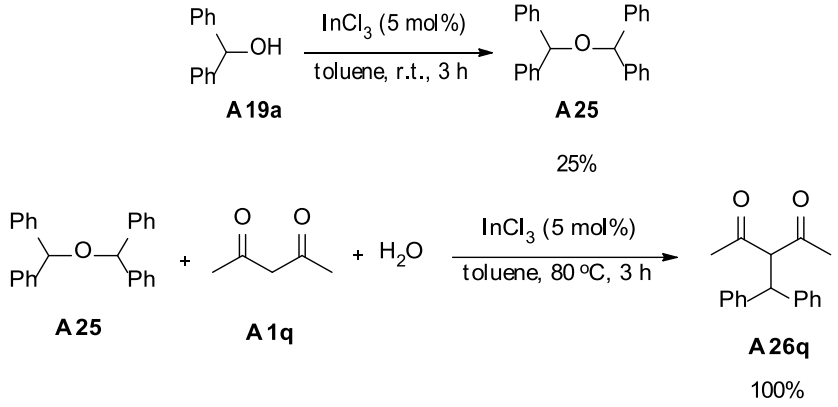
1.1.2 Metal ions-catalyzed approaches

The major contribution in the transformation of alcohols has been described by the activation of alcohols through the substoichiometric amount of metal ions as Lewis acids. Ishii reported the use of metal triflate (e.g. La, Yb, Sc, and Hf triflate) as the catalyst for reactions of benzylic alcohols with carbon (aromatic compounds, olefins, enol acetate), nitrogen (amide derivatives), and alcohol nucleophiles in nitromethane [47]. $Hf(OTf)_4$ was the most active catalyst for this alkylation and trifluoromethanesulfonic acid (triflic acid, TfOH) was also a good catalyst. The catalytic activity of metal triflates and TfOH increased in the following order $La(OTf)_3$ < $Yb(OTf)_3$ < TfOH < $Sc(OTf)_3$ < $Hf(OTf)_4$. Baba and co-workers developed a direct C-C bond formation of allylic alcohols (including cyclic) and benzylic alcohols with various 1,3-dicarbonyl compounds (Scheme A8) [48].



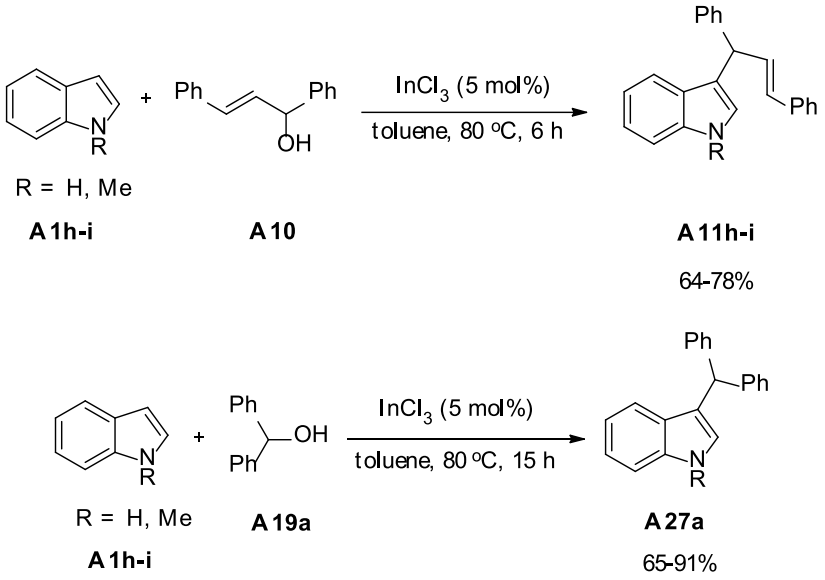
Scheme A8: $InCl_3$-catalyzed direct reaction of **A26** with **A27**.

The reaction was studied with different catalysts (5 mol%), in toluene, 80 °C. $InCl_3$ was found to act as a catalyst for the reaction, as well as $InBr_3$. In the case when the reaction was performed in the absence of nucleophile, dimerization took place. This was then tested with acetylacetone in the presence of water giving the corresponding alkylated product (Scheme A9).



Scheme A9: Effect of the $InCl_3$ on dimerization and alkylation.

The reactions of alcohols were tested also with indoles to give the corresponding products (Scheme A10).

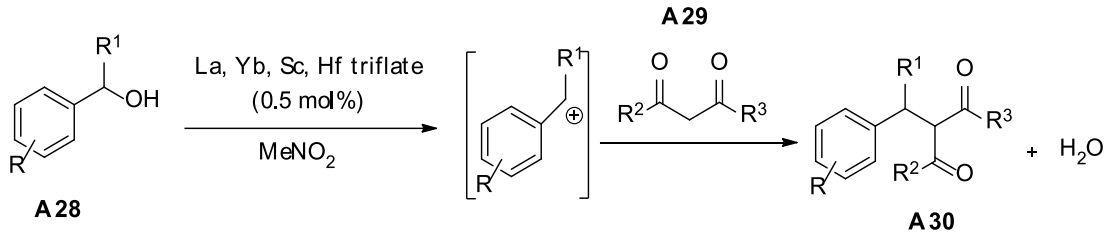


Scheme A10: Alkylation of indoles **A1h-i** catalyzed by $InCl_3$.

Chan and co-workers developed allylic alkylation of 1,3-dicarbonyl compounds with allylic alcohols including primary and terminal ones using $AuCl_3$ (5 mol%) with $AgSbF_6$ (15 mol%) as co-catalyst, in $MeNO_2$ at room temperature [49].

In another research, the direct allylation of alcohols catalyzed by the combined Lewis acid system of $InCl_3$/ Me_3SiBr was shown [50]. This system was tried to the direct allylation between tertiary aliphatic trimethylsilyl ethers and allylsilanes where the yield was only 34%. Utilizing a combination of $InCl_3$/Me_3SiI, which is stronger Lewis acid, proved to be better (61% yield) at room temperature in DCM as the solvent. Furthermore, the use of the combination of $InCl_3$ and I_2, where Me_3SiI was generated *in situ* from I_2 and allylsilane, enhanced the yield up to 76%, while each of them separately had not shown any activity.

Ishii and co-workers developed a convenient secondary benzylation and allylation of 1,3-dicarbonyl compounds in the presence of metal triflate (e.g. La, Yb, Sc, and Hf triflate) (0.5 mol%), in $MeNO_2$ (Scheme A11) [51].



R = 4-OMe, 2,6-diMe, 4-Me, 2-Me, 4-Cl, 4-CO_2Me, 4-NO_2

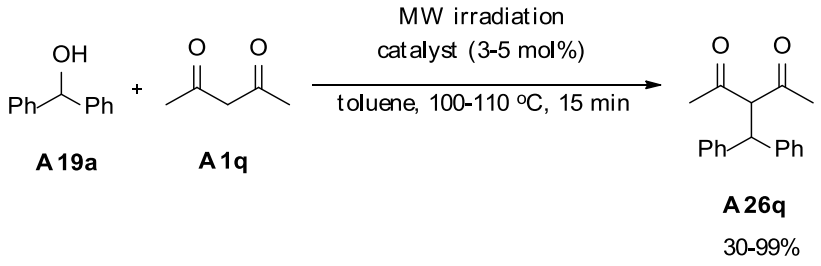
R^1 = alkyl

R^2 = alkyl, aryl

R^3 = alkyl, aryl, OR', NR'R"

Scheme A11: Benzylation of 1,3-dicarbonyl compounds catalyzed by metal triflate.

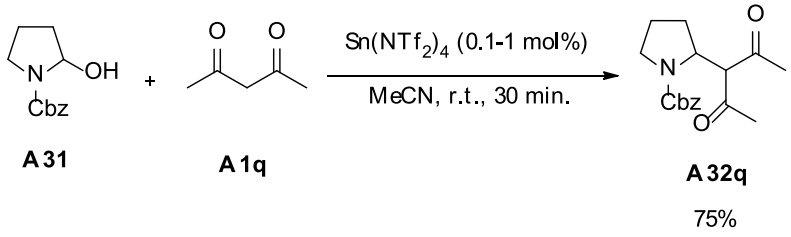
Baba reported a rapid and efficient microwave-irradiated protocol for C-C coupling of a broad range of benzylic/allylic alcohols with 1,3-dicarbonyl compounds, ß-keto esters, and dialkyl malonates catalyzed by transition metal in toluene [52]. Transition-metal catalysts, salts of Zn, Cu, Fe, Sc, Ru, Pt and Ta (3-5 mol%) were found to provide the coupling products (Scheme A12). Among all of these catalysts copper (II) triflate (5 mol%) was observed to be more effective (98% yield) than the other catalysts even in the case of a less reactive benzyl alcohol or diester.



Scheme A12: MW-Irradiated reaction of diphenylmethanol **A19a** with acetylacetone **A1q**.

Later on, Fe(III) chloride catalyst was explored for the α-substitution of Morita-Baylis-Hillman alcohols with carbon-and heteroatom-centred nucleophiles such as alcohols, arenes, 1,3-dicarbonyl compounds and thiols [53].

Kim described the role of $Fe(ClO_4)_3 \bullet H_2O$ as the catalyst for direct C-C bond formation of 1,3-dicarbonyl compounds, electron rich arenes and heteroarenes and 4-hydroxycoumarin with secondary benzylic alcohols [54]. This method was applied to the synthesis of bis-symmetrical triarylmethanes and one-step synthesis of an *anti*-coagulant compound, 4-hydroxy-3-(1,2,3,4-tetrahydronaphthalen-1-yl)-2*H*-chromen-2-one (Coumatetralyl (B)). Dalla and Dunach developed the role of Sn^{IV} triflimidate as the catalyst for the nucleophilic substitution reaction of hydroxy groups of unprotected hydroxy N,O-acetals (Scheme A13) [55].



Scheme A13: Sn^{IV} triflimidate catalyzed nucleophilic substitution of hydroxy N, O-acetals.

Beller and co-workers described the role of $FeCl_3 \bullet 6H_2O$ as an inexpensive catalyst for the addition of various 1,3-dicarbonyl compounds with benzylic alcohols in $MeNO_2$ [56]. The developed protocol was useful for a one-pot synthesis of the pharmaceutical drug Phenprocoumon in 94% yield.

Laali and co-worker reported the condensation of propargylic alcohols with 1,3-dicarbonyl compounds in the presence of $Sc(OTf)_3$ and $Ln(OTf)_3$ and bismuth nitrate in imidazolium ILs. The $[BMIM][PF_6]/Bi(NO_3)_3 \bullet 5H_2O$ system was efficient for propargylation, vinylation, and alkylation of 4-hydroxycoumarins [57].

$Bi(OTf)_3$ catalyzed benzylation and allylic alkylation of 2,4-pentanediones in $MeNO_2$ forming C-C bond in good to excellent yields [58].

$NbCl_5$, a stable solid, was used as an efficient catalyst (5 mol%) for C, N, O and S-nucleophilic substitution reactions of benzylic alcohols with alcohols, naphthols, indoles, resorcinoles, anisole, thiols, NH_4SCN or NaN_3 as a source of nucleophiles. Benzylic alcohols with electron withdrawing groups such as fluoro or nitro were not reactive [59].

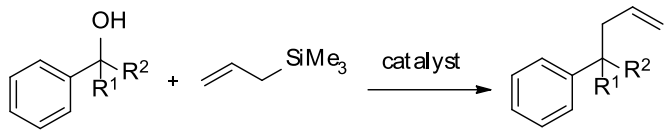
Alkylation of indoles using allylic, benzylic and propargylic alcohols catalyzed by $FeCl_3$ in $MeNO_2$ were reported by Jana [60]. Later on, Jana also described the addition of benzylic alcohols to terminal aryl alkynes catalyzed by $FeCl_3$ in $MeNO_2$ [61]. In the same year, Jana performed amidation reaction of secondary benzylic and allylic alcohols with carboxamides or *p*-toluenesulfonamide in the presence of $FeCl_3$ [62].

Yamamoto's group developed dehydrative coupling of benzylic alcohols with styrenes catalyzed by Pd(II) using PPh_3 as the ligand and $(CF_3CO)_2O$ as an additive [63].

Yi's group reported a C-C bond formation between alkenes and alcohols. The cationic ruthenium complex $[(C_6H_6)(PCy_3)(CO)RuH]^+BF_4^-$ catalyzed the alkylation in solution [64].

The allylic alkylation represents an important transformation in organic chemistry and different metal processes have been described for this reaction. Direct allylation of alcohols [65-73] using allyltrimethylsilane for C-C bond formation in the presence of Lewis acid as a catalyst has been reviewed [33] and selected results are shown in (Table A9).

Table A9: Allylation of alcohols **A33a-i** using allyltrimethysilane **A1w** catalyzed by Lewis acid.



A 33a-i **A 1w** **A 34a-i**

	Alcohol	Catalyst	Reaction conditions solvent/T/t	Yield (%)	Ref.
a:	R =H, R^2=Me	$InCl_3$	1,2 DCE 80 °C/3 h	51	[65]
b:	R^1=H, R^2=CH=CHPh,	$Cu(BF_4)_2$	MeCN rt	86	[66]
c:	R^1=H, R^2=Ph	$TiCl_4$	CH_2Cl_2 rt/1min.	96	[67]
d:	R^1=R^2=Me	$InCl_3$/Me_3SiBr	Hexane 50 °C/0.5 h	75	[68]
e:	R^1=H, R^2=CCH	$FeCl_3$	MeCN rt/2 h	70	[69]
f:	R^1=H, R^2=CCPh	$BiCl_3$	MeCN 35 °C/0.5 h	89	[70]
g:	R^1=H, R^2=CCPh	(dppm)$ReOCl_3$/NH_4PF_6	$MeNO_2$ 65 °C/2 h	79	[71]
h:	R^1=H, R^2=CCPh	$NaAuCl_4$•$2H_2O$	DCM r.t.	97	[72]
i:	R^1=H, R^2=CCPh	$Bi(OTf)_3$	(bmim) BF_4 rt/30 min.	93	[73]

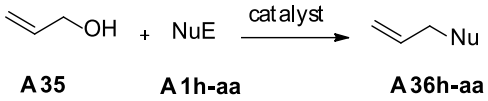
Heterobimetallic 'Pd-Sn' catalyst was used for the direct alkylation of arenes, heteroarenes, 1,3-dicarbonyls and organosilicon nucleophiles with allylic/propargylic/benzylic alcohols in $MeNO_2$ [74].

$FeCl_3$ catalyzed substitution of propargylic alcohols with carbon- and heteroatom-centered nucleophiles, such as alcohols, aromatic compounds, thiols, and amides, forming C-C, C-O, C-S and C-N bonds [69].

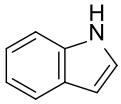
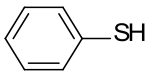
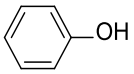
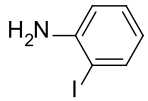
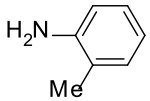
Alkylation of electron rich arenes using secondary and tertiary benzylic, allylic, and propargylic alcohols in the presence of calcium-based catalyst was described by Niggemann [75]. Reactions were performed under the optimized conditions (5 mol% $Ca(NTf_2)_2$ and 5 mol% Bu_4NPF_6 in DCM, at room temperature). Zhan and co-workers described the role of $BiCl_3$ as the catalyst for the formation of C-C, C-O, C-S and C-N bonds between propargylic alcohols and carbon and heteroatom-centered nucleophiles, such as allyl trimethylsilane, alcohols, aromatic compounds, thiols and amides [70]. The reaction was performed using 10 mol% of the catalyst, at room temperature up to 60 °C in MeCN and the obtained corresponding propargylic products, in general, were in high yields. A general and selective C-3 alkylation of indoles with primary alcohols in *o*-xylene catalyzed by reusable alumina-supported Pt nanocluster (Pt/θ-Al_2O_3-1.5 nm, 1 mol%) was reported [76].

Transition metals could catalyze a various transformations of allylic alcohols [77-81] with various nucleophiles. This topic has been reviewed [82] and selected results are shown in (Table A10). The review covers the C-C and C-heteroatom bonds formation.

Table A10: Nucleophilic allylic substitution catalyzed by transition metal.

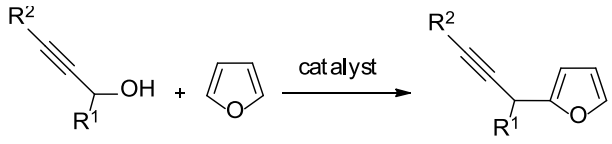


A 35 **A 1h-aa** **A 36h-aa**

	NuE	Catalyst	Reaction conditions Solvent/T/t	Yield (%)	Ref.
h:		[(η^3-allyl)Pd(cod)]BF_4	toluene/50 °C/20 h	80	[77]
x:	CH_3CH_2OH	[RuCp(*o*-EtOdppe)](OTs)	toluene/100 °C/2 h	86	[78]
y:		[RuCp(*o*-EtOdppe)](OTs)	toluene/100 °C/20 h	48	[78]
k:		[$RuCp(PPh_3)_2$](OTs)	toluene/60 °C/3 h	99	[79]
z:		$Pt(acac)_2/PPh_3/Ti(OPr^i)_4$	benzene/reflux/3 h	64	[80]
aa:		$Pt(cod)Cl_2$/DPEphos	dioxane/reflux/6 h	86	[81]

Alkylation of furans by benzyl, allyl, and propargyl alcohols [70,83-86] in the presence of Lewis acids as a catalyst has been reviewed [16] and many results are shown in (Table A11).

Table A11. Catalytic alkylation of furan **A1l** catalyzed by Lewis acid.



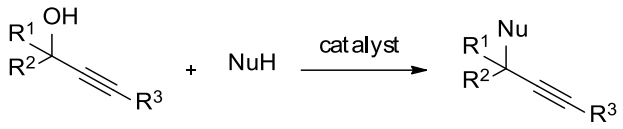
A 12b-e **A 1l** **A 13l**

	Alcohol	Catalyst	Reaction conditions	Yield (%)	Ref.
b:	R^1= R^2=Ph	(dppm)Re(O)Cl_3/KPF_6	$MeNO_2$ 65 °C/5 h	81	[86]
b:	R^1=R^2=Ph	[$ReBr(CO)_3(thf)]_2$	DCM 25 °C/1 h	37	[85]
c:	R^1=Ph, R^2=H	$BiCl_3$	MeCN 35 °C/1 h	50	[70]
d:	R^1=Ph, R^2=H	[Cp*RuCl(μ_2-SMe)$_2$RuCp*Cl]/NH_4BF_4	$ClCH_2CH_2Cl$ 60 °C	68	[83]
e:	R^1=R^2=Ph	[Cp*RuCl(μ-SMe)$_2$Cp*Ru(OH_2)]OTf	$ClCH_2CH_2Cl$ 60 °C	71	[84]

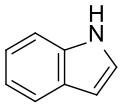
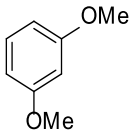
C-C, C-N, C-O and C-S bond forming reactions of furfuryl cations with different nucleophiles catalyzed by $BiCl_3$ (20 mol%) in $MeNO_2$ at room temperature have been developed by Ramasastry [87].

The catalytic nucleophilic substitution of tertiary alcohols [69,75,88,89] using carbon or heteroatom based nucleophiles in the presence of Lewis acid has been reviewed [18] and selected results are shown in (Table A12).

Table A12: Nucleophilic substitution of tertiary alcohols **A37a-b** catalyzed by Lewis acid.

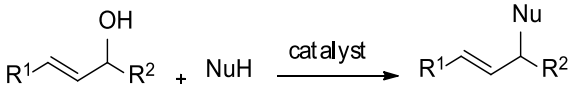


A 37a-b **A 1h-ab** **A 38h-ab**

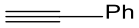
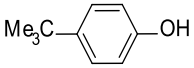
	Alcohol	NuH	Catalyst	Reaction conditions solvent/T/t	Yield (%)	Ref.
a:	R^1=R^2=Me, R^3=Ph	EtOH	$FeCl_3$	MeCN r.t./12 h	82	[69]
b:	R^1=R^2=Ph, R^3=H	n-BuSH	[Cp*RuCl(μ-SMe)$_2$Cp*Ru(OH$_2$)]OTf	Cl(CH$_2$)$_2$Cl 60 °C/24 h	60	[88]
a:	R^1=R^2=Me, R^3=Ph		Al(OTf)$_3$	MeCN 85 °C/200 min.	54	[89]
a:	R^1=R^2=Me, R^3=Ph		Ca(NTf$_2$)$_2$/Bu$_4$NPF$_6$	DCM r.t./2 h	87	[75]

The direct nucleophilic substitution of allylic alcohols [90-93] through S_N1-type reactions in the presence of Lewis acid as a catalyst has been reviewed [23] and selected results are shown in (Table A13).

Table A13: Nucleophilic substitution of allylic alcohols **A10a-b** catalyzed by Lewis acid.

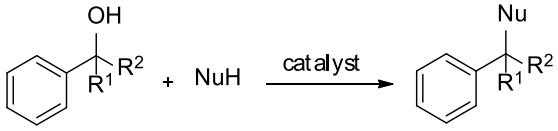


A10a-b **A1p-ae** **A39p-ae**

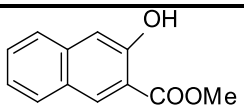
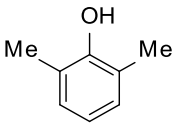
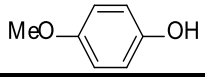
Alcohol		NuH	Catalyst	Reaction conditions solvent/T/t	Yield (%)	Ref.
R^1=R^2=Ph	**ac:**		$Cu(OTf)_2$	$BrCH_2CH_2Br$ 120 °C/12 h	78	[90]
R^1=R^2=Ph	**p:**	TMSCN	$Zn(OTf)_2$	MeNO 100 °C/6 h	77	[92]
R^1=R^2=Ph	**ad:**		$SbCl_3$	MeCN MW/400W 65 °C/25 min.	67	[93]
R^1=H, R^2=CH=CH_2	**ae:**	*p*-xylene	$Ag_3PW_{12}O_{40}$	140 °C/2 h	84	[91]

The direct nucleophilic S_N1-type reactions of alcohols [47,94,95] in the presence of Lewis acid as a catalyst has been reviewed [26] and selected results are shown in (Table A14).

Table A14: Nucleophilic substitution of alcohols **A40a-c** catalyzed by Lewis acid.

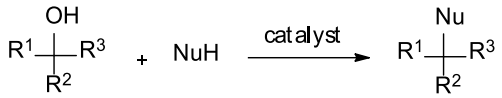


A40a-c **A1af-ah** **A41af-ah**

	Alcohol	NuH	Catalyst	Reaction conditions solvent/T/t	Yield (%)	Ref.
a:	R^1=Me, R^2=H		$La(OTf)_3$	$MeNO_2$ 100 °C/0.25 h	99	[47]
b:	R^1=Ph, R^2=CCPh		$Yb(OTf)_3$	$MeNO_2$ 80 °C/24 h	90	[95]
c:	R^1=H, R^2=Me		$Bi(OTf)_3$	DCM 55 °C/8 h	58	[94]

Recent approaches for direct dehydrative coupling strategies to form C-C bond in the presence of Lewis acid as a catalyst has been reviewed [27] and selected results are shown in (Table A15).

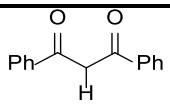
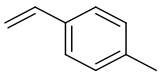
Table A15: Nucleophilic substitution of allylic alcohols **A42a-b** catalyzed by Lewis acid.



A 42a-b **A 1b-ai** **A 43b-ai**

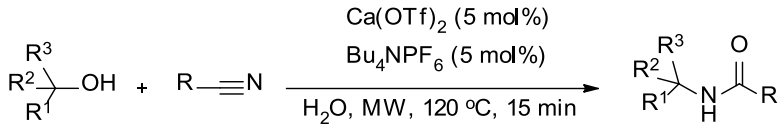
a: $R^1 = R^2 =$ Ph, $R^3 =$ CH= CH_2

b: $R^1 = p$-OMeC_6H_4, $R^2 = R^3 =$ H

	NuH	Catalyst	Reaction conditions solvent/T/t	Yield (%)	Ref.
b:		$AuCl_3/AgSbF_6$	$MeNO_2$ rt/0.5 h	86	[49]
ai:		$(CF_3CO)_2O/Pd(OAc)_2/PPh_3$	DMF 100 °C/39 h	42	[63]

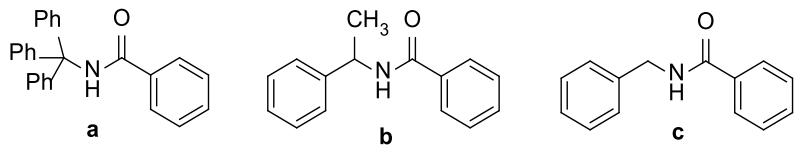
Remarkable progress has been made and developments in the Ritter reaction in the presence of Lewis acid as a catalyst were reviewed in 2012 [34]. A general procedure allowing the conversion of tertiary alcohols with benzonitrile into *tert*-amides in the presence of $Bi(OTf)_3$ (20 mol%) as a catalyst (which was found to be the best compared with different metal triflates) in H_2O at 100 °C for 17 h was developed by Barrett [96]. Recent developments in Ritter reaction catalyzed by Lewis acid have been reviewed [42]. The procedure for the synthesis of amides from benzohydric alcohols and nitriles in the presence of trimesitylphosphane gold (I) complex-$(Mes_3P)AuCl$ with the NTf_2^- counter anion was reported by Hashmi [97]. Reactions were performed under optimized conditions (5 mol% gold (I), 5 mol% $AgNTf_2$ in nitrile at 75 °C) and the obtained products were in general in moderate yields.

Yaragorla [98] demonstrated the protocol using $Ca(OTf)_2$ (5 mol%) as a catalyst and Bu_4NPF_6 (5 mol%) as an additive for the synthesis of various amides from tertiary, secondary and benzyl alcohols and nitriles under microwave irradiation in 15 min. in good to excellent yields (Scheme A14).



A 44a-c **A 45a-c** **A 46a-c**

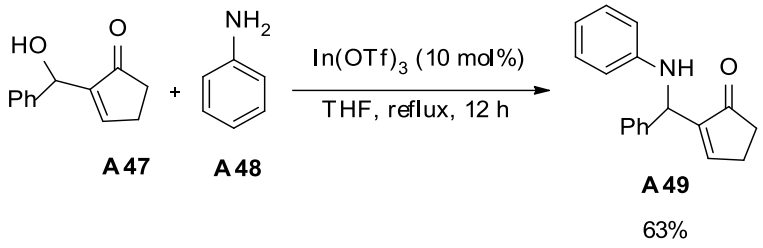
Selected products:



Scheme A14: Ca (II) catalyzed amydation of alcohols **A44a-c** with nitriles **A45a-c**.

Wang and co-workers developed a convenient method for direct nucleophilic substitution of alcohols with aniline, amide, sulfonamid, 2,4-DNPH, and 1,3-dicarbonyl compounds catalyzed by zinc based ionic liquids $[CHCl][ZnCl_2]_2$ (1.5 equiv., 100 °C, 1 h), which acted also as the solvent, and the obtained yields were good to excellent [99]. The authors reported that the reaction worked through the carbocation mechanism, as detected by UV-VIS spectroscopy.

The highly α-regioselective $In(OTf)_3$ (10 mol%) catalyzed N-nucleophilic substitution of Baylis-Hillman adducts bearing five or six-membered ring moieties with aromatic amines gave α-product in good yield (Scheme A15) [100].

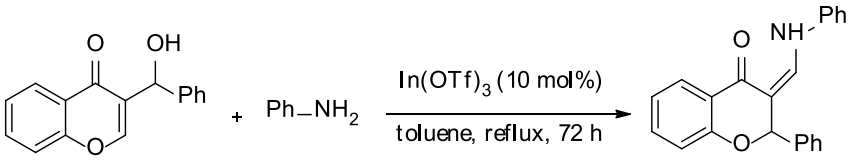


A47 **A48** **A49**

63%

Scheme A15: Amination of a Baylis-Hillman adduct catalyzed by $In(OTf)_3$.

The reaction of chromone-derived cyclic Morita-Baylis-Hillman alcohols in the presence of $In(OTf)_3$ as the catalyst gave 2-substituted- 3- aminomethylenechromans in excellent yield (Scheme A16) [101].



A50 **A48** **A51**

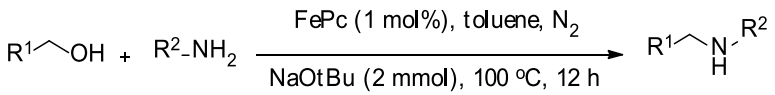
99%

Scheme A16: Reaction of Morita-Baylis-Hillman alcohols **A50** with amines **A51** catalyzed by $In(OTf)_3$.

Aluminium triflate $Al(OTf)_3$ catalyzed the direct amination of allylic/propargylic/benzylic alcohols, and benzhydrols with electron-withdrawing substituents, with various nitrogen nucleophiles, in $MeNO_2$, to achieve the corresponding biarylamines in high yield, and the dibromosubstituted product was further converted into letrozole in high yield [102].

NiCuFeOx catalyst was designed and prepared by Shi's group for the synthesis of *N*-substituted primary, secondary, tertiary and cyclic amines (with up to 98%) using ammonia, primary amines, or secondary amines as the nitrogen source and alcohols as the alkylation reagents [103]. The authors supposed that the synergism between the Ni, Cu, and Fe species might be crucial to achieve the borrowing-hydrogen transformation.

Singh reported *N*-alkylation of aminobenzothiazoles, aminopyridines and aminopyrimidines with alcohols catalyzed by iron phthalocyanine (1 mol%) [104]. The process is also useful for the efficient synthesis of 2-substituted benzimidazoles, benzothiazoles and benzoxazole by the *N*-alkylation of ortho-substituted anilines (-NH_2, -SH, and –OH) (Scheme A17).

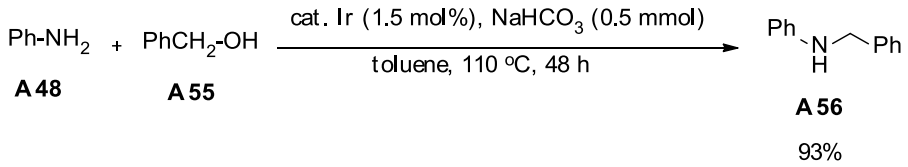


A52 **A53** **A54**

Scheme A17: N-alkylation of various amines **A53** with alcohols **A52**.

In 2013, *N*-alkylation of amines and ß-alkylation of secondary alcohols with primary alcohols was achieved using a mesoporous silica (SBA-15)-supported pyrimidine-substituted N-heterocyclic carbene iridium complex as the catalyst. The catalyst could be easily recycled and re-used twelve cycles for *N*-alkylation of aniline with benzyl alcohol, nine cycles for *N*-alkylation

of different amines with different alcohols, and eight cycles for ß-alkylation of 1 phenylethanol with benzyl alcohol (Scheme A18) [105].

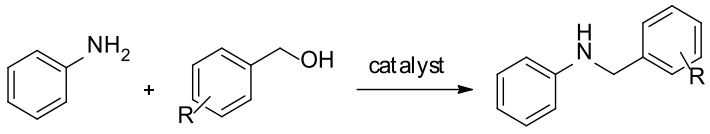


Scheme A18: N-alkylation of aniline **A48** with phenylmethanol **A55** catalyzed by iridium.

Niggemann developed the method for direct amination of secondary and tertiary benzylic and allylic as well as tertiary propargylic alcohols with various nitrogen nucleophiles such as carbamates, tosylamides and anilines under the optimized conditions (5 mol% $Ca(NTf_2)_2/Bu_4NPF_6$, in DCM, at r.t.) [106].

Amination of alcohols [107-113] in the presence of Lewis acid as a catalyst has been reviewed [114] and selected results are shown in (Table A16).

Table A16: Amination of alcohols **A49a-b** catalyzed by Lewis acid.



A 48 **A 49a-b** **A 57a-b**

	Alcohol	Catalyst	Reaction conditions solvent/T/t	Yield (%)	Ref.
a:	R=H	$[Cp^*IrCl_2]_2/NaHCO_3$	Toluene 110 °C/17 h	94	[107]
a:	R=H	$[Ru(p\text{-cymene})Cl_2]_2$/DPEphos	SFRC MW/115 °C	91	[108]
a:	R=H	Pd/Fe_2O_3	160 °C/2 h	90	[109]
a:	R=H	$[Cp^*Ir(NH_3)_3][I]_2$	H_2O reflux/under air/6 h	92	[110]
b:	R=4-Cl	$FeBr_3$/$_{DL}$-pyroglutamic acid/Cp*H	1,2,4-TMB 160 °C/24 h	91	[111]
a:	R=H	$[IrCl(cod)]_2/Py_2NP\textit{i}Pr_2$	KO-*t*-Bu/diglyme 110 °C/17 h	92	[112]
a:	R=H	$Ru(OH)_3$-Fe_3O_4	KOH/toluene 130 °C/2 d	99	[113]

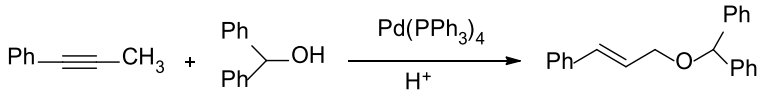
For the amination of allylic alcohols $Pd(Xantphos)Cl_2$, was used as the catalyst [115].

Boyer reported the procedure based on the utilization of $BiBr_3$ for the benzylation of aliphatic alcohols with various benzylic alcohols under mild conditions [116].

Yamamoto and co-workers developed a simple and efficient method for the synthesis of various allylic ethers from alcohols and alkynes using a substoichiometric amount of $Pd(PPh_3)_4/PhCO_2H$ in dioxane at 100 °C in good to high yields [117].

Preparation of diphenylmethanol ethers of alcohols and phenol catalyzed by $Fe(NO_3)_3 \bullet 9H_2O$ under solvent-free reaction conditions at 80 °C in good yields was described by Varma [118].

Zhang reported the coupling of alkynes with alcohols to give allylic ethers in the presence of palladium as a catalyst. With phenols the C-alkylation products were obtained in moderate yields (Scheme A19) [119].



A 58 **A 19a** **A 59a**

85%

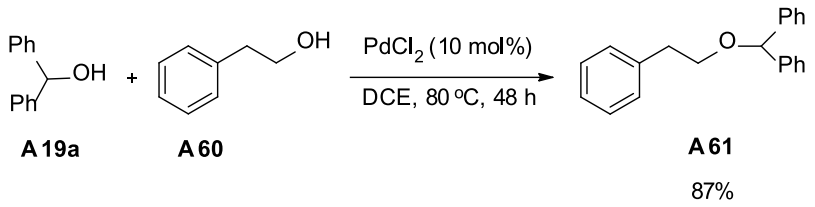
Scheme A19: Coupling of alkyne **A58** with alcohol **A19a** catalyzed by $Pd(PPh_3)_4$.

The use of palladium complex as a catalyst for the direct preparation of symmetric and unsymmetric aromatic ethers (by coupling of two different alcohols), for the amination of secondary benzylic alcohols (with electron-deficient anilines) and for the direct formation of

thioethers (by the direct action of thiols on *sec*-phenylethyl alcohol) was described by Abu-Omar [120].

Ikariya has shown the role of triphenyl phosphite-palladium complex as the catalyst for the substitution reactions of allylic alcohols *via* a direct C-O bond cleavage to give the corresponding allylic ethers and the related C-C and C-N bond-forming products [121].

Pale and co-workers developed a method for the protection of alcohols by the synthesis of diphenylmethyl ethers or bis(methoxyphenyl) methyl ethers catalyzed by $PdCl_2$ [122] or $PdCl_2(CH_3CN)_2$ [123] (Scheme A20).



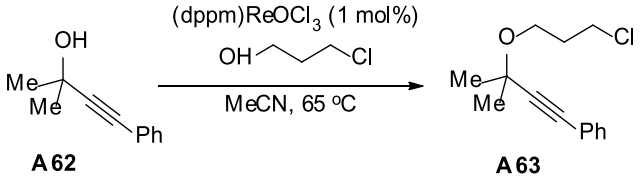
Scheme A20: Formation of DPM ether **A61** in the presence of $PdCl_2$ as the catalyst.

Asensio and co-workers reported the preparation of unsymmetrical ethers from alcohols using $NaAuCl_4$ (2-5 mol%) as simple gold catalyst [124]. The procedure enables the etherification of benzylic and tertiary alcohols under mild conditions with moderate to good yields.

Kerton reported the procedure based on the utilization of $Pd(CH_3CN)_2Cl_2$ for the etherification of benzyl alcohol in hydrophobic ionic liquids (1-Butyl-3-methyl imidazolium hexafluorophosphate, [BMIM]PF_6) using a microwave or conventional heating [125]. In the presence of NH_4Cl chlorination of benzyl alcohol occurred.

Palladium on magnesium oxide (Pd/MgO) catalyzed the formation of thioethers from thiols and aldehydes formed *in situ* from the alcohol by means of a borrowing hydrogen method. It was noticed that in the absence of the catalyst the reaction did not occur [126].

Toste described the role of rhenium (V)-oxo complex catalyst for the formation of C-O bond by the coupling of simple alcohols and propargyl alcohols (Scheme A21) [127].



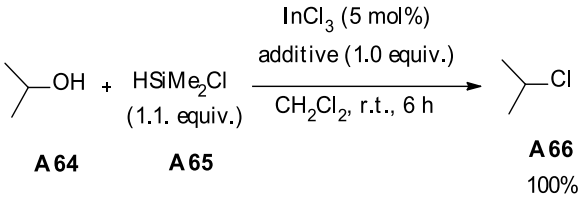
Scheme A21: Re-oxo-catalyzed etherification of 2-methyl-4-phenylbut-3-yn-2-ol **A62**.

The reaction of alcohols with silanes is a widely used methodology for the transformation of a hydroxyl group into an organic molecule. The introduction of TMS group into an organic molecule is achieved using hexamethyldisilazane (HMDS) in the presence of $LiClO_4$ (solid) [128] or $LaCl_3$ [129] as catalysts.

The role of $InBr_3$ as the catalyst was reported by Ding for the direct cyanation of alcohols with TMSCN in the presence of DCM as the solvent where different benzylic alcohols could be converted to the corresponding nitriles in yields of 46-99% [130]. The reaction was studied with different Lewis acids. $InCl_3$ and $InBr_3$ turned out to be the best catalysts. In the absence of the catalyst, no reaction was observed. The authors speculated that the catalytic cycle involved some type of carbenium intermediates which were formed by the heterolytic cleavage of C-O bond of the alcohols with the assistance of Lewis acid In(III) (and TMSCN).

Furthermore, chlorination of alcohols has been accepted as one of the most important transformations in organic chemistry and has attracted significant interest over the years.

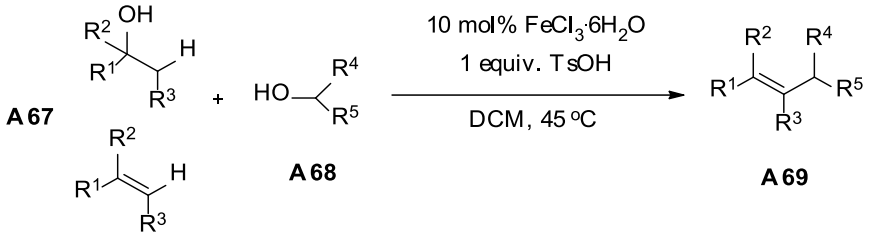
The substoichiometric amount of $InCl_3$ in the presence of an equimolar amount of benzil [131] or a combination of $GaCl_3$ (5 mol%) and diethyl tartrate (10 mol%) [132] are required for the direct chlorination of alcohols using $HSiMe_2Cl$ (Scheme A22).



Scheme A22: Chlorination of propan-2-ol **A64** catalyzed by $InCl_3$.

1.1.3 Lewis/Brønsted acid combination-catalyzed approaches

Liu described $FeCl_3 \bullet 6H_2O$ catalyzed and mediated by TsOH direct coupling of various olefins with different types of alcohols under the typical conditions (10 mol% $FeCl_3 \bullet 6H_2O$, 1.0 equiv. of TsOH, in DCM, 45 °C) providing the corresponding substituted alkene in good yields. Sterically hindered olefins such as 1-phenyl-1-cyclohexene gave the coupling product in excellent yield. Since alkenes could be formed by dehydroxylation of the corresponding secondary and tertiary alcohols, the authors performed direct coupling of benzylic alcohols providing the corresponding coupling product (Scheme A23) [133].



Scheme A23: Direct coupling of alcohols and alkenes with alcohols catalyzed by $FeCl_3 \bullet 6H_2O$.

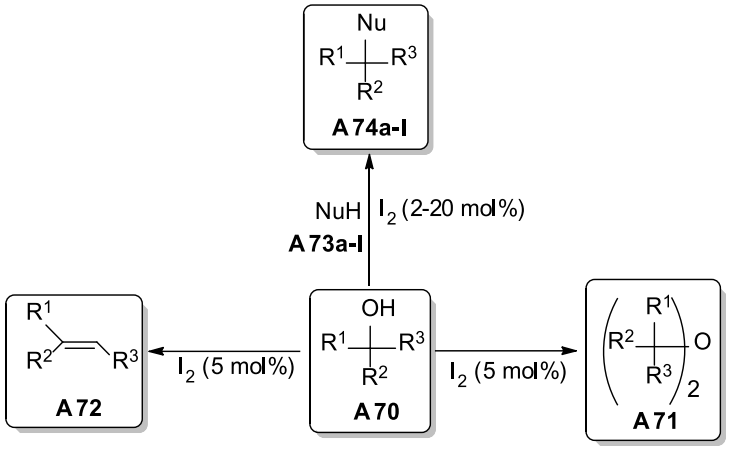
Lau's group developed addition reaction of ß-diketones to secondary alcohols and styrenes to yield the α-alkylated ß-diketones catalyzed by perchlorate salt of the dicationic bipy-ruthenium complex *cis*-$[Ru(6,6'\text{-}Cl_2bipy)_2(H_2O)_2]^{2+}$ [134]. It was proposed and confirmed by independent experiments that the catalytic addition of ß-diketones to the secondary alcohols was catalyzed by the Brønsted acid $HClO_4$ generated by the reaction of the metal complex with the ß-diketone.

1.2 Other promoters-catalyzed approaches

1.2.1 Molecular iodine-catalyzed approaches

Iodine could catalyze various transformations of alcohols, which has been reviewed [135] and many results are shown in Table A17.

Benzyl [136-141], allyl [139], [142-148] and propargyl [139], [149,150] alcohols **A70** were treated with various nucleophiles in the presence of I_2 (2-20 mol%) and formed different types of products (Scheme A24, Table A17).



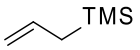
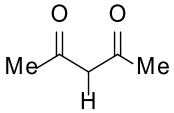
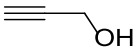
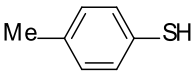
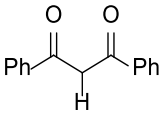
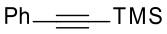
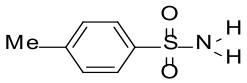
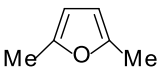
$R^1=R^2=R^4=Ph$, (93%) [151]

$R^1=R^2=H$, $R^3=Ph$, (89%) [151]

A74a: $R^1=Ph$, $R^2=H$, $R^3=CHCHPh$, Nu=allyl [142],
A74b: $R^1=Ph$, $R^2=H$, $R^3=Me$, $Nu=CH(COMe)_2$ [136],
A74c: $R^1=4\text{-}OMeC_6H_4$, $R^2=H$, $R^3=Me$, $Nu=OCH_2CCH$ [137],
A74d: $R^1=Me$, $R^2=H$, $R^3=CHCHPh$, $Nu=4\text{-}MeC_6H_4S$ [143],
A74e: $R^1=Ph$, $R^2=H$, $R^3=CCPh$, $Nu=4\text{-}OHC_6H_4$ [149],
A74f: $R^1=4\text{-}MeC_6H_4$, $R^2=H$, $R^3=CHCH(4\text{-}MeC_6H_4)$, $Nu=CH(COPh)_2$ [144,145],
A74g: $R^1=Ph$, $R^2=H$, $R^3=Nu=CCPh$ [150],
A74h: $R^1=4\text{-}MeC_6H_4$, $R^2=H$, $R^3=CHCHPh$, Nu=NHTs [146,147],
A74i: $R^1=R^2=Ph$, $R^3=H$, Nu=NHCOPh [139],
A74j: $R^1=Ph$, $R^2=R^3=H$, $Nu=4\text{-}OMeC_6H_4$ [138],
A74k: $R^1=Ph$, $R^2=H$, $R^3=Me$, Nu=NHCOMe [140],
A74l: $R^1=Ph$, $R^2=H$, $R^3=Me$, $Nu=C_6H_7O$ [136]

Scheme A24: Substitution, dimerization or elimination of alcohols catalyzed by iodine.

Table A17: Nucleophilic substitution of alcohols catalyzed by iodine.

NuE	I_2 (mol%)	Solvent	T (°C)	t (h)	Product	Yield (%)	Ref.
	10	CH_2Cl_2	rt	0.25	**A74a**	94	[142]
	10	$MeNO_2$	80	1	**A74b**	99	[136]
	5	MeCN	0	0.25	**A74c**	92	[137]
	10	1,4-Dioxane	rt	1.5	**A74d**	92	[143]
Phenol	5	MeCN	-10	0.5	**A74e**	90	[149]
	5	CH_2Cl_2	rt	1.5	**A74f**	90	[144,145]
	10	CH_2Cl_2	0	3	**A74g**	96	[150]
	5	CH_2Cl_2	rt	3[a]	**A74h**	85	[146,147]
$PhCONH_2$	2	MeCN	Reflux	2	**A74i**	98	[139]
Anisole	10	SFRC	60	4[b]	**A74j**	88	[138]
$MeCN/H_2O$	20	PhMe	110	4[c]	**A74k**	85	[140]
	10	$MeNO_2$	80	/	**A74l**	78	[136]

[a] Reaction was carried out in the presence of $CaSO_4$. [b] Reaction was carried out in the presence of molecular sieves. [c] Water (2 equiv.) was added.

Primary and secondary benzylic alcohols supplied ethers, such as **A71** (R^1=R^2=H, R^3=Ph), under SFRC [151].

Tertiary alcohols underwent elimination of water in the absence of nucleophiles providing the corresponding alkenes such as **A72** (R^1=R^2=R^4=H), in high yields (Scheme 1) [151].

Liu described C-C and C-N bonds formation from allylic/propargylic and other alcohols with various C- and N- nucleophiles in the presence of iodine catalyst (10 mol%) in MeCN, at room temperature [152].

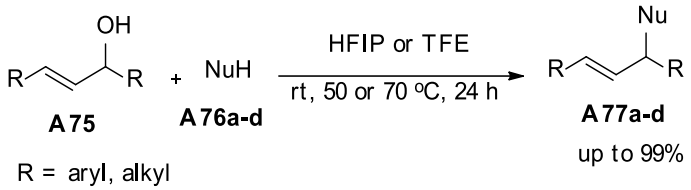
Jereb reported an environmentally friendly synthesis of trimethylsilyl ethers from alcohols, phenols and carbohydrates in the presence of HMDS under solvent-free conditions, at room temperature. Sterically hindered phenols, carbohydrates and most of the alcohols required a substoichiometric amount of iodine (up to 2 mol%) [153].

Das reported one-spot synthesis of pentasubstituted pyrroles by the tandem reaction of amines, dialkyl acetylenedicarboxylates, and propargylic alcohols catalyzed by iodine (10 mol%), in toluene and the obtained corresponding products were in high yields (75-88%) [154].

1.2.2 HFIP and TFE-catalyzed approaches

In 2012, Najera and co-workers investigated the fluorinated alcohols, such as 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) and 2,2,2-trifluoroethanol (TFE), used as solvents and promoted direct substitution reaction of allylic alcohols with nitrogen, silyl, and carbon nucleophiles (Scheme A25). The reactions were performed at room temperature up to 70 °C and afforded

allylic substitution product in high yields, especially when HFIP was employed as the solvent [155].

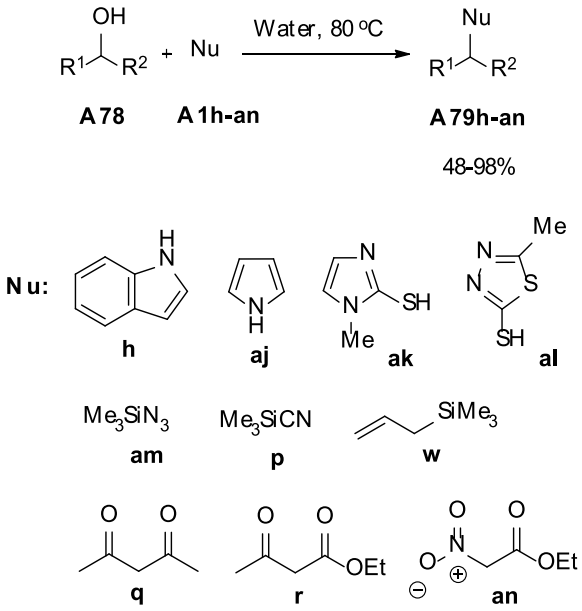


NuH: a: RNH_2, **b:** TMSNu, **c:** ArH, **1d:** 3-dicarbonyl compounds

Scheme A25: Direct allylic substitution of alcohols **A75** promoted by fluorinated alcohols.

1.2.3 H_2O-catalyzed approaches

Cozzi and Zoli performed the direct nucleophilic substitution of alcohol "on water" without the addition of any Brønsted/Lewis acid (Scheme A26) [156]. Reactions depend on the stability of the corresponding carbocation. The reactions were performed in deionized water at 80 °C. Various nucleophiles reacted smoothly with the selected alcohols.



Scheme A26: Nucleophilic substitution of alcohols **A78** "on water".

Hirashita's group described the hydrothermal conditions utilizing ion-exchanged water at 220 °C [157].

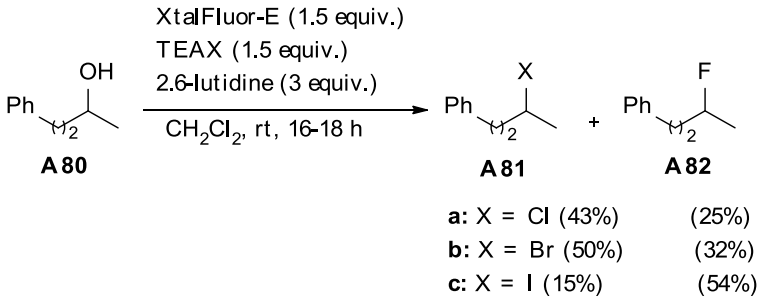
1.2.4 Miscellaneous

Utilizing trimethylsilyl trifluoromethanesulfonate (TMSOTf) as an efficient catalyst for direct benzylation of 1,3-dicarbonyl compounds with various benzylic alcohols in CH_3NO_2 was described by Lalitha [158].

Chlorination and bromination reactions of alcohols have been developed by Denton using catalytic phosphorus (V) in oxalyl chloride $(COCl)_2$, $CHCl_3$ or $(COCl)_2LiBr$, $CHCl_3$, at room temperature [159].

In 2012, Paquin and co-workers described chlorination/bromination (up to 92% yield) and iodination (in lower yields) of primary alcohols using a combination of tetraethylammonium

halide (1.5 equiv.) and $[Et_2NSF_2]BF_4$ (XtalFluor-E) (1.5 equiv.), 2,6-lutidine, in CH_2Cl_2, at r.t., 12 h [160]. Halogenation was limited to primary alcohols. In the case of 4-phenyl-2-butanol the halogenation was slower; as a result, fluorination became somewhat competitive (Scheme A27).

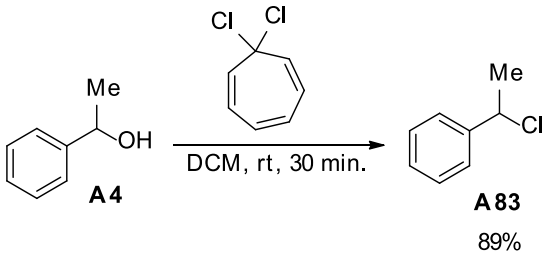


Scheme A27: Halogenation of 4-phenyl-2-butanol **A80**.

Lambert performed a convenient and efficient method for converting alcohols to alkyl chlorides in excellent yields using dichlorodiphenylcyclopropene in DCM at room temperature [161]. Later on, Lambert performed chlorodehydration of alcohols catalyzed by cyclopropene (10 mol%) in oxalylchloride ($COCl_2$), producing chlorinated products in good to excellent yields [162]. In the absence of the catalyst no chlorinated product was observed and chloroxalate was the only product.

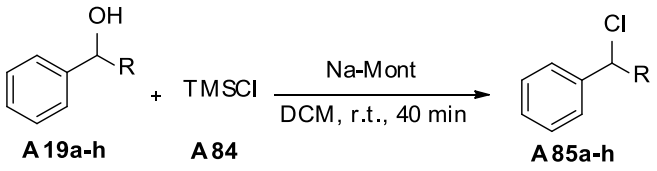
Lautens and co-workers have shown that the combination of bromotrichloromethane ($CBrCl_3$) and triphenylphosphine (PPh_3), in DCM, at r.t., for 1 h could convert benzyl alcohols into benzyl chlorides in excellent yields [163]. Qi described the treatment of substituted benzyl alcohols and pyridine methanols with tosyl chloride (TsCl) and the corresponding chlorides were the main products [164]. For substituted benzyl alcohols and pyridine methanols it was possible to predict whether chlorination or tosylation would occur.

Nguyen developed a new method for the nucleophilic substitution of alcohols using aromatic tropylium cation activation and the chlorinated products were obtained in high yields (Scheme A28) [165].

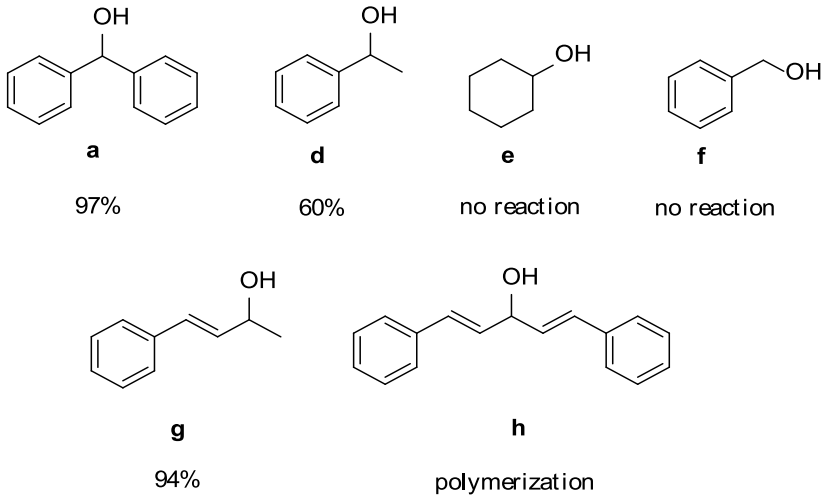


Scheme A28: Chlorination of 1-phenylethanol **A4**.

The most recently developed method for alcohol chlorination with silanes utilizes TMSCl and natural sodium montmorillonite (Na-Mont) as the catalyst in DCM [166]. In the absence of the catalyst, the efficiency of the transformation was reported to be very low (8%). The scope of this reaction is limited to secondary benzyl alcohols and strongly activated primary benzyl alcohols (Scheme A29).



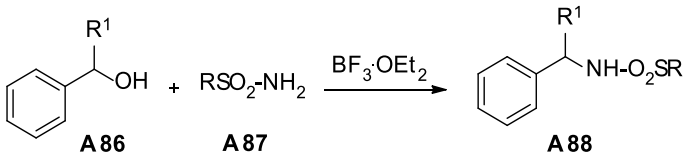
Selected products:



Scheme A29: Chlorination of alcohols **A19a-h** catalyzed by Na-Mont.

Organohalides were found as effective catalysts for dehydrative O-alkylation of different alcohols, providing homo- and cross-etherification methods for a general preparation of the useful symmetrical and unsymmetrical aliphatic ethers [167]. Hypervalent [bis(trifluoroacetoxy)iodo]benzene ($PhI(OCOCF_3)_2$, PIFA) catalyst has been found to function as Lewis acid for nucleophilic substitution reactions of propargylic alcohols with various of C-, O-, S-, and N-nucleophiles in the presence of CH_3CN as the solvent [168].

Xiong and co-workers developed a method for direct *N*-benzylation of sulfonamides with primary and secondary benzyl alcohols using boron trifluoride-diethyl ether complex (BF_3•OEt) (Scheme A30) [169].



Scheme A30: N-benzylation of sulfonamides **A87** with benzylalcohols **A86**.

Takemoto and co-workers developed a combination of a halogen bond (XB) donor with trimethyl-silyl halide (TMSX) as an efficient cocatalytic system for the direct dehydroxylative coupling reaction of alcohol with different nucleophiles bearing TMS groups, such as allyltrimethylsilane and trimethylsilylcyanide, to provide the corresponding adduct [170].

Chapter 2

Aim of the work

Following the growing ecological awareness, it is becoming essential to design environmentally friendly methods for chemical transformations. Particularly the replacement of harmful, toxic and expensive organic solvents with alternative solvents such as water should be considered as a priority goal for organic synthesis. Efforts in discovering of suitable reaction conditions, such as using environmentally desirable solvents and catalysts or reagents that allow comprehensive direct transformation of target organic molecules and following also other principles of green chemistry in the best possible way, are an ever present challenge.

The aim of this work is to develop new methodologies for comprehensive direct transformation of various alcohols, in a way and under reaction conditions following as much as possible the principles of green chemistry, especially the principles that include catalytically supported transformations under SFRC, HCRC or in aqueous media.

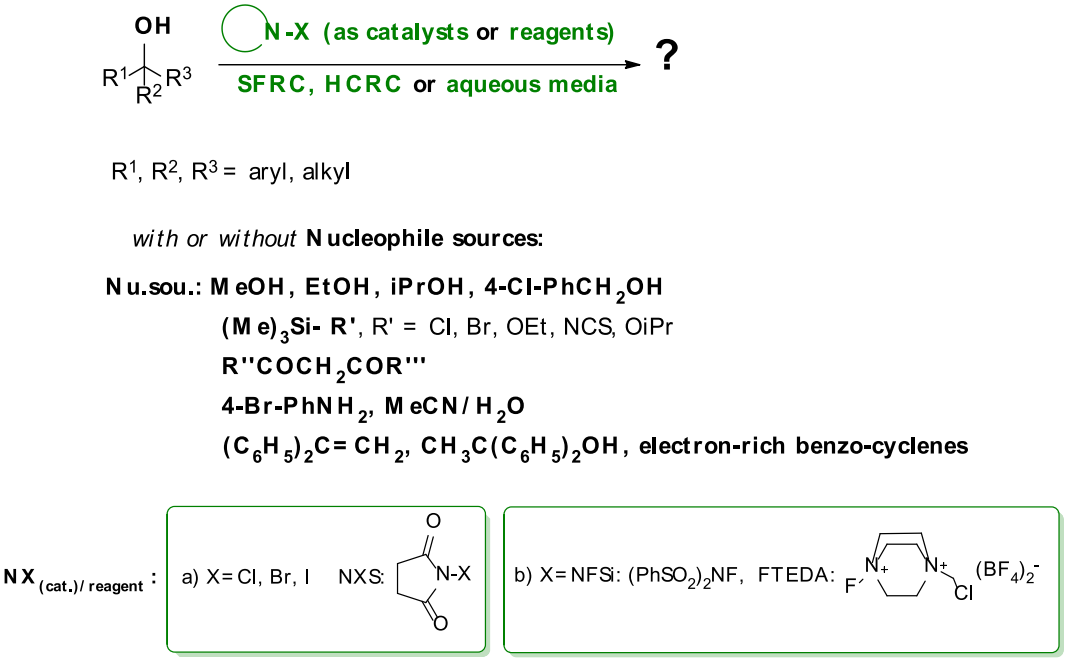
According to the knowledge collected in the introduction part of this PhD thesis, I believe that there should be space for a new type of catalysts for comprehensive direct transformation of alcohols into the corresponding new valuable products, bearing the newly formed C-C and C-heteroatom bonds. *N*-halo organic compounds typically used in organic synthesis as a halogen atom source for halogenation of organic molecules. However in the framework of my thesis, I intend to check and evaluate the role of these valuable compounds as potential catalysts for comprehensive direct transformation of alcohols.

I chose the following *N*-halo organic molecules bearing an active *N*-halogen bond: *N*-halosuccinimides, (*N*-chlorosuccinimide, *N*-bromosuccinimide and *N*-iodosuccinimide), 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis-tetrafluoroborate *(Selectfluor™ F-TEDA-BF_4)* and *N*-fluorobenzenesulfonimide *(Accufluor™ NFSi)* as testing candidates for achieving the above-mentioned goal of this thesis under green reaction conditions if possible. Additionally, I would like to explore and evaluate the role of following participating molecules, in the *N*-halo organic compounds catalyzed transformation of alcohols: primary, secondary and tertiary alcohols, phenyl substituted alkenes, heteroatom benzo-cyclenes, 1,3-dicarbonyl compounds, nitriles and anilines. Those molecules are electron rich compounds and thus potential nucleophiles. Moreover, trimethyl substituted silanes are also chosen as testing compounds as they are source of nucleophile as well.

Within the scope of this research I intend to verify the following hypotheses:

1. *N*-halo organic compounds could catalytically activate the hydroxyl functional group in a target molecule, thus forming an active specie, which could react with other organic molecules, bearing an appropriate reaction centre. Thus, new C-C or C-heteroatom bonds could be formed, opening new possibilities for formation of diverse molecules in organic synthesis. In case that the nature of this active intermediate is electron deficient, reactions of variety of organic compounds possessing electron rich active sites, could be present.
2. *N*-halo organic compounds, such as 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis-tetrafluoroborate (*Selectfluor™ F-TEDA-BF_4)* [171] and also *N*-halosuccinimides, could be used as reagents for direct transformation of tertiary alcohols bearing a ß-hydrogen atom, into the corresponding vicinal halohydrins or similar compounds.

The aim based on these hypotheses is graphically illustrated in Scheme 2.1.



Scheme 2.1: General concept and work-plan of the research.

The research work will be divided into the following chapters:

1. **Various transformations of alcohols catalytically supported by *N*-halo organic compounds**

2. **Etherification of alcohols catalyzed by *N*-halosuccinimides or *N*-fluoro organic compounds**

3. ***N*-halo compounds catalysis of new carbon-carbon bond formation in organic molecules**

a. C-C bond formation through ß-diketones
b. C-C bond formation through electron rich C=C bond

4. **Various transformations of alcohols using trimethylsilyl derivatives**

a. Halofunctionalization of organic compounds using trimethylsilyl halogenides
b. Various transformations of alcohols using trimethylsilyl derivatives

5. Transformation of tertiary alcohols to vicinal halo-substituted derivatives using *N*-halosuccinimides

a. Halogenation of tertiary alcohols in organic solvents
b. Halogenation of tertiary alcohols in water in the presence of amphiphile

Chapter 3

Materials and methods

Used chemicals and solvents
All alcohols used as substrates were purchased from commercial sources (Sigma Aldrich) and were used without further purification.

Evaporation of (volatile) solvents and thermostated reactions
For evaporation Rotary Evaporator Büchi R-124 was used. The reactions at elevated temperatures were performed using a lab oven or magnetic stirrer with heating plate.

The chromatographic methods
The thin-layer chromatography (TLC) analysis was performed using Silica gel plates/TLC-cards-DC-Alufolien manufacturer Fluka Kieselgel with 0.2 mm applying gel on an aluminum carrier. For the detection of compounds on chromatographic plates, a UV lamp (254 nm) was used.

Column chromatography (CC) was performed using silica gel Kieselgel 60 manufacturer Fluka (particle size: 0.063-0.200 mm).

Spectroscopic methods
^{1}H, ^{13}C and ^{19}F NMR spectra were recorded at the Slovenian NMR center (National Institute of Chemistry). NMR spectra were obtained at ambient temperature on a 300 MHz spectrometer using $CDCl_3$ as the solvent with $SiMe_4$ (TMS) for ^{1}H and ^{13}C or $CFCl_3$ for ^{19}F as an internal standard. Chemical shifts (δ) are given in ppm according to internal standard.

Mass Spectra (ESI) and HR-MS were recorded by Q-TOF Premier (Waters-Micromass) the Center for Mass Spectroscopy at the Jožef Stefan Institute. Under this technique only a few compounds could give a satisfactory mass spectrum.

Determination of melting point
Melting point was determined in a capillary tube by Buchi 535 equipment at the Jožef Stefan Institute.

Safety
The ordinary safety precautions for working in the laboratory of organic chemistry should be used.

Chapter 4

Various transformations of alcohols catalytically supported by *N*-halo organic compounds

The development of protocols for the transformation of organic compounds under more environmentally acceptable conditions, particularly an achieving high atom economy, selectivity and efficiency of the processes at the same time is currently one of the main trends in organic synthesis. From this point of view, planning organic reactions and processes following the principles of green chemistry [1] is a major challenge in organic chemistry. Organic reactions in aqueous media, under HCRC or under SFRC mainly fulfill these principles.

Since alcohols are versatile compounds, their direct transformation under green reaction conditions would be an important process to provide useful building blocks in organic synthesis. Because of their lower leaving ability group, hydroxyl moieties are rarely substituted under mild conditions and must often be activated before treatment with nucleophiles [65].

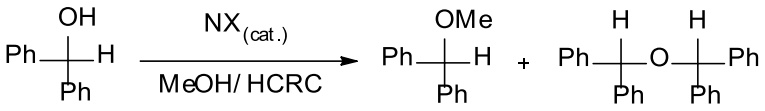
Numerous related methodologies have been elaborated using a substoichiometric amount of Brønsted acids, metals ions, molecular iodine or other promoters which are described in the first chapter.

Accordingly, the development of efficient, selective and environmentally benign catalytic methodologies for comprehensive direct transformation of various alcohols for new C-C and C-heteroatom bonds formation remains an attractive research subject. On the basis of our research group's continuing interest in developing greener methods for the efficient and selective direct transformations of organic compounds, I report the introduction of organic compounds bearing an active *N*-halogen bond. Namely *N*-halosuccinimides (chloro, bromo and iodo) and 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis-tetrafluoroborate *(Selectfluor™ F-TEDA-BF_4)* and *N*-fluorobenzenesulfonimide *(Accufluor™ NFSi),* as a new type of non-metal, non-acidic, and environmentally friendly catalysts for comprehensive direct transformations of various alcohols, selectively and efficiently into the corresponding new valuable products, bearing new formed C-C and C-heteroatom bonds under SFRC or under HCRC.

4.1 Results and discussion

Initially, I chose diphenylmethanol **1** as the model substrate to investigate the efficiency of *N*-halo organic compounds as a catalyst and to find the best reaction conditions for alcohol transformation (Table 4.1). As can be seen from Table 4.1, the transformation of diphenylmethanol **1** catalyzed by *N*-halo organic compounds in the presence of methyl alcohol under HCRC gave ether **2** (entries 1-5), while in the absence of MeOH under SFRC, dimerization process took place, resulting in the formation of the symmetric ether **3**, (entry 6). I found that under the same reaction conditions, *N*-halosuccinimides (NIS, NCS and NBS) expressed higher catalytic activity for the transformation of secondary benzyl alcohol **1** (entries 3-5) into the corresponding ether **2** than *N*-fluoro organic compounds (FTEDA and NFSi), (entries 1 and 2), which gave a lower yield.

Table 4.1: The catalytic effect of *N*-halo catalysts on conversion of diphenylmethanol **1** with MeOH under HCRC[a].



1 **2** **3**

Entry	$NX_{(cat.)}$	Mol%	MeOH (mmol)	Conv.[b] [%] of **1**	Relative distribution[c] [%]	
					2	**3**
1	**NFSi**	3	1	32	27	3[e]
2	**FTEDA**	3	1	36	32	3[e]
3	**NCS**	3	1	100	92	5[e]
4	**NBS**	3	1	100	92	5[e]
5	**NIS**	**3**	**1**	**100**	**100**	**/**
6[d]	**NIS**	**2**	**/**	**100**	**/**	**100**

[a] Reaction conditions: diphenylmethanol **1** (0.5 mmol), 70-75 °C, 6 h. [b] Determined from ^{1}H NMR spectra of isolated crude reaction mixtures. [c] Yields calculated relative to alcohol **1**. [d] 3.5 h. [e] Benzophenone 1-3%.

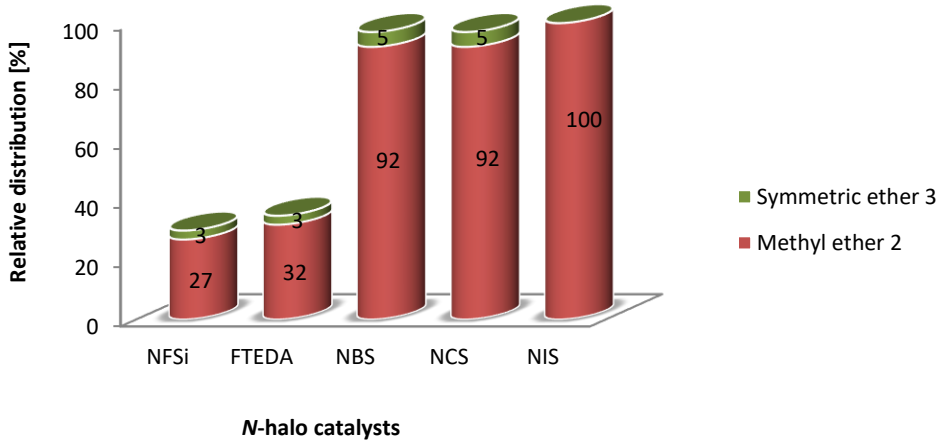
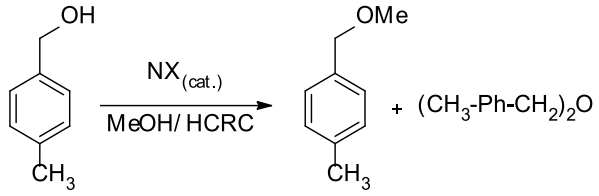


Figure 4.1: The catalytic effect of *N*-halo catalysts on conversion of diphenylmethanol **1** with MeOH under HCRC.

Inspired by this result, I further examined the role of NIS as the catalyst by direct etherification of primary benzyl alcohol bearing electron-donating substituent on the aromatic ring, with MeOH under HCRC. Surprisingly, etherification of 4-methylbenzyl alcohol **4** with MeOH under HCRC or in solution, employing NIS as the catalyst, was not efficient enough (entries 1-5, Table 4.2). In order to improve the efficiency of this transformation in the continuation of my work, I investigated if another type of catalyst from *N*-fluoro organic compounds shows catalytic activity on the course of the reaction. I performed the same reaction in the presence of NFSi as the catalyst under HCRC, I found out that the reaction resulted in the formation of ether **5** in good yield (entry 7). Additionally, the transformation of 4-methylbenzyl alcohol **4** catalyzed by NIS in the absence of MeOH under SFRC gave symmetric ether in quantitative yield **6** (entry 8).

Table 4.2: The catalytic effect of NIS and NFSi on conversion of 4-methylbenzyl alcohol **4** with MeOH under HCRC[a].



4 **5** **6**

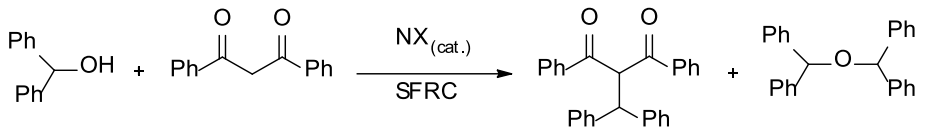
Entry	$NX_{(cat.)}$	Mol%	MeOH (mmol)	Conv.[b] [%] of **4**	Relative distribution[c,d] [%]	
					5	**6**
1	**NIS**	3	1	39	23	14
2	**NIS**	5	1	49	32	14
3[e]	**NIS**	3	1	/	/	/
4	**NIS**	3	1[f]	/	/	/
5	**NIS**	3	2	15	9	5
6	**NFSi**	1	2	36	27	7
7	**NFSi**	**5**	**2**	**75**	**61**	**12**
8	**NIS**	**3**	**/**	**100**	**/**	**100**

[a] Reaction conditions: 4-methylbenzyl alcohol **4** (0.5mmol), 70-80 °C, 24 h. [b] Determined from ^{1}H NMR spectra of isolated crude reaction mixtures. [c] Yields calculated relative to alcohol **4**. [d] Oxidised alcohol 1-3%. [e] rt. [f] 1 mL.

Furthermore, I investigated the role of *N*-halo organic compounds as a catalyst for direct new C-C bond formation by direct coupling reactions of different types of electron rich compounds including 1,3-dicarbonyl compound, tertiary benzyl alcohol bearing vicinal hydrogen atom or phenyl substituted alkene with secondary benzyl alcohol under SFRC. I have examined the reaction of diphenylmethanol **1** with dibenzoylmethane **7** under SFRC and results are summarised in Table 4.3.

In the presence of NCS or FTEDA as the catalyst, I did not observe any conversion of the diphenylmethanol **1** (entries 1 and 2), while in the presence of NBS I observed a low conversion of the diphenylmethanol **1** into the dimeric ether **3** (entry 3), and in the presence of NFSi as a catalyst, I observed good conversion of the diphenylmethanol **1** into the dimeric ether **3** as the main product (entry 4). Moreover, in the presence of NIS as the catalyst, the coupling of benzyl moiety with one of ß-dicarbonyl took place, providing efficiently and selectively the corresponding product **8** with the new C-C bond formed between benzyl carbon atom and C-2 carbon of dicarbonyl target **8** (entries 5 and 6).

Table 4.3: The effect of substoichiometric amount of *N*-halo catalysts on conversion of diphenylmethanol **1** with dibenzoylmethane **7** under SFRC[a].



1 **7** **8** **3**

Entry	$NX_{(cat.)}$	Mol%	Conv.[b] [%] of **1**	Relative distribution[c] [%]	
				8	**3**
1	**NCS**	3	/	/	/
2	**FTEDA**	3	/	/	/
3	**NBS**	3	4	/	4
4	**NFSi**	3	75	27	48
5	**NIS**	3	100	100	/
6	**NIS**	**1**	**100**	**100**	**/**

[a] Reaction conditions: diphenylmethanol **1** (0.5mmol), dibenzoylmethane **7** (0.5 mmol), 70-75 °C, 24 h. [b] Determined from ^{1}H NMR spectra of isolated crude reaction mixtures. [c] Yields calculated relative to alcohol **1**.

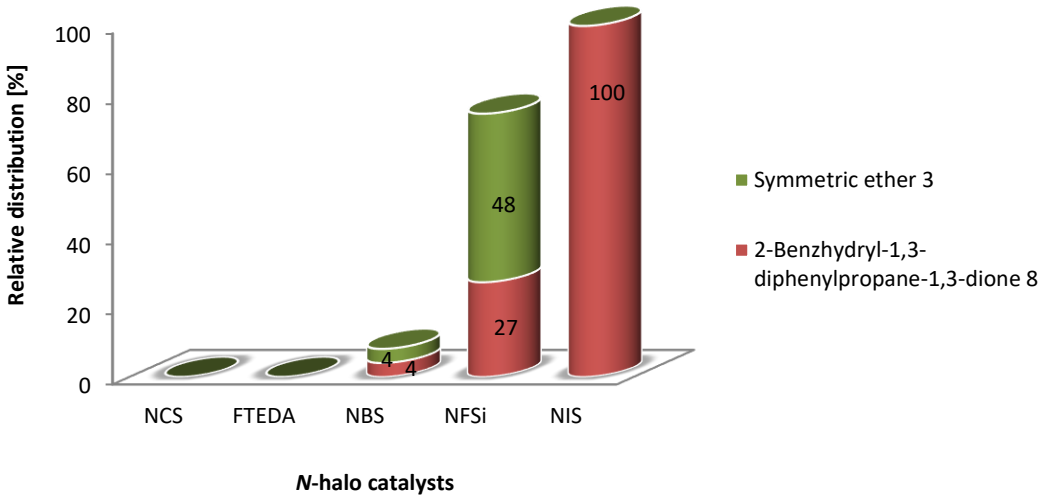
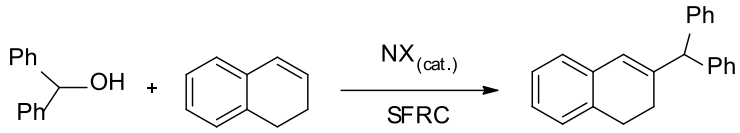


Figure 4.2: The effect of substoichiometric amount of *N*-halo catalysts on conversion of diphenylmethanol **1** with dibenzoylmethane **7** under SFRC.

On the other hand, the catalytic effect of *N*-halo organic compounds for direct new C-C bond formation by direct coupling of phenyl substituted alkene with secondary benzyl alcohol under SFRC was studied and results are collected in Table 4.4. Initially, I chose diphenylmethanol **1** and 1,2-dihydronaphthalene **9** as model compounds to find the best reaction conditions for this reaction. When the reaction was performed in the presence of NCS as the catalyst, I did not observe any conversion of the diphenylmethanol **1**, while in the presence of FTEDA, NBS or NFSi

as the catalyst, I observed low conversion of the diphenylmethanol **1** into the dimeric ether **3**. NIS as the catalyst was found to promote most efficiently and selectively the direct coupling of diphenylmethanol **1** with 1,2-dihydronaphthalene **9** under SFRC, furnishing the corresponding substituted alkene **10** accompanied by a small amount of dimeric ether **3**.

Table 4.4: The catalytic effect of *N*-halo catalysts on conversion of diphenylmethanol **1** with 1,2-dihydronaphthalene **9** under SFRC[a].



1 **9** **10**

Entry	$NX_{(cat.)}$	Mol%	Conv.[b] [%] of **9**	Yield[c] [%]
				10
1	**NCS**	10	/	/
2	**FTEDA**	10	/	/
3	**NBS**	10	/	/
4	**NFSi**	10	/	/
5	**NIS**	**10**	**100**	**100**

[a] Reaction conditions: diphenylmethanol **1** (0.5 mmol), 1,2-dihydronaphthalene **9** (0.4 mmol), 70-75 °C, 24 h. [b] Determined from ^{1}H NMR spectra of isolated crude reaction mixtures. [c] Yield calculated relative to **9**.

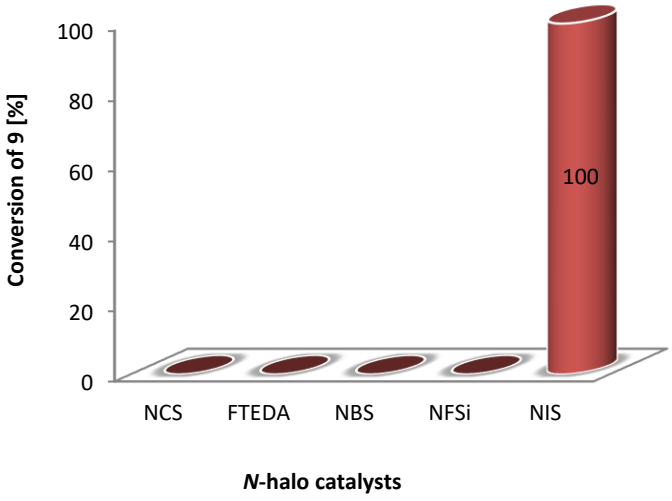
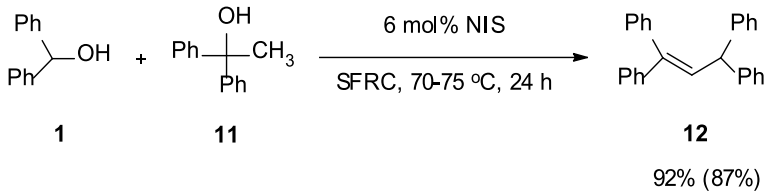


Figure 4.3: The catalytic effect of *N*-halo catalysts on conversion of 1,2-dihydronaphthalene **9** with diphenylmethanol **1** under SFRC.

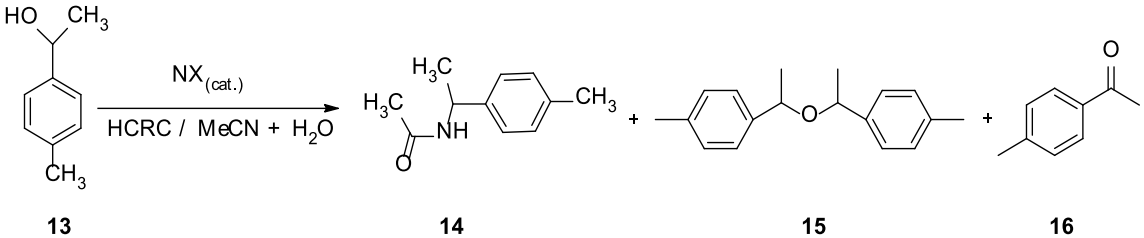
Additionally, I found that the C-C bond formation could also be achieved by direct coupling of secondary benzyl alcohol and *in situ* formed electron rich alkenes derived from dehydration of tertiary alcohol bearing a vicinal hydrogen atom, in the presence of NIS as the catalyst under SFRC. Thus, I performed direct coupling of diphenylmethanol **1** with 1,1-diphenylethanol **11** in the presence of NIS as the catalyst, under SFRC, nearly quantitatively resulting in the formation of prop-1-ene-1,1,3,3-tetrayltetrabenzene **12**, accompanied by less than 10% of side products identified as benzophenone and dimeric ether **3** (Scheme 4.1).



Scheme 4.1: Direct coupling of diphenylmethanol **1** with 1,1-diphenylethanol **11** catalyzed by NIS under SFRC.

On the other hand, the role of *N*-halo organic compounds as catalysts was observed also in reactions of alcohol with acetonitrile in a solution, where a product with new C-N bond formation could be obtained. The results are summarised in Table 4.5. The example of this possibility was demonstrated by the reaction 1-(*p*-tolyl)ethan-1-ol **13**, with acetonitrile, producing efficiently the corresponding *N*-acyl benzyl product **14** (entries 1-5) in moderate to high yield, accompanied with the formation of a small amount of dimeric ether **15** (entry 4) and oxidized alcohol **16** (entries 1-5). I found that NCS, FTEDA and NIS were more convenient catalysts for this transformation than NFSi and NBS.

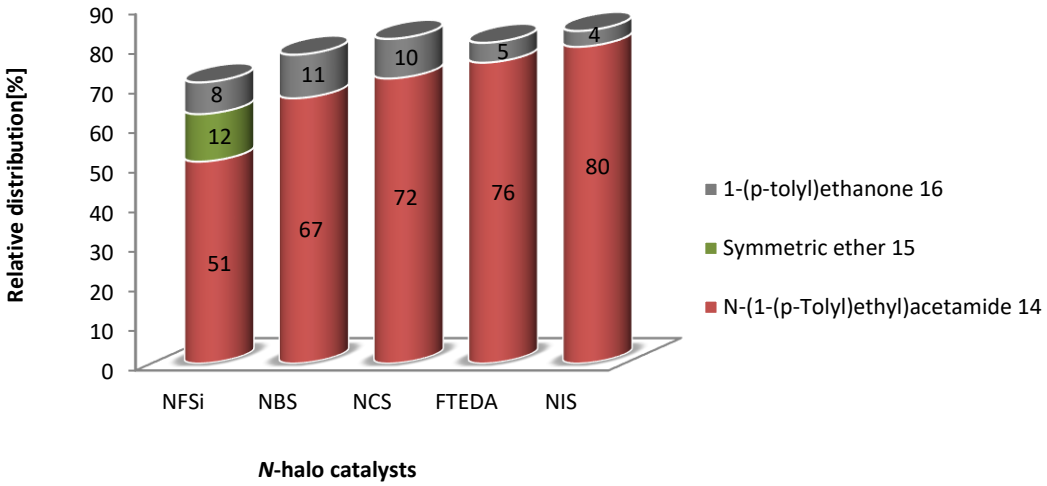
Table 4.5: The catalytic effect of *N*-halo catalysts on conversion of 1-(*p*-tolyl)ethan-1-ol **13** in acetonitrile solution[a].



13 **14** **15** **16**

Entry	$NX_{(cat.)}$	Mol%	Conv.[b] [%] of **13**	Relative distribution[c] [%]		
				14	**15**	**16**
1	**NFSi**	10	71	51	12	8
2	**NBS**	10	78	67	/	11
3	**NCS**	10	82	72	/	10
4	**FTEDA**	10	81	76	/	5
5	**NIS**	**10**	**84**	**80**	**/**	**4**

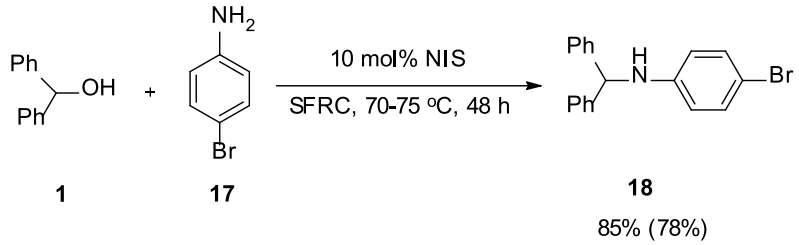
[a] Reaction conditions: 1-(*p*-tolyl)ethan-1-ol **13** (0.5mmol), MeCN (1/2 mL), H_2O (2 mmol), 70-75 °C, 24 h. [b] Determined from ^1H NMR spectra of isolated crude reaction mixtures. [c] Yields calculated relative to alcohol **13**.



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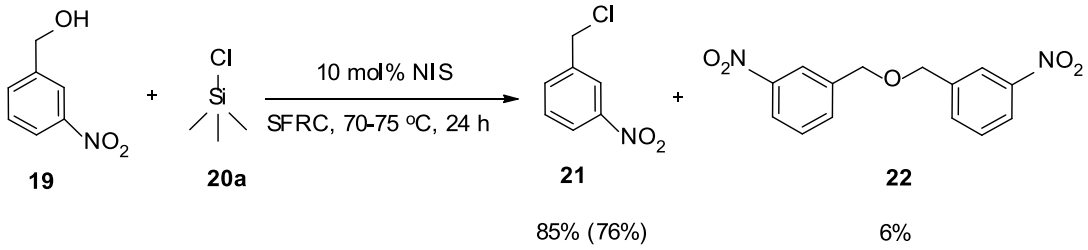
Figure 4.4: The catalytic effect of *N*-halo catalysts on conversion of 1-(*p*-tolyl)ethan-1-ol **13** in acetonitrile solution.

Additionally, the direct coupling of aniline, bearing an electron withdrawing group on the aromatic ring, with diphenylmethanol **1** in the presence of NIS as the catalyst and under SFRC, afforded the corresponding *N*-alkylated compound in high yield **18** accompanied with a small amount of oxidized alcohol (Scheme 4.2).



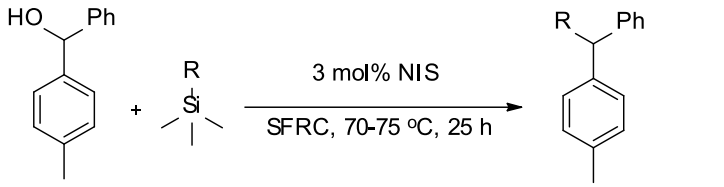
Scheme 4.2: Direct coupling of diphenylmethanol **1** with 4-bromoaniline **17** catalyzed by NIS under SFRC.

I further investigated reactions of primary benzyl alcohol with trimethylchlorosilane (TMSCl) **20a** and impact of *N*-halo organic compound as a catalyst in this transformation under SFRC. In the case of performing the reaction of 3-nitrobenzyl alcohol **19** by adding a NIS catalyst under SFRC, quantitative conversion of starting material into corresponding chloride **21** was achieved accompanied by a small amount of dimer **22** which is known compound based on ^{1}H NMR spectra of isolated crude reaction mixture (Scheme 4.3).



Scheme 4.3: Chlorination of 4-nitrobenzyl alcohol **19** with TMSCl under SFRC.

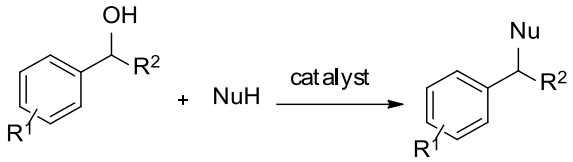
Based on transformations of alcohols with TMSCl **20a**, I was curious to find out if it is possible to introduce other functional groups in a similar way, such as isothiocyanate **20b** and ethoxy **20c** into organic molecules. I performed the reactions of diphenylmethanol **1** and phenyl(*p*-tolyl)methanol **23** as the model compounds under the mentioned reaction conditions, using (trimethylsilyl)isothiocyanate (TMSNCS) or ethoxytrimethylsilane (TMSOEt) as the sources of nucleophiles where isothiocyanate and ethoxy were introduced successfully into organic molecules **24** and **25** (Scheme 4.4).

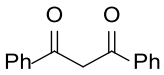
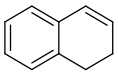
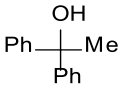
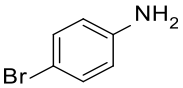


Scheme 4.4: Isothiocyanation or ethoxylation of phenyl(*p*-tolyl)methanol **23** with TMSNCS or TMSOEt catalyzed by NIS under SFRC.

The collected results in Table 4.6 are organized primarily stressing the type of bond formation.

Table 4.6: Nucleophilic substitution of alcohols using *N*-halo catalysts[a].



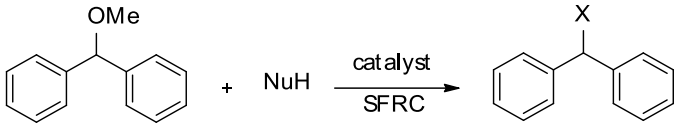
Entry	Bond formation		R^1, R^2	NuH	Catalyst	Conv.[b] [%]		Yield[c] [%]
1	**C-O**	**1**	R^1=H R^2=Ph	MeOH	NIS	100	**2**	98
2		**1**	R^1=H R^2=Ph	/	NIS	100	**3**	99
3		**4**	R^1=4-Me R^2=H	MeOH	NFSi	75 (12)[d]	**5**	55
4	**C-C**	**1**	R^1=H R^2=Ph		NIS	100	**8**	99
5		**1**	R^1=H R^2=Ph		NIS	100	**10**	70
6		**1**	R^1=H R^2=Ph		NIS	100 (8)[d]	**12**	87
7	**C-N**	**13**	R^1=4-Me R^2=Me	MeCN/H_2O	NIS	84 (4)	**14**	72
8		**1**	R^1=H R^2=Ph		NIS	85 (2)[e]	**18**	79
9		**23**	R^1=4-Me R^2=Ph	TMSNCS	NIS	100	**24**	98
10	**C-O**	**23**	R^1=4-Me R^2=Ph	TMSOEt	NIS	100 (7)[e]	**25**	89
11	**C-Cl**	**19**	R^1=3-NO_2 R^2=H	TMSCl	NIS	91 (6)	**21**	76

[a] Reaction conditions: alcohol (0.5 mmol), NuH (0.4 mmol-0.5 mL), NXS (1-10 mol%), 70-80 °C, 3.5-48 h. [b] Determined from ^{1}H NMR spectra of isolated crude reaction mixtures; values in parentheses are dimers. [c] Isolated yields. [d] Values in parentheses are oxidized alcohol and dimeric ether. [e] Values in parentheses are oxidized alcohol.

Encouraged by results of reactions of secondary benzyl alcohols, I further investigated reactions of secondary benzyl ethers with TMSCl or TMSBr and impact of NIS as the catalyst in these transformations under SFRC. The example of this possibility was demonstrated by the reaction (methoxymethylene)dibenzene **26** with TMSCl **20a** or TMSBr **20d** producing the

corresponding chlorinated or brominated compounds, although in moderate yields **27** and **28** (entries 1 and 2) (Table 4.7).

Table 4.7: Nucleophilic substitution of (methoxymethylene)dibenzene **26** with TMSCl or TMSBr under SFRC[a].



26 **20a** or **20d** **27** or **28**

Entry	Bond formation	NuH	Catalyst	Conv.[b] [%]	Yield[c] [%]
1	**C-Cl**	TMSCl	NIS	55 (5)	50
2	**C-Br**	TMSBr	NIS	71 (17)	54

[a] Reaction conditions: ether **26** (0.5 mmol), TMSX (0.55 mmol) NIS (5-10 mol%), 70-75 °C, 24 h. [b] Determined from ^{1}H NMR spectra of isolated crude reaction mixtures; values in parentheses are benzophenone 5-17%. [c] Yield calculated relative to ether.

4.2 Conclusion

A group of organic molecules bearing an active *N*-halogen bond: *N*-halosuccinimides (chloro, bromo or iodo, respectively), 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis-tetrafluoroborate (*Selectfluor™ F-TEDA-BF_4)* and *N*-fluorobenzenesulfonimide (*Accufluor™ NFSi* were introduced, tested and applied as new, efficient, non-metal and non-acidic catalysts for reactions of a comprehensive range of alcohols with various type of electron rich organic molecules or reactive anionic species thus forming new carbon-carbon or carbon-heteroatom bonds in target alcohol molecules. Green chemical profiles of these valuable transformations were enhanced by leading reactions under solvent-free reaction conditions (SFRC) or high concentration reaction conditions (HCRC). A scope of the reaction was preliminarily tested by selecting a most convenient structural type of alcohol and electron rich organic molecule as reactants and *N*-halo compound from the mentioned list as the most efficient catalyst for each of the particular transformations. After these general reaction parameters were determined, each type of the transformation was studied and developed in details.

Diphenylmethanol **1** was chosen as a basic model compound and its dimerization to bis(diphenylmethyl)ether **3** was established in the presence of substoichiometric amounts (2 mol%) of named *N*-halo compounds under SFRC, *N*-iodosuccinimide giving the highest efficiency. In the case when a two-molar excess of methanol was present in the reaction mixture the formation of methyl diphenylmethyl ether **2** was observed. 4-Methylbenzyl alcohol **4** was further examined as primary benzyl alcohol target and under both mentioned reaction conditions dimerization to the corresponding dibenzyl ether **6** or corresponding methyl benzyl ether **5** was established. 1,3-Dicarbonyl compound and phenyl substituted alkenes were selected as electron rich organic molecules and the formation of a new C-C bond between benzyl carbon atom and the most electron rich carbon atom on di-carbonyl or alkene target was formed. *N*-iodosuccinimide was established as the most efficient catalyst in these cases too. Additionally, C-C bond formation could also be achieved by direct coupling of secondary benzyl alcohol and *in situ* formed electron rich alkenes derived from dehydration of tertiary alcohol bearing a vicinal hydrogen atom in the presence of NIS as the catalyst under SFRC. New C-N bond

formation in target secondary benzyl alcohol was accomplished when the reaction was performed in the presence of acetonitrile and the corresponding Ritter-type *N*-acyl benzyl product was formed **14**, while aniline-type substrate afforded *N*-benzyl phenyl amine derivative **18**. Various trimethylsilyl derivatives were further used as potential sources of nucleophilic species and corresponding chlorobenzyl derivative **21** was formed from primary benzyl alcohol bearing deactivated ring, while the formation of the corresponding benzyl-substituted isothiocyanate **24** was established using (trimethylsilyl)isothiocyanate as the nucleophile source.

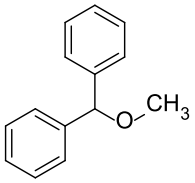
The presented methodology is the new highly efficient and easy to perform approach to the synthesis of a comprehensive new type of derivatives starting from hydroxyl functional group targets and applying solvent-free reaction conditions as a green chemical reaction protocol.

4.3 Experimental work

General procedure for etherification of alcohols catalyzed by NIS or NFSi on half mmol scale: A mixture of benzyl alcohol (0.5 mmol) and NIS or NFSi catalyst (2-5 mol%), which had been powdered in a mortar, was transferred to a 4 mL screw-capped vial, and finally added liquid component (MeOH 1-2 mmol) and heated at 70-80 °C for 3.5 h-24 h. The progress of the reaction mixture was monitored by TLC. Upon completion of the reaction, the crude reaction mixture was cooled down to room temperature, diluted with ethyl acetate (15 mL), washed with $Na_2S_2O_3$ (6 mL), $NaHCO_3$ (6 mL) and water (10 mL), and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the crude reaction mixture obtained was analysed by ^{1}H NMR. Finally, if necessary, the pure final products were obtained after column chromatography. Detailed experimental information, such as catalyst loading, isolated yields, and spectroscopic and other identification data, are given below.

The isolated known compounds were identified by comparing the spectroscopic data with the literature.

(Methoxymethylene)dibenzene (2) [172]



$C_{14}H_{14}O$ (Mr = 198.26);

Reaction conditions: 0.5 mmol diphenylmethanol **1** (92.1 mg), 1 mmol MeOH (40 μl), 3 mol% NIS (3.4 mg, 0.03 mmol), 70-75 °C, 6 h – HCRC;

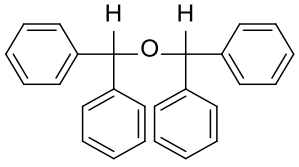
Purification: Not necessary;

Yield: 97 mg (98%), colourless oil;

^{1}H NMR (300 MHz, TMS): δ (ppm) = 7.36 – 7.20 (m, 10H), 5.23 (s, 1H), 3.37 (s, 3H);

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 142.2, 128.5, 127.6, 127.0, 85.5, 57.1.

(Oxybis(methanetriyl))tetrabenzene (3) [151]



$C_{26}H_{22}O$ (Mr = 350.45);

Reaction conditions: 0.5 mmol diphenylmethanol **1** (92.1 mg), 2 mol% NIS (2.2 mg, 0.02 mmol), 70-75 °C, 3.5 h – SFRC;

Purification: Not necessary;

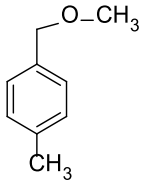
Yield: 87 mg (99%), white solid;

Mp.: 105-106 °C, (lit.[151] 107.5-110 °C);

^{1}H NMR (300 MHz, TMS): δ (ppm) = 7.38 – 7.19 (m, 20H), 5.39 (s, 2H);

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 142.3, 128.5, 127.6, 127.4, 80.1.

1-(Methoxymethyl)-4-methylbenzene (5) [173]



$C_8H_{10}O$ (Mr = 136.19);

Reaction conditions: 0.5 mmol *p*-tolylmethanol **4** (61 mg), 2 mmol MeOH (80 µl), 5 mol% NFSi (7.8 mg, 0.05 mmol), 75-80 °C, 24 h – HCRC;

Purification: CC (SiO_2, EtOAc/hexane 4:6);

Yield: 37 mg (55%), yellow oil;

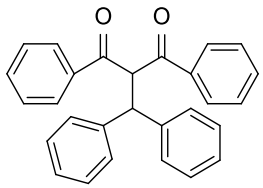
^{1}H NMR (300 MHz, TMS): δ (ppm) = 7.22 (d, *J* = 8.0 Hz, 2H), 7.15 (d, *J* = 7.9 Hz, 2H), 4.41 (s, 2H), 3.36 (s, 3H), 2.34 (s, 3H);

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 137.5, 135.3, 129.2, 127.9, 74.7, 58.1, 21.3.

General procedure for new carbon-carbon bond formation through ß-dicarbonyl compounds in organic molecules catalyzed by NIS on half mmol scale: In a 4 mL screw-capped vial, a mixture of solid reaction components previously powedered in a mortar was transferred: ß-dicarbonyl compound (0.5 mmol), benzyl alcohol (0.5 mmol) and NIS (1 mol%). The vial was then heated at 70-75 °C for 24 h. The progress of the reaction mixture was monitored by TLC. Upon completion of the reaction, the crude reaction mixture was cooled down to room temperature, diluted with ethyl acetate (15 mL), washed with $Na_2S_2O_3$ (6 mL), $NaHCO_3$ (6 mL) and water (10 mL), and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the crude reaction mixture obtained was analysed by ^{1}H NMR. No further purification was necessary. Detailed experimental information, such as catalyst loading, isolated yield, and spectroscopic and other identification data, are given below.

The isolated known compound was identified by comparing the spectroscopic data with the literature.

2-Benzhydryl-1,3-diphenylpropane-1,3-dione (8) [174]



$C_{28}H_{22}O_2$ (Mr = 390.47);

Reaction conditions: 0.5mmol 1,3-diphenylpropane-1,3-dione **7** (112.1 mg), 0.5 mmol diphenylmethanol **1** (92.1 mg), 1 mol% NIS (1.1 mg, 0.01 mmol), 70-75 °C, 24 h – SFRC;

Purification: Not necessary;

Yield: 194 mg (99%), white solid;

Mp.: 220-223 °C, (lit.[175] 220-222 °C);

^{1}H NMR (300 MHz, TMS): δ (ppm) = 7.82 (dd, *J* = 8.3, 1.1 Hz, 4H), 7.50 – 7.43 (m, 2H), 7.36 – 7.29 (m, 4H), 7.27 – 7.23 (m, 4H), 7.18 – 7.10 (m, 4H), 7.08 – 7.01 (m, 2H), 6.36 (d, *J* = 11.6 Hz, 1H), 5.31 (d, *J* = 11.6 Hz, 1H);

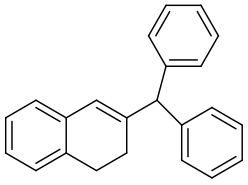
^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 193.9, 141.6, 136.7, 133.2, 128.5, 128.4, 128.2, 128.1, 126.5, 61.8, 52.4.

HR-MS [MH^+]: Calculated for $C_{28}H_{23}O_2$: 391.1698; measured: 391.1688.

General procedure for new carbon-carbon bond formation through C=C bond in organic molecules catalyzed by NIS on half mmol scale: A mixture of benzyl alcohol (0.5-0.55 mmol) and NIS (6-10 mol%), which had been powdered in a mortar in the case of solid state reactants, was transferred into a 4 mL screw-capped vial, and finally added eventual liquid reaction component and heated at 70-75 °C for 24 h. The progress of the reaction mixture was monitored by TLC. Upon completion of the reaction, the crude reaction mixture was cooled down to room temperature, diluted with ethyl acetate (15 mL), washed with $Na_2S_2O_3$ (6 mL), $NaHCO_3$ (6 mL) and water (10 mL), and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the crude reaction mixture obtained was analysed by ^{1}H NMR. The pure final products were obtained after column chromatography or preparative thin layer chromatography. Detailed experimental information, such as catalyst loading, isolated yields, and spectroscopic and other identification data, are given below.

The isolated known compounds were identified by comparing the spectroscopic data with the literature.

3-Benzhydryl-1,2-dihydronaphthalene (10) [30]



$C_{23}H_{20}$ (Mr = 296.40);

Reaction conditions: 0.4 mmol 1,2-dihydronaphthalene **9** (52 μl), 0.5 mmol diphenylmethanol **1** (92.1 mg), 10 mol% NIS (11.2 mg, 0.1 mmol), 70-75 °C, 24 h – SFRC;

Purification: preparative TLC (SiO_2, CH_2Cl_2/hexane 1:1);

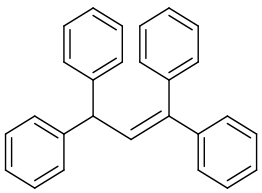
Yield: 83 mg (70%), white solid;

Mp.: 76-78 °C, (lit.[30] 79-81 °C);

^{1}H NMR (300 MHz, TMS): δ (ppm) = 7.34 – 7.28 (m, 4H), 7.23 (dd, *J* = 6.2, 3.6 Hz, 6H), 7.13 – 7.07 (m, 3H), 6.94 – 6.88 (m, 1H), 5.97 (d, *J* = 1.2 Hz, 1H), 4.89 (s, 1H), 2.85 – 2.78 (m, 2H), 2.27 (t, *J* = 8.0 Hz, 2H);

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 143.8, 142.2, 134.7, 134.7, 129.5, 128.5, 127.3, 126.8, 126.61, 126.55, 126.2, 126.0, 58.7, 28.5, 28.2.

Prop-1-ene-1,1,3,3-tetrayltetrabenzene (12) [133]



$C_{27}H_{22}$ (Mr = 346.46);

Reaction conditions: 0.55 mmol diphenylmethanol **1** (101.3 mg), 0.5 mmol 1,1-diphenylethanol **11** (99.1 mg), 6 mol% NIS (6.7 mg, 0.06 mmol), 70-75 °C, 24 h – SFRC;

Purification: CC (SiO_2, CH_2Cl_2/hexane 1:1);

Yield: 150 mg (87%), white solid;

Mp.: 128-130 °C, (lit.[10] 131-132 °C);

^{1}H NMR (300 MHz, TMS): δ (ppm) = 7.36 – 7.29 (m, 3H), 7.29 – 7.21 (m, 8H), 7.21 – 7.12 (m, 9H), 6.55 (d, *J* = 10.6 Hz, 1H), 4.82 (d, *J* = 10.6 Hz, 1H);

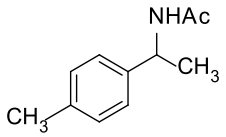
^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 144.6, 142.3, 141.8, 139.8, 131.1, 129.9, 128.6, 128.5, 128.4, 128.3, 127.6, 127.42, 127.38, 126.4, 50.7.

Calculated based on 1,1-diphenylethanol **11** as the starting material.

General procedure for new carbon-nitrogen bond formation in organic molecules catalyzed by NIS on half mmol scale: In a 4 mL screw-capped vial, a mixture of benzyl alcohol (0.5 mmol), acetonitrile (0.5 mL), water (2 mmol) and NIS (10 mol%), or a mixture of solid reaction components previously powedered in a mortar was transferred: benzyl alcohol (0.5 mmol), aniline (0.55 mmol) and NIS (10 mol%). The vial was then heated at 70-75 °C for 24 h-48 h. The progress of the reaction mixture was monitored by TLC. Upon completion of the reaction, the crude reaction mixture was cooled down to room temperature, diluted with ethyl acetate (15 mL), washed with $Na_2S_2O_3$ (6 mL), $NaHCO_3$ (6 mL) and water (10 mL), and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the crude reaction mixture obtained was analysed by ^{1}H NMR. The pure final products were obtained after column chromatography or preparative thin layer chromatography. Detailed experimental information, such as catalyst loading, isolated yields, and spectroscopic and other identification data, are given below.

The isolated known compounds were identified by comparing the spectroscopic data with the literature.

***N*-(1-(*p*-Tolyl)ethyl)acetamide (14)** [176]



$C_{11}H_{15}NO$ (Mr = 177.24);

Reaction conditions: 0.5 mmol 1-(*p*-tolyl)ethanol **13** (68.9 μl), 0.5 mL MeCN, 2 mmol H_2O (36 μl), 10 mol% NIS (11.2 mg, 0.1 mmol), 70-75 °C, 24 h, stirring 300 – solution;

Purification: preparative TLC (SiO_2, CH_2Cl_2/hexane 9:1);

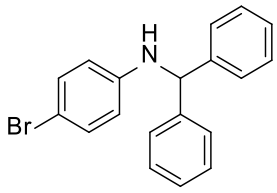
Yield: 64 mg (72%), white solid;

Mp.: 76-78 °C, (lit.[176] 80-82 °C);

^{1}H NMR (300 MHz, TMS): δ (ppm) = 7.18 (dd, 4H), 5.90 (br, 1H), 5.08 (p, *J* = 7.0 Hz, 1H), 2.32 (s, 3H), 1.95 (s, 3H), 1.46 (d, *J* = 6.9 Hz, 3H);

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 169.2, 140.3, 137.1, 129.4, 126.2, 48.6, 23.5, 21.8, 21.1.

***N*-Benzhydryl-4-bromoaniline (18)** [177]



$C_{19}H_{16}BrN$ (Mr = 338.24);

Reaction conditions: 0.5 mmol diphenylmethanol **1** (92.1 mg), 0.55 mmol 4-bromoaniline **17** (94.6 mg), 10 mol% NIS (11.2 mg, 0.1 mmol), 70-75 °C, 48 h – SFRC;

Purification: CC (SiO_2, CH_2Cl_2/hexane 9:1);

Yield: 132 mg (78%), yellow oil;

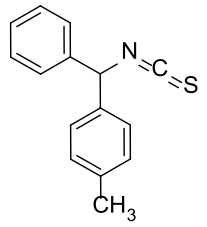
^{1}H NMR (300 MHz, TMS): δ (ppm) = 7.33 – 7.23 (m, 10H), 7.17 (d, *J* = 8.9 Hz, 2H), 6.40 (d, *J* = 8.9 Hz, 2H), 5.44 (d, 1H), 4.25 (s, 1H);

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 146.3, 142.5, 131.9, 128.9, 127.7, 127.5, 115.2, 109.5, 63.1.

General procedure for halo functionalization of organic compounds using trimethylsilyl derivatives catalyzed by NIS on half mmol scale: A mixture of benzyl alcohol or ether (0.5 mmol) and NIS (3-10 mol%) which had been powdered in a mortar in the case of solid state reactants, was transferred to a 4 mL screw-capped vial, then added trimethylsilyl derivatives (0.55 mmol) and heated at 70-75 °C for 24-25 h. The progress of the reaction mixture was monitored by TLC. Upon completion of the reaction, the crude reaction mixture was cooled down to room temperature, diluted with ethyl acetate (15 mL), washed with $Na_2S_2O_3$ (6 mL), $NaHCO_3$ (6 mL) and water (10 mL), and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the crude reaction mixture obtained was analysed by ^{1}H NMR. The pure final products were obtained after flash chromatography or column chromatography. Detailed experimental information, such as catalyst loading, isolated yields, and spectroscopic and other identification data, are given below.

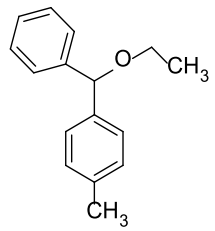
The isolated known compounds were identified by comparing the spectroscopic data with the literature.

1-(Isothiocyanato(phenyl)methyl)-4-methylbenzene (24) [178]



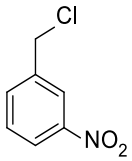
	$C_{15}H_{13}NS$ (Mr = 239.34);
Reaction conditions:	0.5 mmol phenyl(*p*-tolyl)methanol **23** (99.1 mg), 0.55 mmol TMSNCS **20b** (77.5 μl), 3 mol% NIS (3.4 mg, 0.03 mmol), 70-75 °C, 25 h – SFRC;
Purification:	FC (SiO_2, CH_2Cl_2);
Yield:	116 mg (97%), light yellow oil;
^{1}H NMR (300 MHz, TMS):	δ (ppm) = 7.35 – 7.15 (m, 9H), 5.93 (s, 1H), 2.32 (s, 3H);
^{13}C NMR (76 MHz, $CDCl_3$):	δ (ppm) = 139.5, 138.3, 136.5, 134.4, 129.7, 129.0, 128.3, 126.64, 126.63, 64.5, 21.2.

1-(Ethoxy(phenyl)methyl)-4-methylbenzene (25) [179]



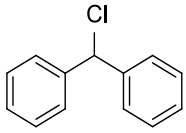
	$C_{16}H_{18}O$ (Mr = 226.31);
Reaction conditions:	0.5 mmol phenyl(*p*-tolyl)methanol **23** (99.1 mg), 0.55 mmol TMSOEt **20c** (85.9 μl), 3 mol% NIS (3.4 mg, 0.03 mmol), 70-75 °C, 25 h – SFRC;
Purification:	CC (SiO_2, CH_2Cl_2/hexane 1:1);
Yield:	101 mg (89%), colourless oil;
^{1}H NMR (300 MHz, TMS):	δ (ppm) = 7.36 – 7.17 (m, 7H), 7.13 – 7.08 (m, 2H), 5.31 (s, 1H), 3.50 (q, *J* = 7.0 Hz, 2H), 2.30 (s, 3H), 1.25 (t, *J* = 7.0 Hz, 3H);
^{13}C NMR (76 MHz, $CDCl_3$):	δ (ppm) = 142.9, 139.7, 137.1, 129.2, 128.4, 127.3, 127.1, 126.9, 83.4, 64.6, 21.2, 15.5.

1-(Chloromethyl)-3-nitrobenzene (21) [180]



	$C_7H_6ClNO_2$ (Mr = 171.58);
Reaction conditions:	0.5 mmol (3-nitrophenyl)methanol **19** (76.6 mg), 0.55 mmol TMSCl **20a** (69.8 μl), 10 mol% NIS (11.2 mg, 0.1 mmol), 70-75 °C, 24 h – SFRC;
Purification:	CC (SiO_2, CH_2Cl_2/hexane 1:1);
Yield:	65 mg (76%), white solid;
Mp.:	45-47 °C, (lit.[181] 45-46 °C);
^{1}H NMR (300 MHz, TMS):	δ (ppm) = 8.27 (s, 1H), 8.18 (dd, *J* = 6.0 Hz, 1H), 7.74 (d, *J* = 6.0 Hz, 1H), 7.56 (t, *J* = 7.9 Hz, 1H), 4.67 (s, 2H);
^{13}C NMR (76 MHz, $CDCl_3$):	δ (ppm) = 148.3, 139.4, 134.6, 129.8, 123.4, 123.3, 44.7.

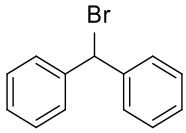
Diphenylmethyl chloride (27) [182]



	$C_{13}H_{11}Cl$ (Mr = 202.68);
Reaction conditions:	0.5 mmol (methoxymethylene)dibenzene **26** (96.2 mg), 0.55 mmol TMSCl **20a** (69.8 μl), 10 mol% NIS (11.2 mg, 0.1 mmol), 70-75 °C, 24 h – SFRC;
Purification:	CC (dried-SiO_2, CH_2Cl_2/hexane 9:1)[a];
Yield:	47 mg (46%), colourless oil;
^{1}H NMR (300 MHz, TMS):	δ (ppm) = 7.42 – 7.24 (m, 10H), 6.12 (s, 1H);
^{13}C NMR (76 MHz, $CDCl_3$):	δ (ppm) = 141.2, 128.7, 128.2, 127.9, 64.4.

[a]if SiO_2 is not dried, hydrolysis takes place.

Diphenylmethyl bromide (28) [183]



	$C_{13}H_{11}Br$ (Mr = 247.13);
Reaction conditions:	0.5 mmol (methoxymethylene)dibenzene **26** (96.2 mg), 0.55 mmol TMSBr **20d** (72.5 μl), 5 mol% NIS (5.6 mg, 0.05 mmol), 70-75 °C, 24 h – SFRC;
Purification:	CC (dried-SiO_2, CH_2Cl_2/hexane 9:1)[a];
Yield:	62 mg (50%), colourless oil;
^{1}H NMR (300 MHz, TMS):	δ (ppm) = 7.47 – 7.23 (m, 10H), 6.28 (s, 1H);
^{13}C NMR (76 MHz, $CDCl_3$):	δ (ppm) = 141.2, 128.7, 128.6, 128.2, 55.5.

[a]if SiO_2 is not dried, hydrolysis takes place.

Chapter 5

Etherification of alcohols catalyzed by *N*-halosuccinimides or *N*-fluoro organic compounds

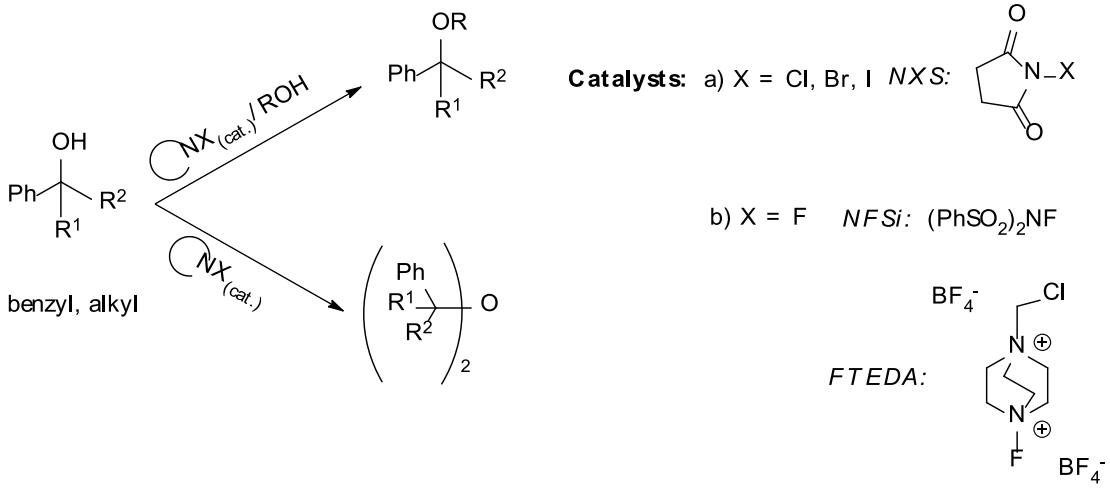
Alkyl aryl ethers are important solvents and synthetic building blocks for the production of fragrances, cosmetics, pharmaceuticals, and dyestuffs [184].

C-O bond formation by direct coupling of alcohols with other alkyl or benzyl alcohols could be a very attractive strategy from a practical, atom-efficient and environmental point of view, producing water as only a by-product of the reaction [185]. Because of their lower leaving group ability, hydroxyl moieties rarely substituted under mild conditions and must often be activated before treatment with nucleophiles [65].

Numerous related methodologies have been developed using a substoichiometric amount of $NaAuCl_4$ as the simple gold catalyst for the etherification of benzylic and tertiary alcohols under mild conditions [124], rhenium (V)-oxo complex for the formation of C-O bond by the coupling of simple alcohols and propargyl alcohols [127], $Pd(PPh_3)_4/PhCO_2H$ in dioxane at 100 ^oC for the synthesis of various allylic ethers from alcohols and alkynes [117], $BF_3{\cdot}OEt_2$ [186].

The aforementioned methods suffer some disadvantages, such as the need for expensive metals as the catalyst, the use of an environmentally undesirable solvents and the requirement for a high temperature. Thus, the development of an efficient and environmentally benign catalytic methodology for C-O bond formation is still of general interest to date. On the basis of our research group's continuing interest in developing greener methods for comprehensive types of organic molecule transformation, I found it challenging to develop a new efficient and selective methodology for the direct C-O bond formation through the direct coupling of various types of alcohols (primary, secondary and tertiary benzyl alcohols and tertiary alkyl alcohol) with other alkyl or benzyl alcohols, catalyzed by *N*-halo organic compounds as a new type of metal- and acid-free catalysts under HCRC or SFRC, which offers a potential solution to environmental issues, producing only water as a by-product of the reaction.

The general concept of the investigation is schematically presented in Scheme 5.1



Scheme 5.1: General concept and work-plan for the etherification of alcohols.

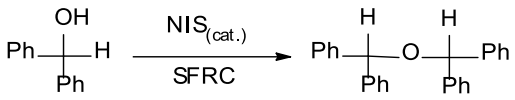
Phenyl substituted alcohols undergo at least three different reaction pathways: transformation to phenyl-substituted alkenes, dimerization and formation of ethers. The type of transformation depends on the reaction conditions and the structure of an alcohol.

5.1 Results and discussion

Based on results reported in the first chapter (Table 4.1), the transformation of diphenylmethanol **1** catalyzed by *N*-halo organic compound in the presence of MeOH under HCRC, provided ether **2**, while in the absence of MeOH under SFRC a dimerization process occurred, resulting in the formation of symmetric ether **3**. I observed that *N*-halosuccinimides (NIS, NCS and NBS) expressed higher catalytic activity for the transformation of secondary benzyl alcohol into the corresponding ether **3** than *N*-fluoro organic compounds (FTEDA or NFSi).

The loading of NIS as the catalyst for the reaction of diphenylmethanol **1** in the absence of MeOH under SFRC was examined (Table 5.1). To increase the yield of the product, different concentrations of the catalyst were used. Employing 0.5 mol% of the catalyst, the formation of the corresponding product **3** in good yield was observed accompanied with a trace of oxidised alcohol (entry 1). By increasing the catalyst loading to 1 mol%, I observed the high conversion of the starting material **1** into the corresponding product **3,** accompanied with a trace of oxidised alcohol (entry 2). I found that for the efficient and selective transformation of the starting material **1** into the desired product **3**, 2 mol% of the catalyst was effective (entry 3).

Table 5.1: The effect of loading of NIS on the conversion of 1,1 diphenylmethanol **1** under SFRC[a].



1 **3**

Entry	NIS (Mol%)	Conv.[b] [%] of 1	Yield[c] [%] 3
1	0.5	79	78[d]
2	1	90	89[d]
3	2	100	100

[a] Reaction conditions: diphenylmethanol **1** (0.5 mmol), 70-75 °C, 3.5 h. [b,c] Determined from ^{1}H NMR spectra of isolated crude reaction mixtures. [d] Benzophenone.

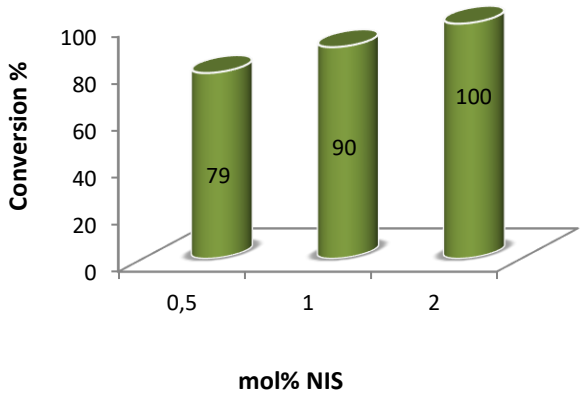
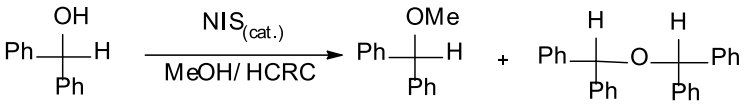


Figure 5.1: The effect of loading of NIS on the conversion of diphenylmethanol **1** under SFRC.

Different parameters, such as loading of the NIS as the catalyst (Table 5.2) and temperature (Table 5.3) for the reaction of diphenylmethanol **1** with MeOH under HCRC, were first studied. The loading of NIS as the catalyst was examined (Table 5.2). To increase the yield of the product, different concentrations of the catalyst were employed. In the reaction of diphenylmethanol **1** with MeOH using 0.5 mol% of the catalyst, I observed the formation of the corresponding product **2** in good yield accompanied with a small amount of dimeric ether **3** (entry 1). Similar results were achieved when I increased the amount of MeOH to 2 mmol (entry 2). By increasing the catalyst loading to 1 mol%, I observed quantitative conversion of the starting material **1** into the corresponding product **2**, accompanied with a small amount of dimeric ether **3** (entry 3). Similar results were achieved when the catalyst loading was increased up to 2 mol% (entry 4). The improvement of 100% yield without formation of the dimeric ether is attained by increasing the catalyst loading to 3 mol% (entry 5).

Table 5.2: The effect of loading of NIS on the conversion of diphenylmethanol **1** under HCRC[a].



1 **2** **3**

Entry	NIS (Mol%)	Conv.[b] [%] of **1**	Relative distribution[c] [%]	
			2	**3**
1	0.5	83	78	5
2[d]	0.5	81	79	2
3	1	100	94	6
4	2	100	95	5
5	3	100	100	/

[a] Reaction conditions: diphenylmethanol **1** (0.5 mmol), MeOH (1 mmol), 70-75 °C, 6 h. [b] Determined from ^{1}H NMR spectra of isolated crude reaction mixtures. [c] Yields calculated relative to alcohol **1**. [d] 2 mmol MeOH.

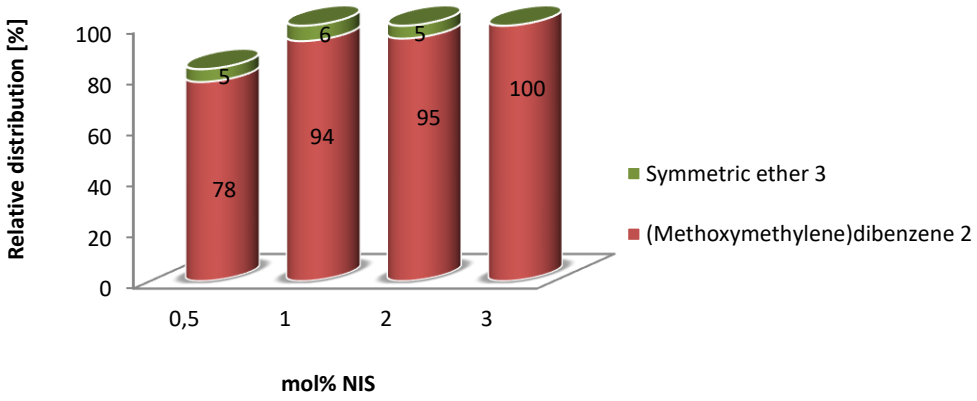
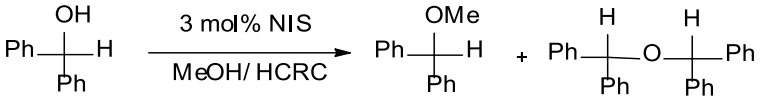


Figure 5.2: The effect of loading of NIS on the conversion of diphenylmethanol **1** under HCRC.

The effect of temperature on the course of the reaction was examined by the reaction of diphenylmethanol **1** with MeOH catalyzed by NIS under HCRC (Table 5.3). When the reaction was carried out at room temperature, no transformation took place (entry 1). When the reaction was performed at 40-45 °C the desired product **2** in low yield and small amount of dimeric ether were obtained **3** (entry 2). The increase of reaction temperature up to 50-55 °C provided the corresponding product **2** in moderate yield, accompanied with a small amount of symmetric ether **3** (entry 3). Further optimization revealed that the reaction could undergo smoothly by increasing the temperature up to 60-65 °C. The improvement of 100% yield without formation of the symmetric ether is attained by increasing the reaction temperature up to 70-75 °C.

Table 5.3: The catalytic effect of NIS on the conversion of diphenylmethanol **1** based on temperature under HCRC[a].



1 **2** **3**

Entry	T(°C)	Conv.[b] [%] of **1**	Relative distribution[c] [%]	
			2	**3**
1	rt	/	/	/
2	40-45	26	23	3
3	50-55	61	56	5
4	60-65	86	81	3[d]
5	70-75	100	100	/

[a] Reaction conditions: diphenylmethanol **1** (0.5 mmol), MeOH (1 mmol), 6 h. [b] Determined from ^{1}H NMR spectra of isolated crude reaction mixtures. [c] Yields calculated relative to alcohol **1**. [d] Benzophenone 2%.

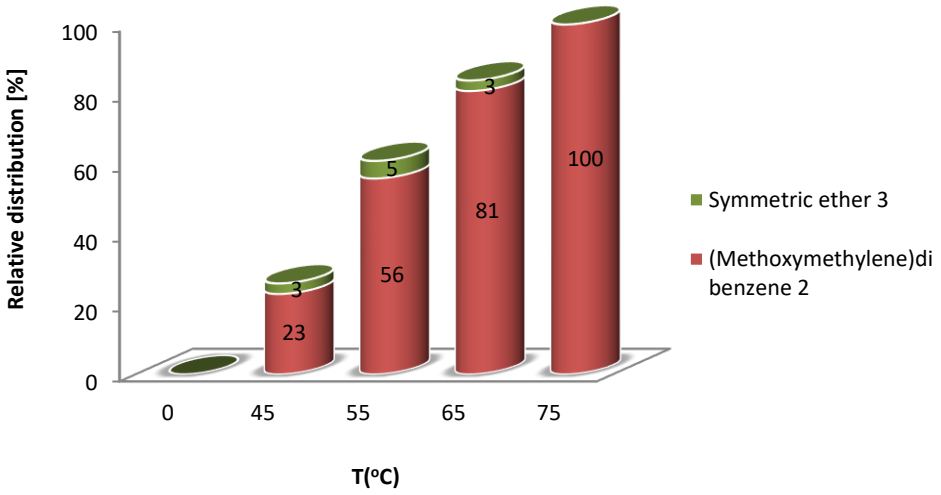
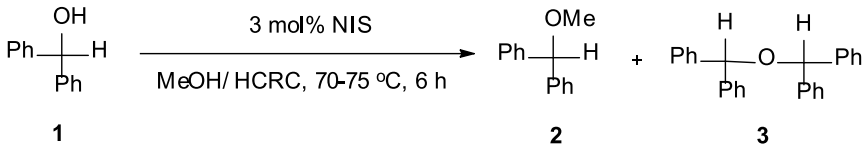


Figure 5.3: The catalytic effect of NIS on the conversion of diphenylmethanol **1** based on temperature, under HCRC.

Screening on catalyst loading and reaction temperature showed that 3 mol% NIS, 70-75 °C, and 6 h were the best conditions ensuring complete conversion of **1** into the corresponding ether **2**, (Scheme 5.2).

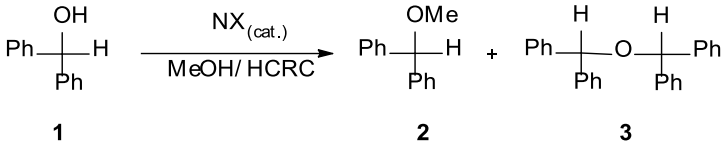


1 **2** **3**

Scheme 5.2: Direct etherification of diphenylmethanol with MeOH catalyzed by NIS under HCRC.

Based on results reported in the first chapter (Table 4.1), *N*-fluoro organic compounds (NFSi or FTEDA) exhibited low catalytic activities for the transformation of diphenylmethanol **1** into the corresponding ether **2** under HCRC. I supposed that in both cases (using NFSi or FTEDA as the catalyst) better results could be obtained. So, further optimization of the reaction conditions revealed that *N*-fluoro organic compounds could express high catalytic activities by prolonging the reaction time, in some cases increasing the amount of nucleophile and decreasing the catalyst loading. These parameters are essential requirements to give good to high selectivity and yield of the corresponding ether **2** with detection of small amounts of dimeric ether **3** and oxidised alcohol and results given in Table 5.4.

Table 5.4: The effect of loading of NFSi or FTEDA on the conversion of diphenylmethanol **1** under HCRC[a].



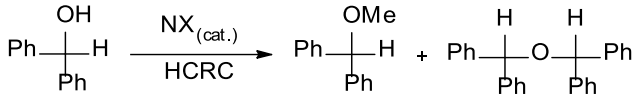
1 **2** **3**

Entry	$NX_{(cat.)}$	Mol (%)	Reaction conditions	Conv.[b] [%] of **1**	Relative distribution[c] [%]	
					2	**3**
1	FTEDA	6	MeOH (1mmol), 70-75 °C, 25 h	93	85	5[d]
2	FTEDA	2	MeOH (1mmol), 70-75 °C, 25 h	87	79	6[d]
3	FTEDA	1	MeOH (2mmol), 70-75 °C, 20 h	97	92	3[d]
4	NFSi	6	MeOH (1mmol), 70-75 °C, 23 h	100	91	5[d]
5	NFSi	2	MeOH (1mmol), 70-75 °C, 21.5 h	100	87	6[d]
6	NFSi	1	MeOH (2mmol), 70-75 °C, 23 h	93	86	3[d]
7	NFSi	0.5	MeOH (2mmol), 70-75 °C, 24 h	90	85	3[d]

[a] Reaction conditions: diphenylmethanol **1** (0.5 mmol). [b] Determined from ^{1}H NMR spectra of isolated crude reaction mixtures. [c] Yields calculated relative to alcohol **1**. [d] Benzophenone 2-7%.

Based on the results reported in the first chapter (Table 4.1) and results reported in this chapter (Table 5.4), I presented the general table (Table 5.5) of optimal reaction conditions for the highest conversion of diphenylmethanol **1** into the corresponding ether **2**, catalyzed by *N*-halosuccinimides and *N*-fluoro organic compounds, under HCRC.

Table 5.5: Optimal reaction conditions for the highest conversion of diphenylmethanol **1** into the (methoxymethylene)dibenzene **2** in the presence of *N*-halo catalysts under HCRC[a].



1 **2** **3**

Entry	$NX_{(cat.)}$	Mol (%)	Reaction conditions	Conv.[b] [%] of **1**	Relative distribution[c] [%]	
					2	**3**
1	NIS	3	MeOH (1mmol), 70-75 °C, 6 h	100	100	/
2	NCS	3	MeOH (1mmol), 70-75 °C, 6 h	100	92	5[d]
3	NBS	3	MeOH (1mmol), 70-75 °C, 6 h	100	92	5[d]
3	FTEDA	1	MeOH (2mmol), 70-75 °C, 20 h	97	92	3[d]
4	NFSi	2	MeOH (1mmol), 70-75 °C, 21.5 h	100	87	6[d]

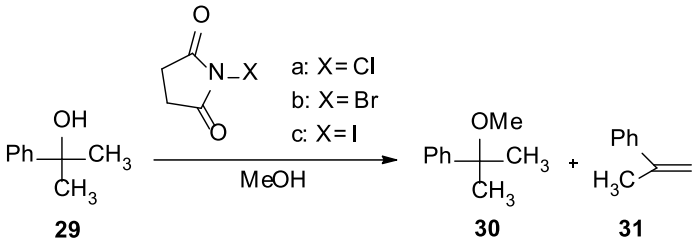
[a] Reaction conditions: diphenylmethanol **1** (0.5 mmol). [b] Determined from ^{1}H NMR spectra of isolated crude reaction mixtures. [c] Yields calculated relative to alcohol **1**. [d] Benzophenone 2-7%.

I further investigated reactions of primary benzyl alcohols bearing electron-withdrawing as well as electron-donating substituents on the aromatic ring with MeOH under HCRC.

In the case of primary benzyl alcohol, in the presence of NIS as the catalyst, without nucleophile, under SFRC, I observed 66% conversion of the starting material into the dimeric ether, while in the presence of nucleophile no transformation took place. Based on results reported in the first chapter (Table 4.2), etherification of 4-methylbenzyl alcohol **4** with MeOH under HCRC or in solution, using NIS as the catalyst was not efficient enough. NFSi was found as the convenient catalyst for improving the efficiency and selectivity of etherification of 4-methylbenzyl alcohol. 4-chlorobenzyl alcohol in the presence of *N*-fluoro organic compounds, NIS and NCS was unable to undergo this conversion.

Similarly to secondary alcohol, efficient and selective transformation was observed in the reaction with tertiary benzyl alcohol and results are given in Table 5.6. It could be seen that 2-phenylpropan-2-ol **29** was readily catalyzed by *N*-halosuccinimide to afford high to quantitative yield of target ether **30**, in methanol solution (entries 3, 7 and 10).

Table 5.6: The catalytic effect of *N*-halo catalysts on conversion of 2-phenyl-2-propanol **29** under HCRC or in solution[a].



29 **30** **31**

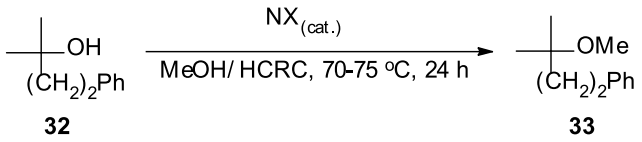
Entry	NX	Mol%	Reaction conditions MeOH/T/t	Conv.[b] [%] of **29**	Relative distribution[c] [%]	
					30	**31**
1	NCS	5	/, 60-65 °C, 48 h	/	/	/
2	NCS	5	MeOH (1mmol), 60-65 °C, 24 h	8	8	/
3	**NCS**	**3**	**MeOH (1ml), 50-55 °C, 24 h**	**100**	**100**	/
4	NBS	5	/, 60-65 °C, 48 h	79	/	69[d]
5	NBS	5	MeOH (1mmol), 50-55 °C, 18 h	86	72	14
6	NBS	3	MeOH (1ml), 50-55 °C, 24 h	82	73	9
7	**NBS**	**1**	**MeOH (5 ml), 60-65 °C, 22 h**	**100**	**100**	**/**
8	NBS	0.5	MeOH (5 ml), 60-65 °C, 22 h	79	79	/
9	NIS	3	MeOH (1ml), 50-55 °C, 24 h	94	79	15
10	**NIS**	**3**	**MeOH (2 ml), 50-55 °C, 24 h**	**93**	**93**	/

[a] Reaction conditions: 2-phenylpropan-2-ol **29** (0.5 mmol). [b] Determined from ^{1}H NMR spectra of isolated crude reaction mixtures. [c] Yields calculated relative to alcohol **29**. [d] Acetophenone 10%.

In the case of 1,1-diphenylethanol **11** dehydration resulting in the 1,1-diphenylethene **58** was observed in the presence of substoichiometric amounts of *N*-halosuccinimides under SFRC or under MeOH, EtOH, PrOH, or *i*PrOH high concentration reaction conditions.

Furthermore, this method was applied for tertiary alkyl alcohol. It could be seen from Table 5.7 that NCS was ineffective for the reaction of **32** (entry 1), NFSi gave a low yield of the corresponding ether **33** (entry 2), while NIS proved to be an effective catalyst for the etherification of α,α-dimethylbenzenepropanol **32** with MeOH under HCRC (entry 4).

Table 5.7: The catalytic effect of *N*-halo catalysts on conversion of α,α-dimethylbenzenepropanol **32** with MeOH under HCRC[a].



32 **33**

Entry	$NX_{(cat.)}$	Mol%	Conv.[b] [%] of **32**	Yield[c] [%] **33**
1	NCS	10	/	/
2	NFSi	6	26	26
3[d]	NIS	3	16	16
4	NIS	10	74	74

[a] Reaction conditions: α,α-dimethylbenzenepropanol **32** (0.5 mmol), MeOH (1 mmol). [b] Determined from ^{1}H NMR spectra of isolated crude reaction mixtures. [c] Yields calculated relative to alcohol **32**. [d] 48 h.

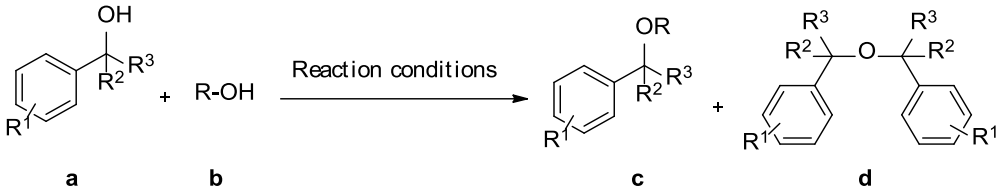
To extend the scope of alcohols, I checked reactions of different alcohols catalyzed by *N*-halo organic compound under SFRC, under HCRC or in solution. The results of reactions are collected in Table 5.8.

The transformation of 4-methylbenzyl alcohol **4** catalyzed by NIS in the absence of MeOH, under SFRC, was efficiently and selectively converted into the dimeric ether **6** (entry 1), while in the presence of MeOH, catalysed by NFSi, under HCRC, it provided corresponding ether in good yield **5** (entry 2).

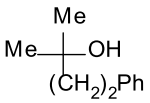
The transformation of diphenylmethanol **1** catalyzed by NIS in the absence of MeOH, under SFRC, quantitatively resulted in the formation of the dimeric ether (**3**, entry 3), while in the presence of MeOH, under HCRC, it efficiently and selectively converted into the corresponding ether **2** (entry 4). Encouraged with this result, I checked the reaction of phenyl(*p*-tolyl)methanol **23** with NIS as the catalyst, in the absence or in the presence of MeOH, where in both cases I established the quantitative formation of the dimeric ether **34** (entry 5) or the corresponding ether **35** (entry 6).

Similarly to primary and secondary benzyl alcohols, an effective transformation was observed in the reaction with tertiary benzyl and alkyl alcohols. 2-Phenylpropan-2-ol **29** in the presence of NCS as the catalyst, in methanol solution, was successfully and selectively converted into the (2-methoxypropan-2-yl)benzene **30** (entry 7). α,α-dimethylbenzenepropanol **32** catalyzed by NIS, in the presence of MeOH under HCRC was successfully converted into their corresponding ether **33** (entry 8). Furthermore, I performed the reaction of diphenylmethanol **1** catalyzed by NIS, in the presence of EtOH, under HCRC, efficiently and successfully resulted in the formation of the corresponding ether **36**, accompanied with a small amounts of dimeric ether **3** and oxidised alcohol (entry 9). The transformation of diphenylmethanol **1** catalyzed by NIS in isopropyl solution, provided the corresponding ether **37** in high yield, accompanied with a small amount of oxidised alcohol (entry 10).

Table 5.8: Transformation of benzyl and tertiary alkyl alcohols **a** with alkyl alcohols **b** in the presence of *N*-halo catalysts under SFRC, under HCRC or in solution[a].



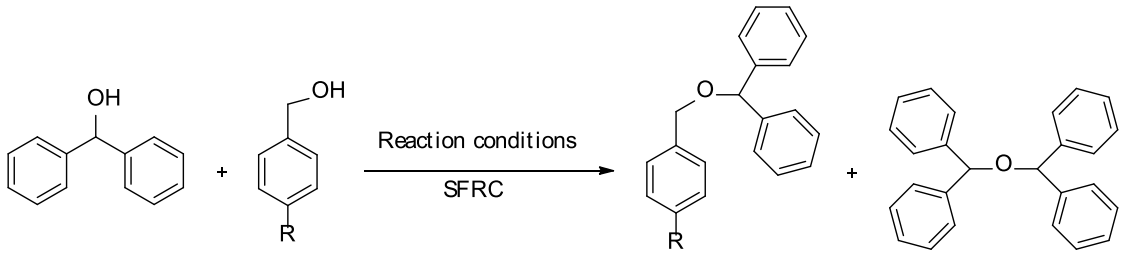
a **b** **c** **d**

Entry		R^1, R^2, R^3	R-OH (mmol/mL)	Reaction conditions[e]	Conv.[b] [%] of **a**	Yield[c] [%]	
						c	**d**
1	**4**	R^1=Me, R^2=R^3=H	/	NIS(3) 70-75 °C, 24 h	100	/	**6:** (97)
2	**4**	R^1=Me, R^2=R^3=H	MeOH (2 mmol)	NFSi(3) 75-80 °C, 24 h	85	**5:** 71 (65)	**6:** 14
3	**1**	R^1=R^2=H, R^3=Ph	/	NIS(2) 70-75 °C, 3.5 h	100	/	**3:** (99)
4	**1**	R^1=R^2=H, R^3=Ph	MeOH (1 mmol)	NIS(3) 70-75 °C, 6 h	100	**2:** (98)	/
5	**23**	R^1=Me, R^2=H, R^3=Ph	/	NIS(3) 70-75 °C, 4.5 h	100	/	**34:** (99)
6	**23**	R^1=Me, R^2=H, R^3=Ph	MeOH (1 mmol)	NIS(3) 70-75 °C, 6 h	100	**35:** 94 (90)	**34:** 6
7	**29**	R^1=H, R^2=R^3=Me	MeOH (1 mL)	NCS(3) 50-55 °C, 24 h	100	**30:** (98)	/
8	**32**		MeOH (1 mmol)	NIS(10) 70-75 °C, 24 h	74	**33:** (64)	**/**
9	**1**	R^1=R^2=H, R^3=Ph	EtOH (1 mmol)	NIS(3) 70-75 °C, 24 h	100	**36:** 94 (89)	**3:** 4[d]
10	**1**	R^1=R^2=H, R^3=Ph	*i*PrOH (1 mL)	NIS(3) 80-85 °C, 24 h	100	**37:** 92 (88)	/[d]

[a] Reaction conditions: alcohol **a** (0.5 mmol). [b] Determined from ^{1}H NMR spectra of isolated crude reaction mixtures. [c] Yields calculated relative to alcohol **a**; values in parentheses are isolated yields. [d] Oxidised alcohol 2-8%. [e] mol%.

To further extend the scope of this etherification protocol, I studied the impact of *N*-halo organic compounds as catalysts for direct etherification of diphenylmethanol **1** with primary benzyl alcohols bearing electron-withdrawing as well as electron-donating substituent on the aromatic ring under SFRC. The results are collected in Table 5.9. Direct etherification of diphenylmethanol **1** with 4-methylbenzyl alcohol **4** was carried out using NIS as the catalyst under SFRC, which leads into the corresponding ether **38** in good yield, while a small amount of oxidized alcohol and dimeric ether **3** were detected as side products (entry 1). In the case of the reaction of diphenylmethanol **1** with 4-chlorobenzyl alcohol **39** in the presence of NIS as the catalyst under SFRC, I observed the quantitative conversion of the starting material **1** into the corresponding ether **40** accompanied by the formation of small amounts of oxidised alcohols (entry 2).

Table 5.9: Direct etherification of diphenylmethanol **1** with primary benzyl alcohols **4** and **39** catalyzed by NIS under SFRC[a].



1 **4** or **39** **38** or **40** **3**

Entry	R	Reaction conditions[d]	Conv.[b] [%] of **1**	Yield[c] [%]	
				38 or **40**	**3**
1	4-Me (0.65 mmol)	NIS(6), 70-75 °C, 24 h	96	78(73)	15[d]
2	4-Cl (0.65 mmol)	NIS(10), 70-75 °C, 24 h	100	94(90)	/[d,e]

[a] Reaction conditions: alcohol **1** (0.5 mmol). [b] Determined from ^{1}H NMR spectra of isolated crude reaction mixtures. [c] Yields calculated relative to alcohol **1**. Values in parentheses are isolated yields. [d] Benzophenone 3%. [e] Aldehyde 3%. [d] mol%.

5.2 Conclusion

In conclusion, I have demonstrated a novel, efficient, selective, metal- and acid-free method for direct conversion of primary and secondary benzyl alcohols to dimeric ethers catalyzed by *N*-halosuccinimides and *N*-fluoro organic compounds under solvent-free reaction conditions.

Direct transformation of primary, secondary and tertiary benzyl alcohols and tertiary alkyl alcohols into the corresponding ethers was discovered and developed using *N*-halosuccinimides and *N*-fluoro organic compounds in substoichiometric amounts in the presence of methanol, ethanol or isopropanol as nucleophile sources, under high concentration reaction conditions or in a solution.

In the case of 1,1-diphenylethanol **11** dehydration resulting in the 1,1-diphenylethene **58** was observed in the presence of substoichiometric amounts of *N*-halosuccinimides under solvent-free reaction conditions, while phenyl-substituted primary and secondary alcohols under the same conditions gave dimeric products. Phenyl-substituted primary, secondary and tertiary alcohols under substrate high concentration reaction conditions gave alkyl ethers, while under the same conditions 1,1-diphenylethanol **11** gave 1,1-diphenylethene **58**.

On the other hand, I have established that the etherification could also be achieved by cross coupling of two different benzyl alcohols catalyzed by *N*-halo organic compounds under solvent-free reaction conditions.

Newly developed methods present a significant contribution from a green chemistry viewpoint, economy of time and reagents.

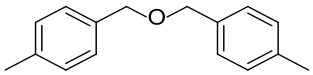
5.3 Experimental work

General procedure for etherification of alcohols catalyzed by *N*-halosuccinimides or *N*-fluoro organic compounds on half mmol scale: A mixture of benzyl or tertiary alkyl alcohol (0.5 mmol), and *N*-halo catalyst (1-5 mol%), which had been powdered in a mortar in the case of solid state reactants was transferred to a 4 mL screw-capped vial, finally added eventual liquid component alkyl alcohol (1-2 mmol or 1mL) or benzyl alcohol (0.65 mmol) and heated at 70-80 °C for 3.5 h-

24 h. The progress of the reaction mixture was monitored by TLC. Upon completion of the reaction, the crude reaction mixture was cooled down to room temperature, diluted with ethyl acetate (15 mL), washed with $Na_2S_2O_3$ (6 mL), $NaHCO_3$ (6 mL) and water (10 mL), and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the crude reaction mixture obtained was analysed by ^{1}H NMR. The pure final products were obtained after flash chromatography, column chromatography or preparative thin layer chromatography. Detailed experimental information, such as catalyst loading, isolated yields, and spectroscopic and other identification data, are given below.

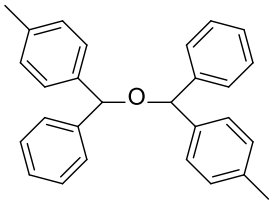
The isolated known compounds were identified by comparing the spectroscopic data with the literature.

4,4'-(Oxybis(methylene))bis(methylbenzene) (6) [187]



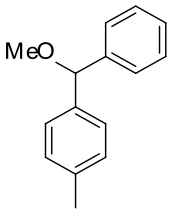
	$C_{16}H_{18}O$ (Mr = 226.31);
Reaction conditions:	0.5 mmol *p*-tolylmethanol **4** (61 mg), 3 mol% NIS (3.4 mg, 0.03 mmol), 70-75 °C, 24 h – SFRC;
Purification:	FC(SiO_2, CH_2Cl_2);
Yield:	55 mg (97%), white solid;
Mp.:	61-62 °C, (lit.[187] 62 °C);
^{1}H NMR (300 MHz, TMS):	δ (ppm) = 7.24 (d, *J* = 8.0 Hz, 4H), 7.14 (d, *J* = 7.8 Hz, 4H), 4.49 (s, 4H), 2.33 (s, 6H);
^{13}C NMR (76 MHz, $CDCl_3$):	δ (ppm) = 137.4, 135.4, 129.2, 128.0, 71.9, 21.3.

(±) 4,4'-(Oxybis(phenylmethylene))bis(methylbenzene) (34) [188]



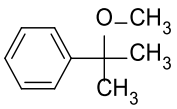
	$C_{28}H_{26}O$ (Mr = 378.51);
Reaction conditions:	0.5 mmol phenyl(*p*-tolyl)methanol **23** (99.1 mg), 3 mol% NIS (3.4 mg, 0.03 mmol), 70-75 °C, 4.5 h – SFRC;
Purification:	Not necessary;
Yield:	94 mg (99%), colourless oil;
^{1}H NMR (300 MHz, TMS):	δ (ppm) = 7.37 – 7.21 (m, 14H), 7.11 (d, *J* = 8.2 Hz, 4H), 5.36 (s, 2H), 2.31 (s, 6H);
^{13}C NMR (76 MHz, $CDCl_3$):	δ (ppm) = 142.7, 142.6, 139.5, 139.4, 137.19, 137.15, 129.21, 129.19, 128.5, 128.44, 128.42, 127.42, 127.37, 127.36, 127.32, 127.26, 79.86, 79.85, 46.1, 21.3;
HR-MS [MNa^+]:	Calculated for $C_{28}H_{26}O$: 401.1881; measured: 401.1890.

(±) 1-(Methoxy(phenyl)methyl)-4-methylbenzene (35) [189]



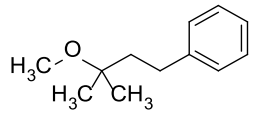
	$C_{15}H_{16}O$ (Mr = 212.29);
Reaction conditions:	0.5 mmol phenyl(*p*-tolyl)methanol **23** (99.1 mg), 1 mmol MeOH (40 µl), 3 mol% NIS (3.4 mg, 0.03 mmol), 70-75 °C, 6 h – HCRC;
Purification:	CC (SiO_2, CH_2Cl_2/hexane 1:1);
Yield:	96 mg (90%), yellow oil;
^{1}H NMR (300 MHz, TMS):	δ (ppm) = 7.36 – 7.20 (m, 7H), 7.12 (d, *J* = 7.9 Hz, 2H), 5.20 (s, 1H), 3.36 (s, 3H), 2.30 (s, 3H);
^{13}C NMR (76 MHz, $CDCl_3$):	δ (ppm) = 142.4, 139.2, 137.2, 129.2, 128.5, 127.5, 127.02, 126.95, 85.4, 57.1, 21.2.
HR-MS [M-H]$^-$:	Calculated for $C_{15}H_{15}O$: 211.1123; measured: 211.1127.

(2-Methoxypropan-2-yl)benzene (30) [190]



	$C_{10}H_{14}O$ (Mr = 150.22);
Reaction conditions:	0.5 mmol 2-phenylpropan-2-ol **29** (68 mg), 1 mL MeOH, 3 mol% NCS (2 mg, 0.03 mmol), 50-55 °C, 24 h, stirring 400 – in solution
Purification:	Not necessary;
Yield:	74 mg (98%), colourless liquid;
^{1}H NMR (300 MHz, TMS):	δ (ppm) = 7.43 – 7.22 (m, 5H), 3.07 (s, 3H), 1.53 (s, 6H);
^{13}C NMR (76 MHz, $CDCl_3$):	δ (ppm) = 146.0, 128.3, 126.9, 125.9, 76.9, 50.8, 28.1.

(3-methoxy-3-methylbutyl)benzene (33) [191]



$C_{12}H_{18}O$ (Mr = 178.27);

Reaction conditions: 0.5 mmol 2-methyl-4-phenylbutan-2-ol **32** (85 μl), 1 mmol MeOH (40 μl), 10 mol% NIS (11.2 mg, 0.1 mmol), 65-70 °C, 24 h – HCRC;

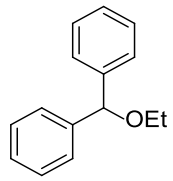
Purification: preparative TLC (SiO_2, EtOAc/hexane 1:9);

Yield: 57 mg (64%), colourless liquid;

^{1}H NMR (300 MHz, TMS): δ (ppm) = 7.31 – 7.13 (m, 5H), 3.23 (s, 3H), 2.67 – 2.60 (m, 2H), 1.81 – 1.73 (m, 2H), 1.21 (s, 6H);

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 143.0, 128.5, 128.4, 125.8, 74.5, 49.3, 41.9, 30.4, 25.2.

(Ethoxymethylene)dibenzene (36) [192]



$C_{15}H_{16}O$ (Mr = 212.29);

Reaction conditions: 0.5 mmol diphenylmethanol **1** (92.1 mg), 1 mmol EtOH (58 μl), 3 mol% NIS (3.4 mg, 0.03 mmol), 70-75 °C, 24 h – HCRC;

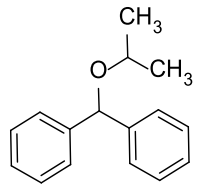
Purification: CC (SiO_2, CH_2Cl_2/hexane 1:1);

Yield: 94 mg (89%), colourless oil;

^{1}H NMR (300 MHz, TMS): δ (ppm) = 7.38 – 7.17 (m, 10H), 5.35 (s, 1H), 3.51 (q, *J* = 7.0 Hz, 2H), 1.26 (t, *J* = 7.0 Hz, 3H);

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 142.7, 128.5, 127.4, 127.1, 83.6, 64.7, 15.5.

Isopropoxydiphenylmethane (37) [192]



$C_{16}H_{18}O$ (Mr = 226.31);

Reaction conditions: 0.5 mmol diphenylmethanol **1** (92.1 mg), 1mL iPrOH, 3 mol% NIS (3.4 mg, 0.03 mmol), 80-85 °C, 24 h, stirring 400 – in solution;

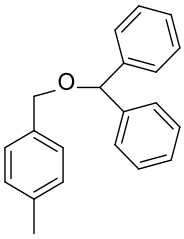
Purification: CC (SiO_2, CH_2Cl_2/hexane 1:1);

Yield: 100 mg (88%), colourless oil;

^{1}H NMR (300 MHz, TMS): δ (ppm) = 7.38 – 7.17 (m, 10H), 5.48 (s, 1H), 3.66 (hept, *J* = 6.1 Hz, 1H), 1.21 (d, *J* = 6.1 Hz, 6H);

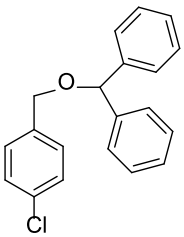
^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 143.1, 128.4, 127.4, 127.2, 80.6, 69.2, 22.4.

(((4-methylbenzyl)oxy)methylene)dibenzene (38) [167]



	$C_{21}H_{20}O$ (Mr = 288.38);
Reaction conditions:	0.5 mmol diphenylmethanol **1** (92.1 mg), 0.65 mmol *p*-tolylmethanol **4** (79.4 mg), 6 mol% NIS (6.7 mg, 0.06 mmol), 70-75 °C, 24 h – SFRC;
Purification:	CC (SiO_2, CH_2Cl_2/hexane 1:1);
Yield:	105 mg (73%); white solid
^{1}H NMR (300 MHz, TMS):	δ (ppm) = 7.39 – 7.12 (m, 14H), 5.42 (s, 1H), 4.49 (s, 2H), 2.34 (s, 3H);
^{13}C NMR (76 MHz, $CDCl_3$):	δ (ppm) = 142.3, 137.3, 135.4, 129.2, 128.5, 128.0, 127.5, 127.3, 82.3, 70.5, 21.3.

(((4-chlorobenzyl)oxy)methylene)dibenzene (40) [193]



	$C_{20}H_{17}ClO$ (Mr = 308.80);
Reaction conditions:	0.5 mmol diphenylmethanol **1** (92.1 mg), 0.65 mmol (4-chlorophenyl)methanol **39** (92.6 mg), 10 mol% NIS (11.2 mg, 0.1 mmol), 70-75 °C, 24 h – SFRC;
Purification:	CC (SiO_2, CH_2Cl_2/hexane 1:1);
Yield:	139 mg (90%), white solid;
Mp.:	57-60 °C;
^{1}H NMR (300 MHz, TMS):	δ (ppm) = 7.40 – 7.19 (m, 14H), 5.41 (s, 1H), 4.49 (s, 2H);
^{13}C NMR (76 MHz, $CDCl_3$):	δ (ppm) = 142.0, 137.0, 133.4, 129.1, 128.61, 128.56, 127.7, 127.2, 82.8, 69.8.

Chapter 6

N-halo compounds catalysis of new carbon-carbon bond formation in organic molecules

C-C bond forming reactions display one of the most important implements for the synthesis of complex organic products, many of them developed bioactivity as drugs or agrochemicals [27]. C-C bond formation by direct coupling of alcohols with other partners could be a very attractive strategy from practical, atom-efficient and environmental point of view, producing water as only a by-product of the reaction [185]. Because of their lower leaving group ability, hydroxyl moieties are rarely substituted under mild conditions and must often be activated before treatment with nucleophiles [65].

Numerous related methodologies have been elaborated using a substoichiometric amount of molecular iodine [135], metals such as indium, iron, ruthenium [27], Brønsted acids such as triflic acid, dodecylbenzenesulfonic acid [27]. The aforementioned methods suffer some disadvantages, including the use of toxic and expensive reagents or environmentally undesirable solvents, long reaction time and a high temperature.

The development of an efficient and environmentally benign catalytic methodology for C-C bond formation remains an attractive research subject. On the basis of our research group's continuing interest in developing greener methods, for comprehensive types of organic molecule transformation, I was motivated to invent and develop some new efficient and selective methodology for the direct C-C bond formation through the direct coupling of various types of alcohols with a different type of electron rich compounds. In this view I have chosen derivatives of 1,3-dicarbonyl compounds, heteroatom benzo-cyclenes, phenyl substituted alkenes as the representative of electron rich carbohydrates, or tertiary benzyl alcohols, bearing a vicinal hydrogen atom as alkene precursors. As I supposed, the mentioned transformation would need catalytic support. *N*-halo organic compounds could be the right choice also in this case as a new type of metal- and acid-free catalysts for these transformations under SFRC, which offers a potential impact to environmental issues, producing only water as a by-product of the reaction.

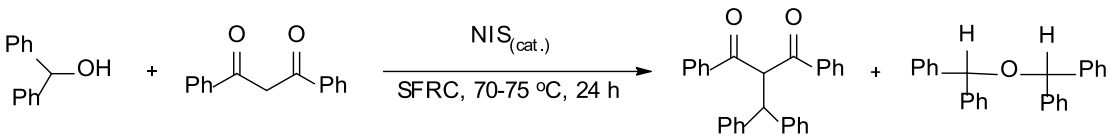
6.1 C-C bond formation through ß-diketones

6.1.1 Results and discussion

Based on results reported in the first chapter (Table 4.3), when the reaction of diphenylmethanol **1** with dibenzoylmethane **7** was performed in the presence of NCS or FTEDA as the catalyst, no conversion of the diphenylmethanol **1** or dibenzoylmethane **7** was observed, while in the presence of NBS or NFSi as the catalyst, low to moderate conversion of the diphenylmethanol **1** into the dimeric ether **3** and oxidized alcohol was noticed. But, in the presence of NIS as the catalyst, the coupling of benzyl moiety with one of ß-dicarbonyl took place, providing efficiently and selectively the corresponding product **8** with the new C-C bond formed between benzyl carbon atom and C-2 carbon of dicarbonyl target.

Different parameters such as the loading of the NIS as the catalyst (Table 6.1), reaction time (Table 6.2), reaction temperature (Table 6.3) and the reactivity of alcohols (Table 6.4) for the reaction of diphenylmethanol **1** with dibenzoylmethane **7** under SFRC were first studied. The loading of NIS as the catalyst was examined (Table 6.1), where different concentrations of the catalyst were employed. In the reaction of diphenylmethanol **1** with dibenzoylmethane **7** with 3 mol% of the catalyst, I observed the quantitative formation of the corresponding product as a major product **8** (entry 1). This reaction was also selective and successful when the catalyst loading was decreased to 2 mol% (entry 2). I found that for a selective and successful transformation of the starting materials **1** and **7** into the desired product **8**, 1 mol% of the catalyst was also effective (entry 3). In the case of decreasing the catalyst loading to 0.5 mol%, diphenylmethanol **1** was completely consumed even though the yield was moderate, and a certain amount of dimeric ether was obtained **3** (entry 4). Using 0.1 mol% of the catalyst, worse reaction yield was observed **8** (entry 5).

Table 6.1: The effect of loading of NIS on the composition of crude reaction mixture under SFRC[a].



1 **7** **8** **3**

Entry	NIS (Mol%)	Relative distribution of reagents and products in the reaction mixture[b] [%]			
		1	**7**	**8**	**3**
1	3	/	/	100	/
2	2	/	/	100	/
3	1	/	/	100	/
4	0.5	/	16	68	16
5	0.1	46	36	12	6

[a] Reaction conditions: diphenylmethanol **1** (0.5 mmol), dibenzoylmethane **7** (0.5 mmol). [b] Determined from ^{1}H NMR spectra of isolated crude reaction mixtures.

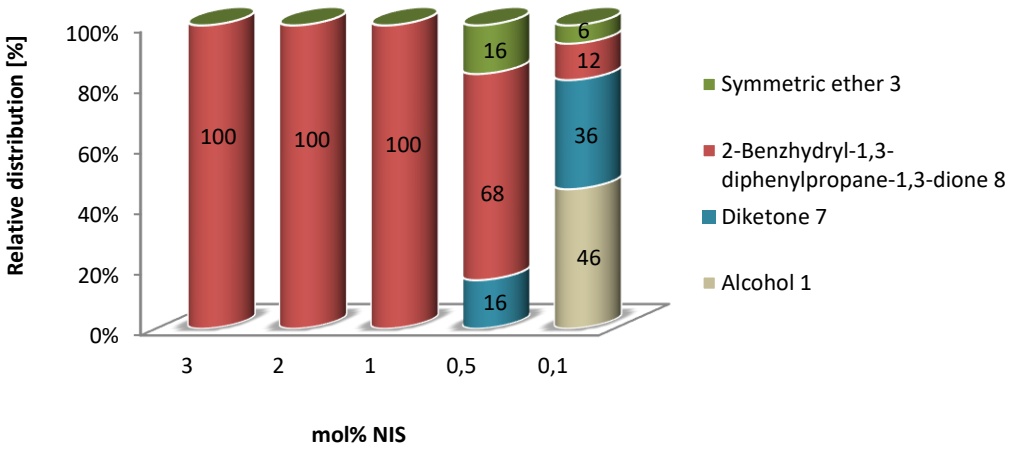
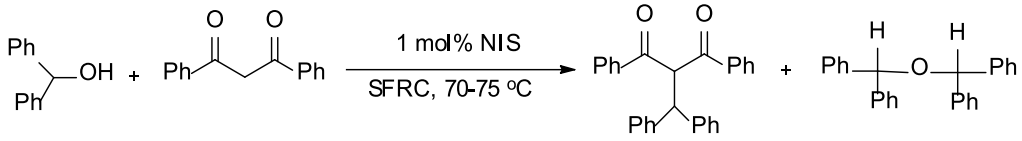


Figure 6.1: The effect of loading of NIS on the composition of crude reaction mixture under SFRC.

I examined the reaction time of coupling of diphenylmethanol **1** with dibenzoylmethane **7** catalyzed by NIS under SFRC (Table 6.2). I observed that if the reaction time was shortened to 6 h, the reaction gave a lower amount of the corresponding product **8**, accompanied with the formation of the symmetric ether **3** (entries 1). In entry 2, diphenylmethanol **1** was completely consumed even though the yield was moderate and a high amount of dimeric ether **3** was obtained. The improvement to 100% yield of the corresponding product **8**, without formation of symmetric ether, is attained by prolonging the reaction time up to 24 h (entry 3).

Table 6.2: The catalytic effect of NIS on the composition of crude reaction mixture based on time under SFRC[a].



1 **7** **8** **3**

Entry	Time (h)	Relative distribution of reagents and products in the reaction mixture[b] [%]			
		1	**7**	**8**	**3**
1	6	8	24	44	24
2	18	/	20	60	20
3	24	/	/	100	/

[a] Reaction conditions: diphenylmethanol **1** (0.5 mmol), dibenzoylmethane **7** (0.5 mmol).
[b] Determined from ^{1}H NMR spectra of isolated crude reaction mixtures.

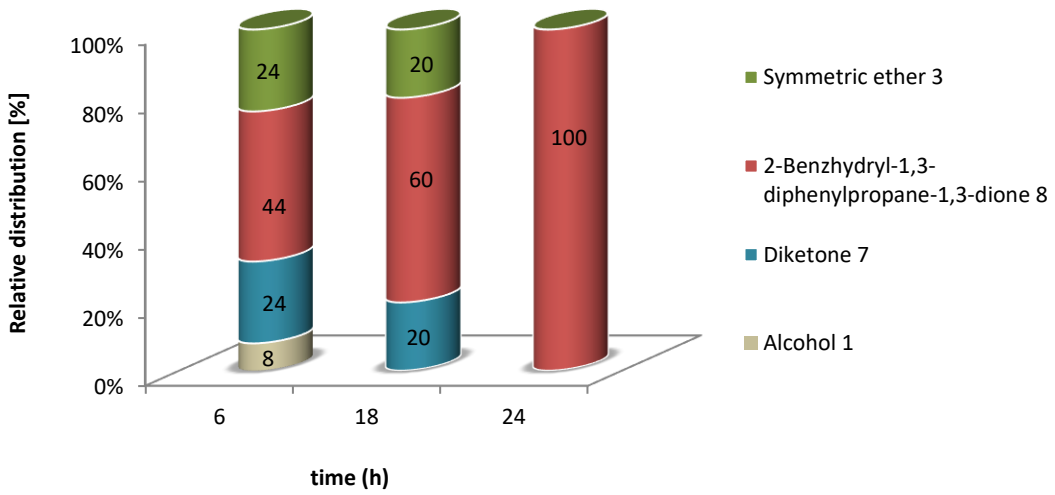
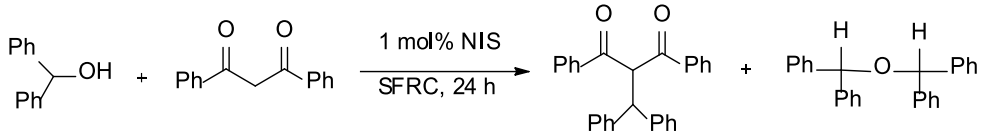


Figure 6.2: The catalytic effect of NIS on the composition of crude reaction mixture based on time under SFRC.

Variation of reaction temperature was examined by the coupling of diphenylmethanol **1** with dibenzoylmethane **7** catalyzed by NIS under SFRC (Table 6.3). When the reaction was carried out at room temperature up to 50-55 °C, no conversion of the starting materials **1** or **7** occurred (entries 1-3). However, raising the temperature up to 60-65 °C, the yield of the corresponding product **8** affected positively after the same reaction time, accompanied by the formation of the symmetric ether **3** (entry 4). The remarkable improvement of the yield was observed by increasing the reaction time up to 70-75 °C, and quantitative formation of the corresponding product **8** as a sole the product without intervention of symmetric ether was established (entry 5).

Table 6.3: The catalytic effect of NIS on the composition of crude reaction mixture based on temperature under SFRC[a].



1 **7** **8** **3**

Entry	Temp. (°C)	Relative distribution of reagents and products in the reaction mixture[b] [%]			
		1	**7**	**8**	**3**
1	r.t.	50	50	/	/
2	40-45	50	50	/	/
3	50-55	50	50	/	/
4	60-65	36	19	26	19
5	70-75	/	/	100	/

[a] Reaction conditions: diphenylmethanol **1** (0.5 mmol), dibenzoylmethane **7** (0.5 mmol). [b] Determined from ^{1}H NMR spectra of isolated crude reaction mixtures.

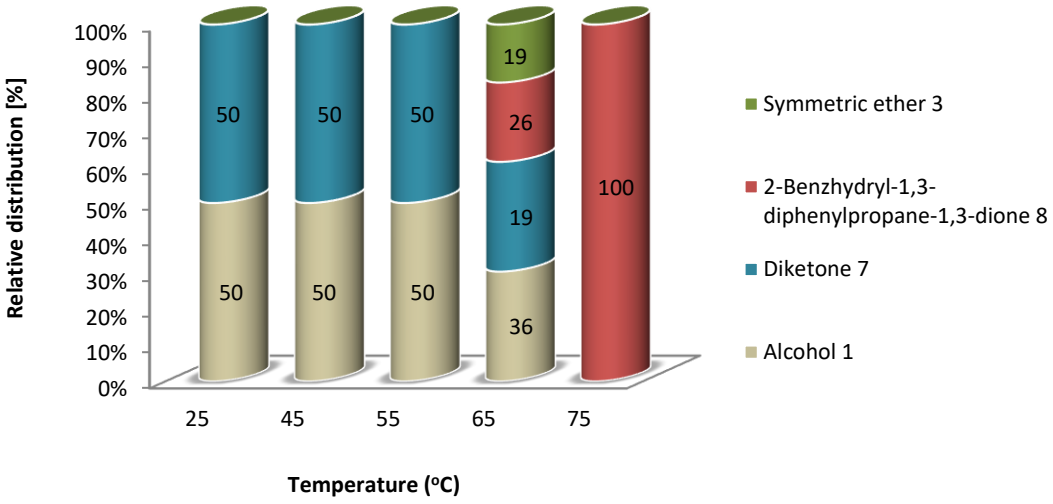
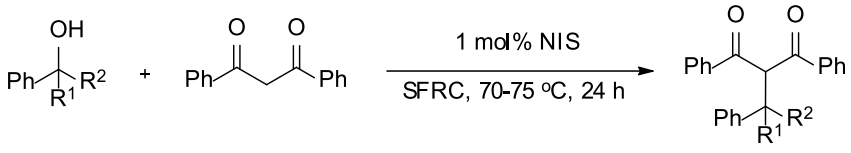


Figure 6.3: The catalytic effect of NIS on the composition of crude reaction mixture based on temperature under SFRC.

Next, I studied the impact of the type (primary, secondary and tertiary) of benzyl alcohols on the course of the reaction with dibenzoylmethane **7** catalyzed by NIS under SFRC, and the results are presented in Table 6.4. It could be seen that under the above-mentioned optimal reaction conditions, the reaction successfully proceeded only in the case of secondary benzyl alcohol, while no reaction was observed with benzyl alcohol **43** as the type of primary alcohol and triphenylmethanol **44** as the type of tertiary alcohol (entries 1 and 3).

Table 6.4: The catalytic effect of NIS on the composition of crude reaction mixture based on the structure of alcohol under SFRC[a]



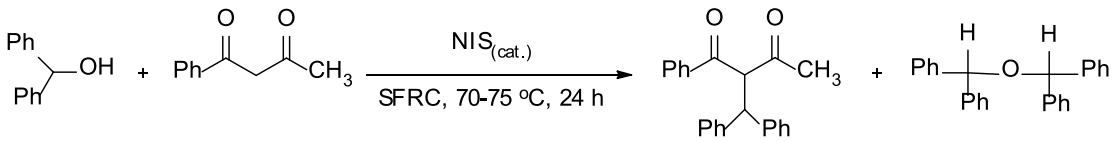
1 or **43-44** **7** **8** or **43a-44a**

Entry	R^1, R^2		Conv.[b] [%] of		Yield[c] [%]
1	R^1=R^2=H	**43**	/	**43a**	/
2	R^1=H, R^2=Ph	**1**	100	**8**	99
3	R^1=R^2=Ph	**44**	/	**44a**	/

[a] Reaction conditions: alcohols **1** or **43-44** (0.5 mmol), dibenzoylmethane **7** (0.5 mmol). [b] Determined from ^{1}H NMR spectra of isolated crude reaction mixtures. [c] Isolated yields.

In the first sight this fact seems to diminish the potential of a scope of the reaction, but by further investigation of the crucial reaction parameters such as the structure of ß-dicarbonyl, the structure of alcohol and loading of the catalyst should show us the real value of the methodology. Thus, I further studied the effect of the structure of ß-diketone on the course of the reaction with diphenylmethanol **1** as the most reactive benzyl alcohol derivative. I selected benzoylacetone as a further candidate and the results are shown in Table 6.5. In the reaction of diphenylmethanol **1** with benzoylacetone **45** with 3 mol% of the catalyst, I noticed the quantitative formation of the corresponding product as a sole product **46** (entry 1). The reaction was also found to proceed efficiently and selectively employing 2 mol% of the catalyst (entry 2). Lowering the catalyst loading to 1 mol% led to an incomplete reaction (entry 3), while in the absence of the catalyst, no reaction took place.

Table 6.5: The effect of loading of NIS on the composition of crude reaction mixture under SFRC[a].



1 **45** **46** **3**

Entry	NIS (Mol%)	Relative distribution of reagents and products in the reaction mixture[b] [%]			
		1	**45**	**46**	**3**
1	3	/	/	100	/
2	2	/	/	100	/
3	1	13	26	28	33

[a] Reaction conditions: diphenylmethanol **1** (0.5 mmol), benzoylacetone **45** (0.5 mmol). [b] Determined from ^{1}H NMR spectra of isolated crude reaction mixtures.

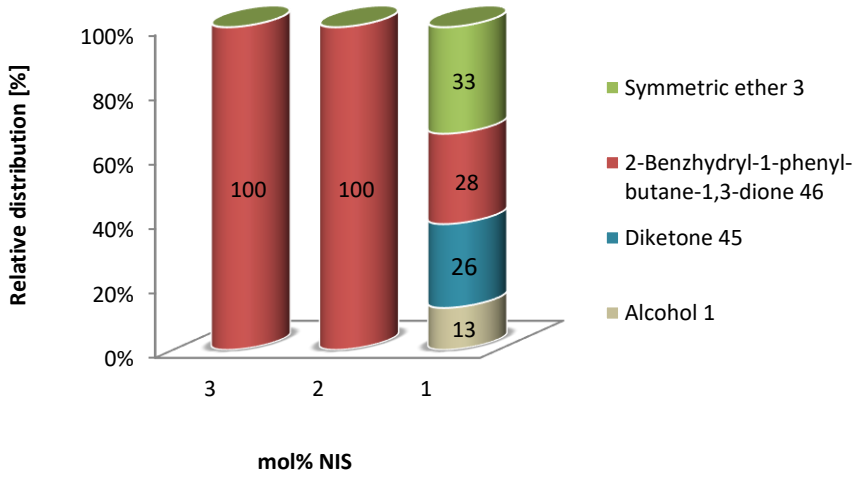
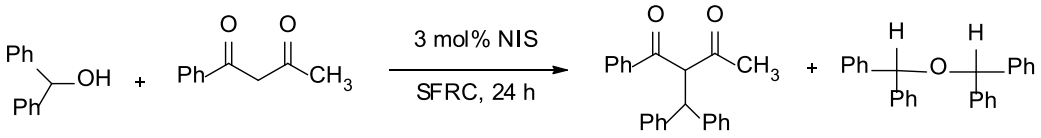


Figure 6.4: The effect of loading of NIS on the composition of crude reaction mixture under SFRC.

According to these facts benzoylacetone **45** is less reactive than dibenzoylmethane **7**.

Variation of reaction temperatures were examined for the coupling of diphenylmethanol **1** with benzoylacetone **45** catalyzed by NIS under SFRC (Table 6.6). When the reaction was carried out at room temperature, no conversion of the starting materials **1** or **45** occurred (entry 1). When the reaction was performed at 40-45 °C or 50-55 °C, the desired product **46** in low yield and dimeric ether were obtained **3** (entry 2 and 3). The increase of reaction temperature up to 60-65 °C, provided the corresponding product **46** in good yield, accompanied by the formation of the symmetric ether **3** (entry 4) in a low amount. The improvement of 100% yield without of formation the symmetric ether is attained by increasing the reaction temperature up to 70-75 °C.

Table 6.6: The catalytic effect of NIS on the composition of crude reaction mixture based on temperature under SFRC[a].



1 **45** **46** **3**

Entry	Temp. (°C)	Relative distribution of reagents and products in the reaction mixture[b,c] [%]			
		1	**45**	**46**	**3**
1	r.t.	50	50	/	/
2	40-45	44	30	11	15
3	50-55	11	29	28	32
4	60-65	6	21	50	23
5	70-75	/	/	100	/

[a] Reaction conditions: diphenylmethanol **2** (0.5 mmol), benzoylacetone **45** (0.5 mmol). [b,c] Determined from ^{1}H NMR spectra of isolated crude reaction mixtures.

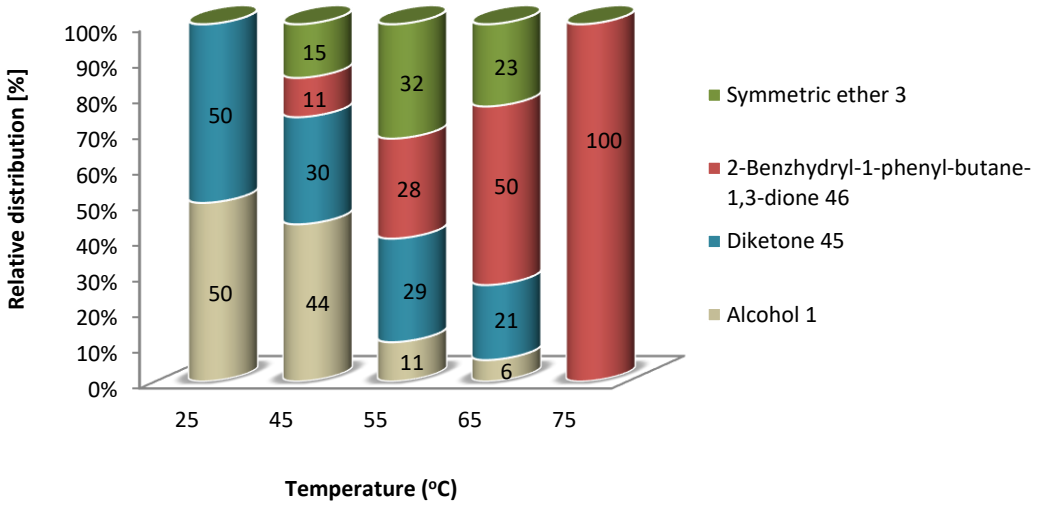
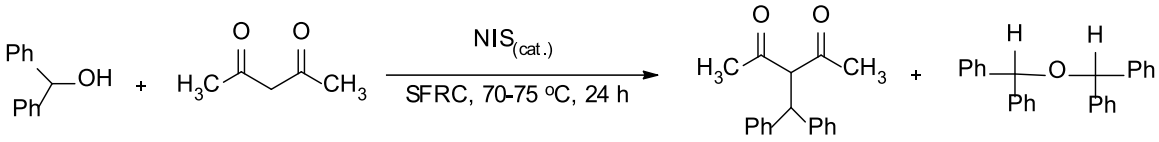


Figure 6.5: The catalytic effect of NIS on the composition of crude reaction mixture based on temperature under SFRC.

In view of the mentioned experience, it seemed that acetylacetone could be the next instructive substrate for realising the effect of the structure of ß-dicarbonyl compound to the course of the reaction and the results are shown in Table 6.7. In this case, even considerable high loading of the catalyst was necessary (8 mol%), for efficient and selective transformation.

Table 6.7: The effect of loading of NIS on the composition of crude reaction mixture under SFRC[a].



1 **47** **48** **3**

Entry	NIS (Mol%)	Relative distribution of reagents and products in the reaction mixture[b] [%]			
		1	**47**	**48**	**3**
1	3	16	26	15	43
2	5	11	16	47	26
3	6	10	12	61	17
4	8	/	/	100	/

[a] Reaction conditions: diphenylmethanol **1** (0.5 mmol), acetylacetone **47** (0.5 mmol). [b] Determined from ^{1}H NMR spectra of isolated crude reaction mixtures.

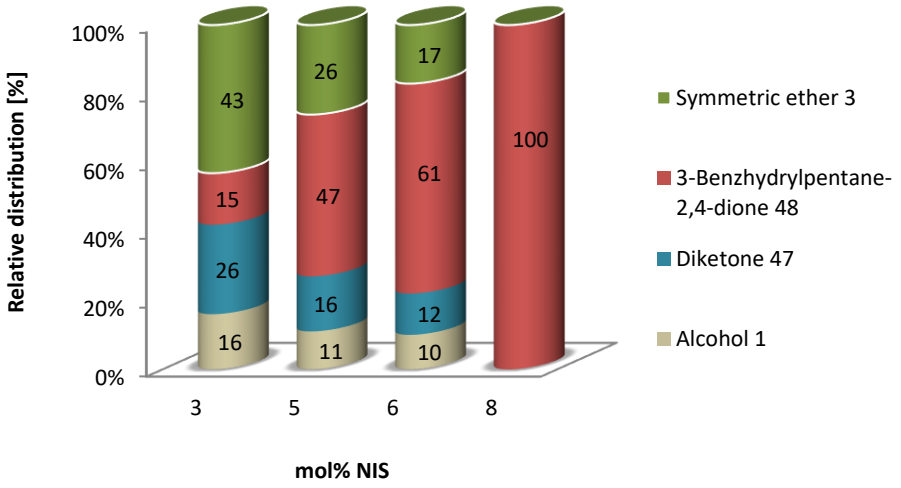
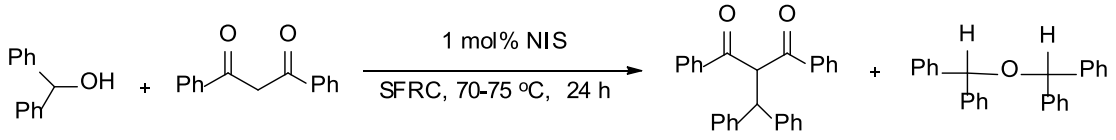


Figure 6.6: The effect of loading of NIS on the composition of crude reaction mixture under SFRC.

According to these results, the most reactive of ß-dicarbonyl compounds (mentioned above) is dibenzoylmethane **7**, optimal loading of NIS as the catalyst is 1 mol%, reaction temperature 70-75 °C and reaction time 24 h (Scheme 6.1).



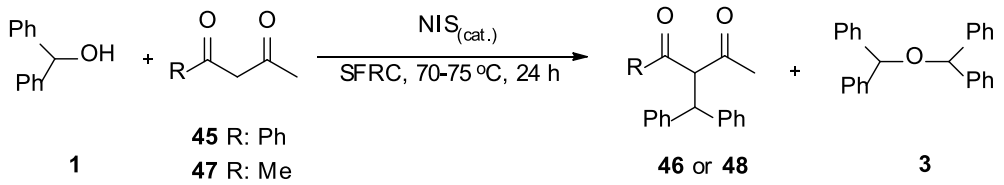
1 **7** **8** **3**

Scheme 6.1: Direct coupling of diphenylmethanol **1** with dibenzoylmethane **7** catalyzed by NIS under SFRC.

I believe that the key point of the reaction is the degree of enolisation of ß-diketon on one side, and a stability of carbocationic intermediate formed from the alcohol on another side. A higher degree of enolisation (pK_E) caused more efficient and selective transformation into the desired coupling between ß-dicarbonyl and alcohol, or more stabilized carbocationic intermediate caused more efficient and selective product formation.

This claim is illustrated by the data collected in Table 6.8.

Table 6.8: Enol stability of benzoylacetone **45** and acetylacetone **47**[a].



45 R: Ph
47 R: Me

1 **46** or **48** **3**

Entry	R		pK_E	NIS (Mol%)		Relative distribution[b] [%]	
						46 or **48**	**3**
1	Ph	**45**	3.77[194]	1	**46**	13	31
2	Ph	**45**	3.77[194]	2	**46**	100	/
3	Me	**47**	4.12[194]	1	**48**	/	/
4	Me	**47**	4.12[194]	8	**48**	100	/

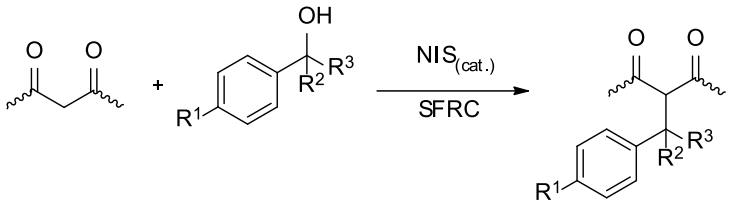
[a] Reaction conditions: diphenylmethanol **1** (0.5 mmol), diketones **45** or **47** (0.5 mmol). [b] Determined from ^{1}H NMR spectra of isolated crude reaction mixtures; Yield calculated relative to alcohol.

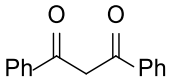
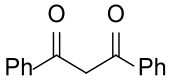
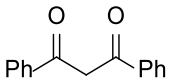
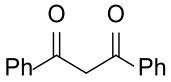
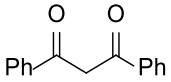
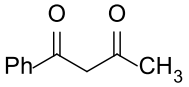
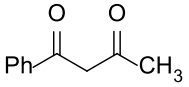
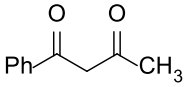
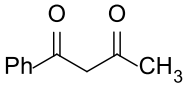
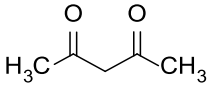
To extend the scope of ß-diketones we checked reactions of different ß-dicarbonyl compounds with different alcohols catalyzed by NIS under SFRC. The results of reactions carried out under SFRC are collected in Table 6.9. In the case of primary benzyl alcohol **43** with dibenzoylmethane **7** in the presence of NIS as the catalyst under SFRC, no transformation took place (entry 1). Effective transformation with dibenzoylmethane **7** was observed in the reaction with primary benzyl alcohol bearing electron-donating group under the same reaction conditions. 4-methoxybenzyl alcohol **49** was efficiently and selectively converted into the 2-(4-methoxybenzyl)-1,3-diphenylpropane-1,3-dione **50** (entry 2). In the case of the reaction of diphenylmethanol **1** with dibenzoylmethane **7** in the absence of a catalyst under SFRC, no reaction occurred. However, in the presence of NIS as the catalyst, the coupling of benzyl moiety with 1,3-dicarbonyl one took place, providing product **8** with the new C-C bond formed between benzyl carbon atom and C-2 of dicarbonyl target (entry 3). Encouraged with this result I checked the reaction of phenyl(*p*-tolyl)methanol **23** with dibenzoylmethane **7** and established the quantitative formation of the corresponding product **51** (entry 4). Moreover, no transformation was observed with sterically more bulky triphenylmethanol **44** with dibenzoylmethane **7** in the presence of NIS as the catalyst under SFRC (entry 5).

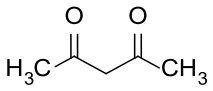
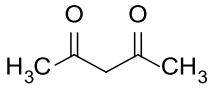
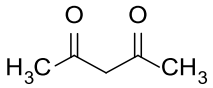
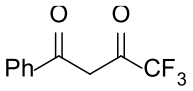
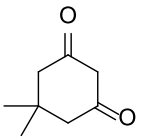
I further investigated the corresponding reactions of alcohols with benzoylacetone **45**. In the case of the reaction of primary benzyl alcohol **43** with benzoylacetone **45** in the presence of NIS as the catalyst under SFRC no transformation took place (entry 6). In the case of the reaction of **45** with diphenylmethanol **1** in the presence of NIS as the catalyst, I observed the quantitative conversion of starting materials **1** or **45** resulting in the formation of the corresponding product **46** (entry 7). The same result was achieved with phenyl(*p*-tolyl)methanol **52** (entry 8). No transformation was observed in the case of triphenylmethanol **44** with benzoylacetone **45** in the presence of NIS as the catalyst under SFRC (entry 9).

Furthermore, I investigated the corresponding reactions of alcohols with acetylacetone **47**. In the case of the reaction of primary benzyl alcohol **43** with acetylacetone 4**7** in the presence of NIS as the catalyst under SFRC no transformation took place (entry 10). Effective transformation of diphenylmethanol **1** and phenyl(*p*-tolyl)methanol **23**, with acetylacetone **47** was observed. In the absence of a catalyst, no reaction occurred. However, in the presence of NIS as the catalyst, under SFRC, I established the quantitative formation of the corresponding products **48** and **53** (entry 11 and 12). No transformation was observed in the case of triphenylmethanol **44** with acetylacetone **47** in the presence of NIS as the catalyst under SFRC (entry 13). In few cases the conversion of less reactive ß-dicarbonyl compounds, such as 4,4,4-trifluoro-1-phenylbutane-1,3-dione **54** and 5,5-dimethylcyclohexane-1,3-dione **55**, led to the formation of the symmetric ethers as the main products accompanied with small amounts of oxidised alcohols (entries 14 and 15).

Table 6.9: Reactions of ß-dicarbonyl compounds with different alcohols catalyzed by NIS under SFRC[a].



Entry			R^1, R^2, R^3		NIS (Mol%)		Yield[b] [%]
1		**7**	R^1=R^2= R^3=H	**43**	10	**43a**	/
2		**7**	R^1=OMe, R^2=R^3=H	**49**	6	**50**	100 (98)
3		**7**	R^1=R^2=H, R^3=Ph	**1**	1	**8**	100 (99)
4		**7**	R^1=Me, R^2=H, R^3=Ph	**23**	3	**51**	100 (99)
5		**7**	R^1=R^2= R^3=Ph	**44**	10	**44a**	/
6		**45**	R^1=R^2= R^3=H	**43**	10	**43b**	/
7		**45**	R^1=R^2=H, R^3=Ph	**1**	2	**46**	100 (98)
8		**45**	R^1=Me, R^2= H, R^3=Ph	**23**	5	**52**	100 (99)
9		**45**	R^1=R^2= R^3=Ph	**44**	10	**44b**	/
10		**47**	R^1=R^2= R^3=H	**43**	10	**43c**	/

11		**47**	R^1=R^2=H, R^3=Ph	**1**	8	**48**	100 (98)
12		**47**	R^1=Me, R^2= H, R^3=Ph	**23**	7	**53**	100 (99)
13		**47**	R^1=R^2= R^3=Ph	**44**	10	**44c**	/
14[c]		**54**	R^1=R^2=H, R^3=Ph	**1**	3	**54a**	**/**
15[c]		**55**	R^1=R^2=H, R^3=Ph	**1**	3	**55a**	**/**

[a] Reaction conditions: alcohols (0.5 mmol), diketones (0.5 mmol), NIS (1-10 mol%), 70-75 °C, 23-26 h. [b] Determined from ^{1}H NMR spectra of isolated crude reaction mixtures; yield calculated relative to alcohol; values in parentheses are isolated yields. [c] Symmetric ether and benzophenone are formed.

To improve the synthetic value of the reported methodology, the following reaction was performed on the 10 mmol scale: coupling of diphenylmethanol **1** with dibenzoylmethane **7** under the above mentioned optimal reaction conditions, affording the desired product **8** in quantitative yield (99%).

6.1.2 Conclusion

Novel, efficient, selective and easily scalable methodology for C-C bond formation through the direct coupling of various ß-dicarbonyl compounds with various benzyl alcohols employing NIS catalysis under SFRC was developed. The reactivity of ß-dicarbonyl compounds was found to be the function of their enolisability, while primary benzyl alcohols target needed strong activation of the ring, comprehensive range of secondary benzyl alcohols gave efficient coupling, while tertiary benzyl alcohols were found as inconvenient targets.

6.1.3 Experimental work

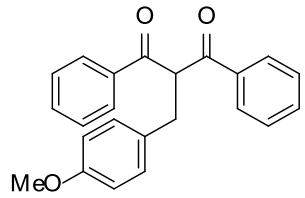
General procedure for new carbon-carbon bond formation through ß-dicarbonyl compounds in organic molecules catalyzed by NIS on half mmol scale: In a 4 mL screw-capped vial a mixture of solid reaction components [ß-dicarbonyl compound (0.5 mmol), benzyl alcohol (0.5 mmol) and NIS (1-8 mol%)] (which had been powdered in a mortar) was transferred and finally an eventual liquid reaction component was added. The vial was then heated at 70-75 °C for 24 h. The progress of the reaction mixture was monitored by TLC. Upon completion of the reaction, the crude reaction mixture was cooled down to room temperature, diluted with ethyl acetate (15 mL), washed with $Na_2S_2O_3$ (6 mL), $NaHCO_3$ (6 mL) and water (10 mL), and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the crude reaction mixture obtained was analysed by ^{1}H NMR. Finally, if necessary, the pure final products were obtained after flash chromatography. Detailed experimental information, such as catalyst loading, isolated yields, and spectroscopic and other identification data, are given below.

The scale-up procedure for the synthesis of 2-benzhydryl-1,3-diphenylpropane-1,3-dione 8 catalyzed by NIS: A mixture of 1,3-diphenylpropane-1,3-dione (10 mmol, 1.8423 g), diphenylmethanol (10 mmol, 2.2425 g) and NIS (1 mol%, 0.1 mol, 22.5 mg) which had been

powdered in a mortar, was transferred to a 20 mL screw-capped glass scintillation vial and heated at 70-75 °C for 24 h. The progress of the reaction mixture was followed by TLC. Upon completion of the reaction, the mixture was cooled down to room temperature. Finally, the crude reaction mixture was washed with hot water and filtered by vacuum filtration to obtain a pure product in almost quantitative yield (white solid, mp. 220-223 °C, 3.9 g, 99%).

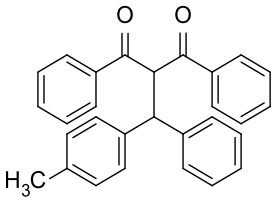
The isolated known compounds were identified by comparing the spectroscopic data with the literature.

2-(4-Methoxybenzyl)-1,3-diphenylpropane-1,3-dione (50) [195]



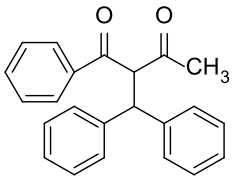
	$C_{23}H_{20}O_3$ (Mr = 344.40);
Reaction conditions:	0.5 mmol (4-methoxyphenyl)methanol **49** (62 µl), 0.5mmol 1,3-diphenylpropane-1,3-dione **7** (112.1 mg), 6 mol% NIS (6.7 mg, 0.06 mmol), 70-75 °C, 24 h – SFRC;
Purification:	FC (SiO_2, CH_2Cl_2);
Yield:	169 mg (98%), colourless solid;
Mp.:	95-97 °C (lit.[195] 96-98 °C)
^{1}H NMR (300 MHz, TMS):	δ (ppm) = 7.91 – 7.87 (m, 4H), 7.53 (t, *J* = 7.4 Hz, 2H), 7.43 – 7.37 (m, 4H), 7.16 (d, *J* = 8.7 Hz, 2H), 6.76 (d, *J* = 8.7 Hz, 2H), 5.49 (t, *J* = 6.7 Hz, 1H), 3.72 (s, 3H), 3.39 (d, *J* = 6.7 Hz, 2H);
^{13}C NMR (76 MHz, $CDCl_3$):	δ (ppm) = 195.6, 158.4, 136.2, 133.6, 131.2, 130.1, 128.9, 128.7, 114.1, 59.5, 55.3, 34.5.

1,3-Diphenyl-2-(phenyl(p-tolyl)methyl)propane-1,3-dione (51) [196]



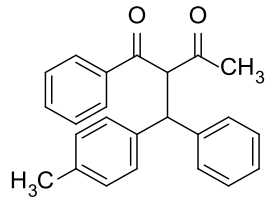
	$C_{29}H_{24}O_2$ (Mr = 404.50);
Reaction conditions:	0.5 mmol phenyl(*p*-tolyl)methanol **23** (99.1 mg), 0.5mmol 1,3-diphenylpropane-1,3-dione **7** (112.1 mg), 3 mol% NIS (3.4 mg, 0.03 mmol), 70-75 °C, 24 h – SFRC;
Purification:	Not necessary;
Yield:	201 mg (99%), white solid;
Mp.:	191-193 °C;
^{1}H NMR (300 MHz, TMS):	δ (ppm) = 7.86 – 7.80 (m, 4H), 7.31 (td, *J* = 7.6, 3.3 Hz, 5H), 7.23 (d, *J* = 6.3 Hz, 3H), 7.12 (t, *J* = 7.8 Hz, 5H), 6.95 (d, *J* = 7.8 Hz, 2H), 6.33 (d, *J* = 11.6 Hz, 1H), 5.29 (d, *J* = 11.7 Hz, 1H), 2.18 (s, 3H);
^{13}C NMR (76 MHz, $CDCl_3$):	δ (ppm) = 194.4, 194.2, 142.1, 138.9, 137.14, 137.13, 136.2, 133.31, 133.30, 129.4, 128.8, 128.74, 128.68, 128.66, 128.6, 128.4, 128.2, 126.7, 62.7, 52.2, 21.0;
HR-MS [MH$^+$]:	Calculated for $C_{29}H_{25}O_2$: 405.1855; measured: 405.1859.

2-Benzhydryl-1-phenyl-butane-1,3-dione (46) [174]



	$C_{23}H_{20}O_2$ (Mr = 328.40);
Reaction conditions:	0.5 mmol diphenylmethanol **1** (91.2 mg), 0.5mmol 1-phenylbutane-1,3-dione **45** (81 mg), 2 mol% NIS (2.2 mg, 0.02 mmol), 70-75 °C, 24 h – SFRC;
Purification:	FC (SiO_2, CH_2Cl_2);
Yield:	160 mg (98%), white solid;
Mp.:	148-150 °C, (lit.[174] 149.8-150.7 °C);
^{1}H NMR (300 MHz, TMS):	δ (ppm) = 7.96 (d, *J* = 8.6 Hz, 2H), 7.56 – 7.00 (m, 13H), 5.61 (d, *J* = 12.0 Hz, 1H), 5.10 (d, *J* = 12.0 Hz, 1H), 2.04 (s, 3H);
^{13}C NMR (76 MHz, $CDCl_3$):	δ (ppm) = 203.0, 194.3, 141.8, 141.3, 137.0, 133.8, 129.1, 128.82, 128.75, 128.2, 127.8, 127.2, 126.8, 69.0, 51.6, 27.9;
HR-MS [MNa$^+$]:	Calculated for $C_{23}H_{20}O_2$: 351.1361; measured 351.1365.

(±) 1-Phenyl-2-(phenyl(p-tolyl)methyl)butane-1,3-dione (52) [196]



$C_{24}H_{22}O_2$ (Mr = 342.43);

Reaction conditions: 0.5 mmol phenyl(*p*-tolyl)methanol **23** (99.1 mg), 0.5mmol 1-phenylbutane-1,3-dione **45** (81 mg), 5mol% NIS (5.6 mg, 0.05 mmol), 70-75 °C, 23 h – SFRC;

Purification: Not necessary;

Yield: 169 mg (99%), white solid;

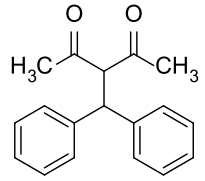
Mp.: 130-132 °C, (lit.[197] 130 °C);

^{1}H NMR (300 MHz, TMS): δ (ppm) = 7.99 – 7.91 (m, 2H), 7.53 – 6.90 (m, 12H), 5.60 (dd, *J* = 12.0, 3.8 Hz, 1H), 5.07 (dd, *J* = 12.0, 2.1 Hz, 1H), 2.27, 2.15 (s, s, 3H), 2.04, 2.02 (s, s, 3H);

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 203.20, 203.16, 194.4, 194.3, 142.0, 141.6, 138.8, 138.3, 137.02, 136.99, 136.8, 136.3, 133.7, 129.8, 129.4, 129.0, 128.9, 128.8, 128.7, 128.2, 128.1, 127.7, 127.6, 127.1, 126.7, 69.10, 69.05, 51.20, 51.16, 27.9, 27.8, 21.1, 21.0;

HR-MS $[M-H]^-$: Calculated for $C_{24}H_{21}O_2$: 341.1542; measured: 341.1550.

3-Benzhydrylpentane-2,4-dione (48) [4]



$C_{18}H_{18}O_2$ (Mr = 266.33);

Reaction conditions: 0.5 mmol diphenylmethanol **1** (92.1 mg), 0.5 mmol pentane-2,4-dione **47** (51 μl), 8 mol% NIS (8.9 mg, 0.08 mmol), 70-75 °C, 24 h – SFRC;

Purification: FC (SiO_2, CH_2Cl_2);

Yield: 131 mg (98%), white solid;

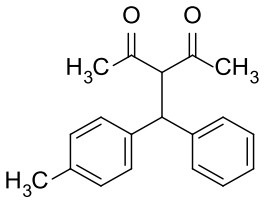
Mp.: 111-113 °C, (lit.[4] 112-114 °C);

^{1}H NMR (300 MHz, TMS): δ (ppm) = 7.26 – 7.22 (m, 8H), 7.20 – 7.13 (m, 2H), 4.81 (d, *J* = 12.3 Hz, 1H), 4.73 (d, *J* = 12.3 Hz, 1H), 1.99 (s, 6H);

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 203.1, 141.4, 129.0, 127.8, 127.1, 74.6, 51.3, 29.8;

HR-MS $[MH^+]$: Calculated for $C_{18}H_{19}O_2$: 267.1385; measured: 267.1382.

3-(Phenyl(*p*-tolyl)methyl)pentane-2,4-dione (53) [196]



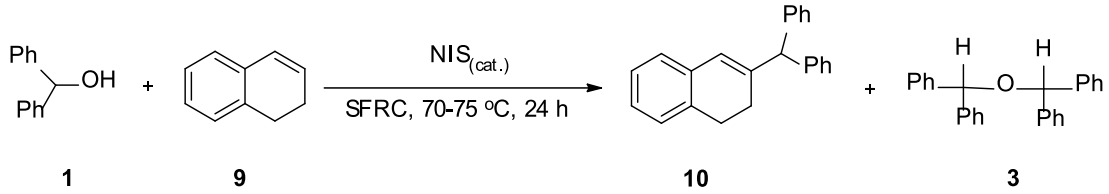
	$C_{19}H_{20}O_2$ (Mr = 280.36);
Reaction conditions:	0.5 mmol phenyl(*p*-tolyl)methanol **23** (99.1 mg), 0.5 mmol pentane-2,4-dione **47** (51 μl), 7 mol% NIS (7.8 mg, 0.07 mmol), 70-75 °C, 24 h – SFRC;
Purification:	Not necessary;
Yield:	139 mg (99%), white solid;
Mp.:	79-82 °C (lit.[175] 79-82 °C);
^{1}H NMR (300 MHz, TMS):	δ (ppm) = 7.25 – 7.04 (m, 9H), 4.78 (d, *J* = 12.4 Hz, 1H), 4.72 (d, *J* = 12.4 Hz, 1H), 2.25 (s, 3H), 2.00 (s, 3H), 1.98 (s, 3H);
^{13}C NMR (76 MHz, $CDCl_3$):	δ (ppm) = 203.18, 203.16, 141.6, 138.3, 136.7, 129.7, 129.0, 127.74, 127.65, 127.0, 74.7, 51.0, 29.9, 29.7, 21.1;
HR-MS [M-H]$^-$:	Calculated for $C_{19}H_{19}O_2$: 279.1385, measured: 279.1379.

6.2 C-C bond formation through electron rich C=C bond

6.2.1 Results and discussion

Besides 1,1-diphenylethene **58**, the list of electron rich benzo-cyclenes with general structure  (X=NAc, O, S, C_2H_4) was chosen as potential partners for the *N*-halo promoted reactions with benzyl alcohols under SFRC. Based on results reported in the first chapter (Table 4.4), when reaction of diphenylmethanol **1** with 1,2-dihydronaphthalene **9** was performed in the presence of NCS as the catalyst I did not observe any conversion of the starting materials **1** and **9,** while in the presence of FTEDA, NFSi or NBS as the catalyst, I observed low to moderate conversion of the diphenylmethanol **1** into the dimeric ether as the sole product **3**. NIS as the catalyst was found to promote most effectively the direct coupling of diphenylmethanol **1** with 1,2-dihydronaphthalene **9** under SFRC, furnishing the corresponding substituted alkene **10**, accompanied with a small amount of dimeric ether **3**. Different parameters such as the loading of the NIS as the catalyst (Table 6.10) and the reaction temperature (Table 6.11) for the reaction of diphenylmethanol **1** with 1,2-dihydronaphthalene **9** under SFRC were first studied. To increase the yield of the product, different concentrations of the catalyst were employed (Table 6.10). In the reaction of diphenylmethanol **1** with 1,2-dihydronaphthalene **9**, with 4 mol% of the catalyst, I observed the formation of the corresponding product in moderate yield **10**, accompanied with the formation of dimeric ether **3** (entry 1). Similar results were achieved when the catalyst loading was increased up to 5 mol% (entry 2). By increasing the catalyst loading to 6 mol%, I observed a slightly higher formation of the corresponding product as the main product **10** (entry 3). I found that for efficient and successful transformation of the starting materials **1** and **9** into the desired product **10**, 10 mol% of the catalyst was the best choice in terms of yield of **10**, accompanied with a small amount of dimeric ether **3** (entry 4).

Table 6.10: The effect of loading of NIS on the composition of crude reaction mixture under SFRC[a].



1 **9** **10** **3**

Entry	NIS (Mol%)	Relative distribution of reagents and products in the reaction mixture[b] [%]			
		1	**9**	**10**	**3**
1	4	/	22	58	20
2	5	/	17	65	18
3	6	/	12	77	11
4	10	/	/	89	11

[a] Reaction conditions: diphenylmethanol **1** (0.5 mmol), 1,2-dihydronaphthalene **9** (0.4 mmol). [b] Determined from ^{1}H NMR spectra of isolated crude reaction mixtures.

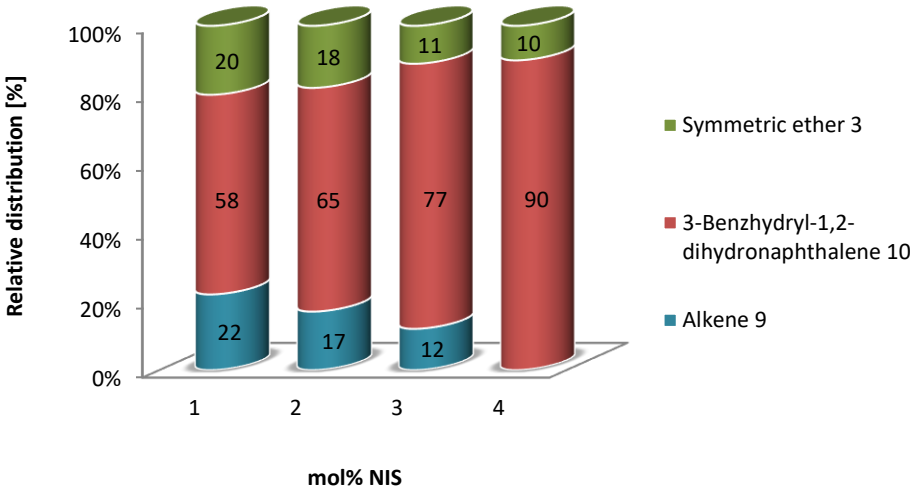
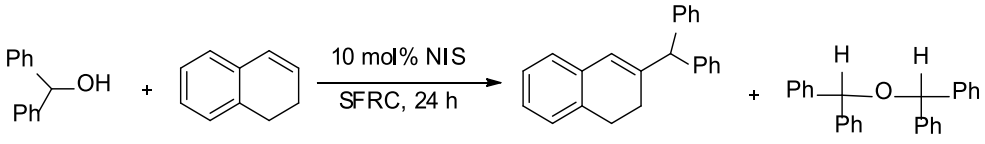


Figure 6.7: The effect of loading of NIS on the composition of crude reaction mixture under SFRC.

Variation of reaction temperature was examined by the coupling of diphenylmethanol **1** with 1,2-dihydronaphthalene **9** catalyzed by NIS under SFRC (Table 6.11). When the reaction was carried out at room temperature, no conversion of the starting materials **1** or **9** took place (entry 1). When the reaction was performed at 40-45 °C or 50-55 °C, the formation of the dimeric ether was observed as the sole product **3** (entry 2 and 3).

The increase of the reaction temperature up to 70-75 °C, provided the corresponding product **10** in good yield, accompanied with the formation of symmetric ether **3** (entry 4).

Table 6.11: The catalytic effect of NIS on the composition of crude reaction mixture based on temperature under SFRC[a].



1 **9** **10** **3**

Entry	Temp. (°C)	Relative distribution of reagents and products in the reaction mixture[b] [%]			
		1	**9**	**10**	**3**
1	r.t.	55	45	/	/
2	40-45	45	45	/	10
3	50-55	14	45	/	41
4	70-75	/	/	90	10

[a] Reaction conditions: diphenylmethanol **1** (0.5 mmol), 1,2-dihydronaphthalene **9** (0.4mmol). [b] Determined from ^{1}H NMR spectra of isolated crude reaction mixtures.

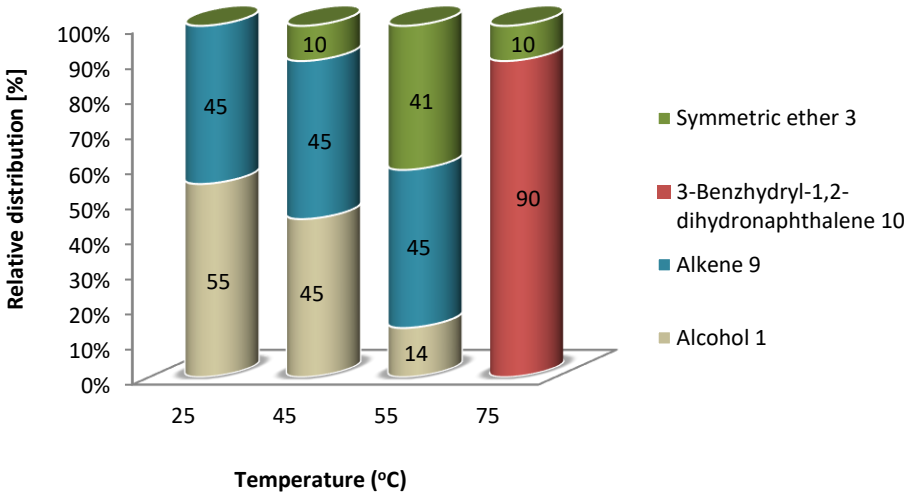
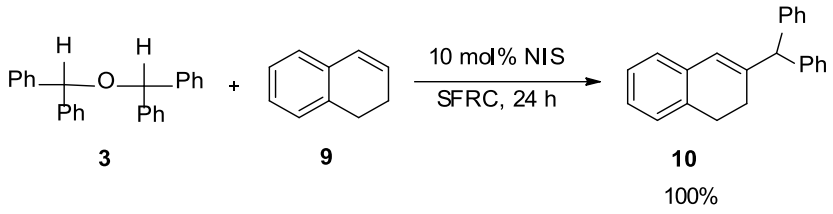


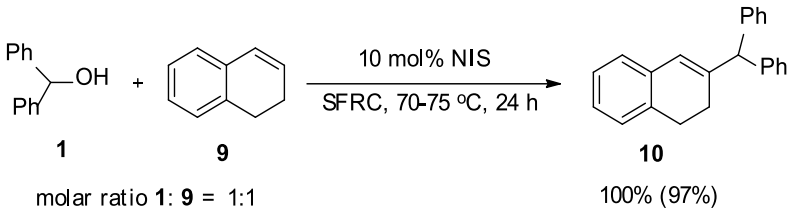
Figure 6.8: The catalytic effect of NIS on the composition of crude reaction mixture based on temperature under SFRC.

According to these results it seems the dimerization of alcohol is primarily the step of the reaction under these reaction conditions, which could in the next step proceed further following the catalyzed reaction between dimer and alkene resulting the final product. In order to verify this assumption, I independently performed the reaction between dimeric ether **3** (0.4 mmol) and 1,2-dihydronaphthalene **9** (0.8 mmol) and I got the corresponding product **10** in quantitative yield (Scheme 6.2)



Scheme 6.2: Direct coupling of diphenylmethyl ether **3** with 1,2-dihydronaphthalene **9** catalyzed by NIS under SFRC.

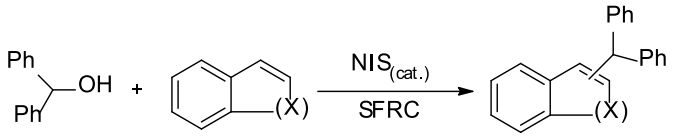
Moreover, during the optimization of reaction conditions, I found that equimolar of **1** and **9** gave the best result in terms of efficiency and selectivity (Scheme 6.3).



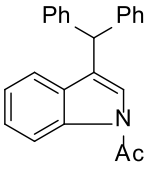
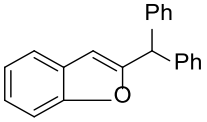
Scheme 6.3: Direct coupling of diphenylmethanol **1** with 1,2-dihydronaphthalene **9** catalyzed by NIS under SFRC.

With the optimized conditions available, I further examined the generality of this methodology with heteroatom benzo-cyclenes **56a** and **56b** with diphenylmethanol **1**, catalyzed by NIS under SFRC. The results of reactions carried out under SFRC are collected in Table 6.12. NIS catalyzed the direct coupling of diphenylmethanol **1** with *N*-based heteroarene such as 1-acetylindole **56a** under SFRC, affording **C-**3 alkylated product in high yield (**57a**, entry 1). The direct coupling of diphenylmethanol **1** with *O*-containing heteroarene such as 2,3-benzofuran **56b** underwent smooth coupling to provide the C-2 alkylated product in good yield (**57b**, entry 2). Finally, the *S*-based heteroarene such as benzo[*b*]thiophene gave a complex reaction mixture**,** providing only 32% yield of the C-2 alkylated product. It could be seen that the electrophilic substitution in 1- acetylindole **56a** takes place at C-3 and not at C-2. This orientation can be explained by comparing the stability of the carbocation resulting from the electrophilic attack at C-2, which is less favorable than the carbocation arising from the electrophilic attack at C-3. The electrophilic substitution at C-2 in benzofuran **56b** and benzo[*b*]thiophene can also be explained in the same way.

Table 6.12: Reactions of diphenylmethanol **1** with heteroarenes **56a-b** catalyzed by NIS under SFRC[a].

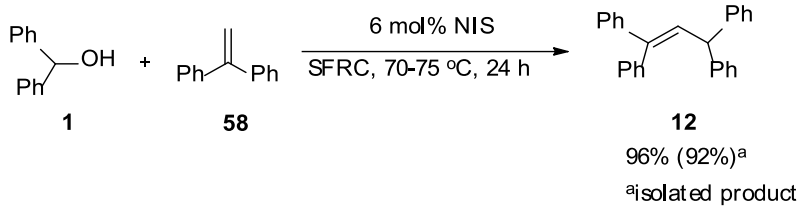


1 **56a-b** **57a-b**

Entry	X		NIS (Mol%)		Product **56a-b**	Yield[b] [%]
1	NAc	**56a**	6	**57a**		91
2	O	**56b**	10	**57b**		61

[a] Reaction conditions: diphenylmethanol **1** (0.5 mmol), Heteroarenes **56a-b** (0.4mmol), 70-75 °C, 24 h. [b] Isolated products; yields calculated relative to heteroatom benzo-cyclenes.

Furthermore, C-C bond formation could also be achieved by direct coupling of alcohols with phenyl substituted alkenes as the representative of electron rich source in the presence of NIS as the catalyst under SFRC. Thus, I chose diphenylmethanol **1** and 1,1 diphenylethene **58** as model substrates to find the best reaction conditions for this reaction. Direct coupling of diphenylmethanol **1** with 1,1-diphenylethene **58** catalyzed by NIS under SFRC, successfully and efficiently produced the corresponding phenyl substituted alkene **12** in nearly quantitative yield, accompanied with a small amount of oxidized alcohol and dimeric ether (Scheme 6.4).



1 **58** **12**

96% (92%)[a]

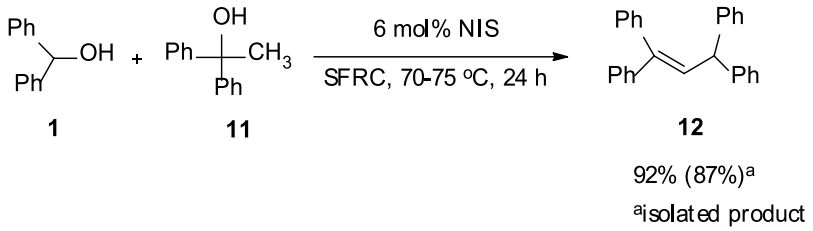
[a]isolated product

Scheme 6.4: Direct coupling of diphenylmethanol **1** with 1,1 diphenylethene **58** catalyzed by NIS under SFRC.

Based on this result I have further examined the reaction of 1,1 diphenylethene with primary benzyl alcohol bearing electron donating group on the aromatic ring. The reaction of 4-methylbenzyl alcohol **4** with 1,1- diphenylethene **58** in the presence of NIS as the catalyst under SFRC, unfortunately, gave dimeric ether **6** as the sole product. In the case of performing the reaction of diphenylmethanol **1** with styrene, the reaction was unsuccessful, only 8% of the dimeric ether was obtained.

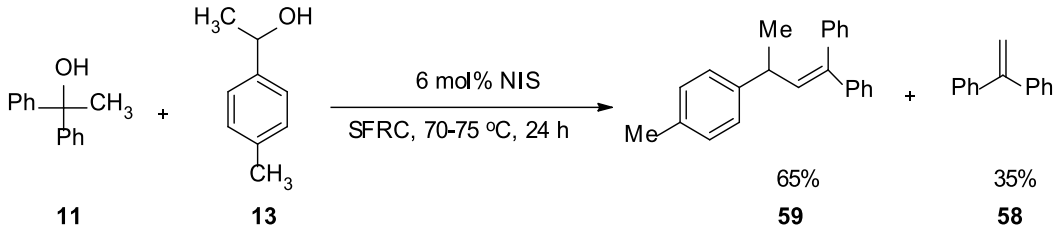
On the other hand, it is well-known that alkenes could be readily formed by dehydration of tertiary alcohols bearing a vicinal hydrogen atom. Inspired by this fact, I performed the reaction between 1,1-diphenylethanol **11** and diphenylmethanol **1** in the presence of NIS as the catalyst under SFRC, and I observed that the direct coupling of two alcohols **1** and **11** forming prop-1-

ene-1,1,3,3-tetrayltetrabenzene **12** as the major product took place, accompanied by less than 10% of side products identified as benzophenone, and dimeric ether **3** (Scheme 6.5).



Scheme 6.5: Direct coupling of diphenylmethanol **1** with 1,1-diphenylethanol **11** catalyzed by NIS under SFRC.

Direct coupling of 1,1-diphenylethanol **11** with 1-(*p*-tolyl)ethanol **13** catalyzed by NIS under SFRC afforded the formation of the (3-(p-tolyl)but-1-ene-1,1-diyl)dibenzene **59** and 1,1 diphenylethene **58** as the main products (Scheme 6.6).



Scheme 6.6: Direct coupling of 1,1-diphenylethanol **11** with 1-(*p*-tolyl)ethanol **13** catalyzed by NIS under SFRC.

6.2.2 Conclusion

In the case of 1,1-diphenyethene **58** as the electron rich moiety, benzylation of the position 2 took place, following the addition-elimination process resulting in the formation of 1,1-diphenil-2-benzyl-ethene derivatives **12**. Benzylation of the position C-2 was observed in the case of 1,2-dihydronaphthalene **9** and 2,3-benzofuran **56b**, while C-3 was benzylated in the case of 1-acetylindole **56a**.

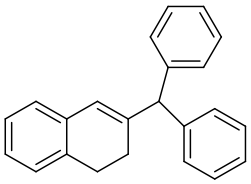
The presented methodology is new, highly efficient and easy to perform approach to the synthesis of various new types of benzyl substituted alkene derivatives starting from benzyl alcohols and applying solvent-free reaction conditions as a green chemical reaction method.

6.2.3 Experimental work

General procedure for new carbon-carbon bond formation through electron rich C=C bond in organic molecules catalyzed by NIS on half mmol scale: A mixture of alkene (0.4-0.5 mmol), benzyl alcohol (0.5 mmol) and NIS (6-10 mol%), which had been powdered in a mortar in the case of solid state reactants was transferred into a 4 mL screw-capped vial, finally eventual liquid component was added, and it was heated at 70-75 °C for 24 h. The progress of the reaction mixture was monitored by TLC. Upon completion of the reaction, the crude reaction mixture was cooled down to room temperature, diluted with ethyl acetate (15 mL), washed with $Na_2S_2O_3$ (6 mL), $NaHCO_3$ (6 mL) and water (10 mL), and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the crude reaction mixture obtained was analysed by ^{1}H NMR. The pure final products were obtained after flash chromatography, column chromatography or preparative thin layer chromatography. Detailed experimental information, such as catalyst loading, isolated yields, and spectroscopic and other identification data, are given below.

The isolated known compounds were identified by comparing the spectroscopic data with the literature.

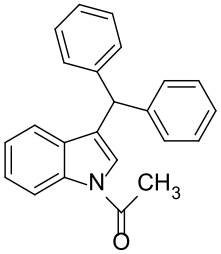
3-Benzhydryl-1,2-dihydronaphthalene (10) [30]



	$C_{23}H_{20}$ (Mr = 296.40);
Reaction conditions:	0.5 mmol diphenylmethanol **1** (92.1 mg), 0.5 mmol 1,2-dihydronaphthalene **9** (65 μl), 10 mol% NIS (11.2 mg, 0.1 mmol), 70-75 °C, 24 h – SFRC;
Purification:	FC (SiO_2, CH_2Cl_2);
Yield:	144 mg (97%), white solid;

Spectroscopic data are given on page 50-51.

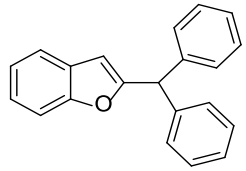
1-(3-Benzhydryl-1H-indol-1-yl)ethanone (57a) [198]



	$C_{23}H_{19}NO$ (Mr = 325.40);
Reaction conditions:	0.4 mmol 1-acetylindole **56a** (46 μl), 0.5 mmol diphenylmethanol **1** (92.1 mg), 6 mol% NIS (6.7 mg, 0.06 mmol), 70-75 °C, 24 h – SFRC;
Purification:	CC (SiO_2, CH_2Cl_2/hexane 9:1);
Yield:	118 mg (91%), light yellow crystals;
Mp.:	134-137 °C, (lit.[198] 133-136 °C)
^{1}H NMR (300 MHz, TMS):	δ (ppm) = 8.42 (d, *J* = 8.0 Hz, 1H), 7.31 – 7.25 (m, 5H), 7.24 – 7.19 (m, 6H), 7.13 – 7.07 (m, 2H), 6.74 (s, 1H), 5.57 (s, 1H), 2.42 (s, 3H);
^{13}C NMR (76 MHz, $CDCl_3$):	δ (ppm) = 168.5, 142.4, 136.4, 130.1, 128.9, 128.6, 126.8, 126.3, 125.4, 124.7, 123.5, 120.2, 116.7, 48.7, 24.0;

HR-MS [MH^+]: Calculated for $C_{23}H_{20}NO$: 326.1545; measured: 326.1543.

2-Benzhydrylbenzofuran (57b) [199]



$C_{21}H_{16}O$ (Mr = 284.35);

Reaction conditions: 0.4 mmol benzofuran **56b** (44 μl), 0.5 mmol diphenylmethanol **1** (92.1 mg), 10 mol% NIS (11.2 mg, 0.1 mmol), 70-75 °C, 24 h – SFRC;

Purification: preparative TLC (SiO_2, CH_2Cl_2/hexane 1:1),

Yield: 69 mg (61%), colourless needles;

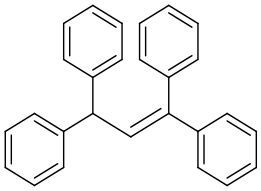
Mp.: 113-114 °C (lit.[199] 113-114 °C);

^{1}H NMR (300 MHz, TMS): δ (ppm) = δ 7.48 – 7.38 (m, 2H), 7.35 – 7.14 (m, 12H), 6.27 (s, 1H), 5.58 (s, 1H);

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 160.0, 155.2, 129.0, 128.7, 127.1, 123.9, 122.8, 120.8, 111.3, 105.8, 51.5;

HR-MS [M-H]: Calculated for $C_{21}H_{15}O$: 283.1123; measured: 283.1126.

Prop-1-ene-1,1,3,3-tetrayltetrabenzene (12) [133] *From alcohol and alkene*



$C_{27}H_{22}$ (Mr = 346.46);

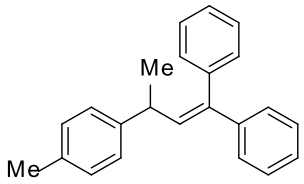
Reaction conditions: 0.5 mmol diphenylmethanol **1** (92.1 mg) 0.5 mmol 1,1-diphenylethene **58** (88.2 μl), 6 mol% NIS (6.7 mg, 0.06 mmol), 70-75 °C, 24 h – SFRC;

Purfication: CC (SiO_2, CH_2Cl_2/hexane 1:1);

Yield: 159 mg (92%), white solid;

Spectroscopic data are given on page 51.

(3-(*p*-tolyl)but-1-ene-1,1-diyl)dibenzene (59) [133]



	$C_{23}H_{22}$ (Mr = 298.42);
Reaction conditions:	0.5 mmol 1,1-diphenylethanol **11** (99.1 mg), 0.55 mmol 1-(*p*-tolyl)ethanol **13** (75,9 µl), 6 mol% NIS (6.7 mg, 0.06 mmol), 70-75 °C, 24 h – SFRC;
Purfication:	CC (SiO_2, CH_2Cl_2/hexane 9:1); purification unsuccessful, less than 15% of 1,1-diphenylethene remained;
1H NMR (300 MHz, TMS):	δ (ppm) = 7.37 – 7.10 (m, 14H), 6.20 (d, *J* = 10.4 Hz, 1H), 3.61 – 3.51 (m, *J* = 10.3, 6.9 Hz, 1H), 2.31 (s, 3H), 1.36 (d, *J* = 6.9 Hz, 3H).

Chapter 7

Various transformations of alcohols using trimethylsilyl derivatives

The halogenation of alcohols *via* a nucleophilic substitution process is an important transformation in organic chemistry that has attracted significant interest in recent years [200]. Halogenated organic compounds play significant role in chemistry and are used as starting compounds, and synthetic intermediates for various coupling reactions in organic, pharmaceutical and agrochemical syntheses[201].

The most frequently used reagent for the selective transformation of alcohols into alkyl chlorides is thionyl chloride [202]. Another classical approach is the use of gaseous or aqueous HCl but these are limited by many factors (e.g. poor selectivity, low yields, and harsh reaction conditions) making them an unsuitable approach in modern organic synthesis [203]. Other chlorination and bromination methods have also been reported including aromatic tropylium cation activation [165], 2,4,6-trichloro-1,3,5-triazine catalyzed by dimethyl sulfoxide [204], improved classical Appel halogenation reactions[182] and other similar modern approaches [205-208].

Numerous accounts of transformations of alcohols into halides using halosilanes have been reported in the literature. The methods for alcohol chlorination using chlorotrimethylsilane demand the use of various catalysts or co-reagents, such as K_2CO_3 [209], $BiCl_3$ [210], DMSO [211], SeO_2 [212], TeO_2 [213], or K_2CrO_4 [214], to convert chlorotrimethylsilane *in situ* into the corresponding terminal chlorinating agent ($SeOCl_2$, $TeOCl_2$ or CrO_2Cl_2). The authors of these previous reports claimed that in the absence of a catalyst, TMSCl does not produce any alkyl chlorides, even after prolonged heating with alcohols. Indeed, the conversion of tertiary alcohols into their corresponding chlorides using these methods was negatively affected by competing for elimination.

Furthermore, the use of $HSiMe_2Cl$ requires a substoichiometric amount of $InCl_3$ in the presence of an equimolar amount of benzil [131] or gallium trichloride/tartrate system in CH_2Cl_2 which was used for chlorination of various secondary alcohols, but in the absence of diethyl tartrate no reaction took place, while tertiary alcohols were chlorinated in the absence of diethyl tartrate [132]. The most recently developed method for alcohol chlorination with silanes utilizes TMSCl and natural sodium montmorillonite as the catalyst in CH_2Cl_2 [166]. In the absence of the catalyst, the efficiency of the transformation was reported to be very low (8%). The scope of this reaction is limited to secondary benzyl alcohols and strongly activated primary benzyl alcohols.

TMSBr was employed for alcohol bromination under organic SFRC in the presence of $BiBr_3$ as a catalyst [210]. The catalyst-free transformation of alcohols into bromides was achieved using a high molar excess of TMSBr in chloroform [215].

The aforementioned methods suffer some disadvantages, such as the need for a catalyst; the use of environmentally undesirable solvents, such as carbon tetrachloride, chloroform and methylene chloride; the requirement of a high number of equivalents of TMSCl or TMSBr; and the low atom economy and selectivity. Thus, the development of an efficient and environmentally benign methodology for C-X bond formation using halotrimethylsilane as a halogen source remains an attractive research subject. On the basis of our research group's continuing interest in developing greener methods for the efficient and selective halo functionalization of organic compounds [216-223], I report, to the best of our knowledge, the

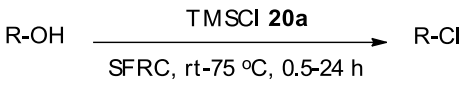
first example of the direct halogenation of alcohols using chloro- and bromotrimethylsilane under catalyst- and organic SFRC.

7.1 Halofunctionalization of organic compounds using trimethylsilyl halogenides

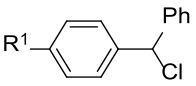
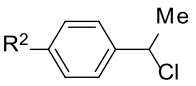
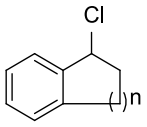
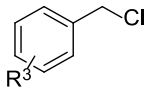
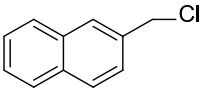
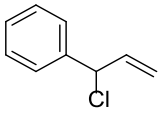
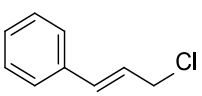
7.1.1 Results and discussion

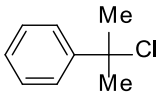
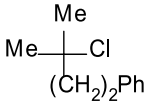
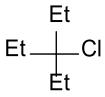
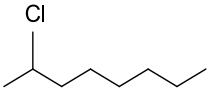
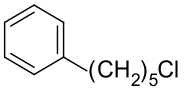
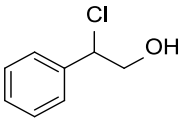
Initially, I chose phenyl(*p*-tolyl)methanol **23** as the model compound to investigate the reactions of alcohols in the presence of 10% excess TMSCl **20a** under catalyst-free and organic SFRC. After 30 min of stirring at room temperature, I observed that the reaction quantitatively resulted in the formation of 1-(chloro(phenyl)methyl)-4-methylbenzene **23a** (entry 1, Table 7.1). I further evaluated the reaction of diphenylmethanol **1**, a less reactive analogue, under the same reaction conditions and observed the quantitative formation of the corresponding chloride **27** (entry 3), however, a longer reaction time was necessary. Both reactions performed in CH_2Cl_2 gave no product (entries 2 and 4), revealing that organic SFRC is critical for a successful reaction. Encouraged by these results, I further extended the scope of the transformation to additional classes of secondary benzyl alcohols including derivatives of 1-phenylethanol carrying electron-donating or electron-withdrawing substituents on the aromatic ring **13a** and **60a-c**. These alcohols were quantitatively converted under organic SFRC, however, the reaction was not observed to be chemoselective because the high-yielding formation of the corresponding chlorides **13b, 61a-c** was accompanied by 10-17% of the dimeric ether (R-O-R) side products (entries 5, 6 and 8,9). By contrast, the analogous benzo-cycloalkan-1-ols **60d** and **60e** were quantitatively and selectively converted into corresponding chlorides **61d** and **61e** (entries 10 and 11). In the case of primary benzyl alcohols, a quantitative and chemoselective reaction was observed for 4-methoxybenzyl alcohol **49** (entry 14) and the 4-methyl-substituted derivative **4** which was quantitatively converted but exhibited only moderate selectivity **62** (entry 15). Benzyl alcohol **43** and its *p*-F and *p*-Cl analogues **60f** and **39** were consumed under the described reaction conditions by only approximately 80% and mainly formed chlorides **61f** and **39a**; these products were accompanied by the formation of symmetric ethers in 10% and 16% yield respectively (entries 12, 16 and 18). Conversely, primary benzyl alcohols bearing strongly deactivated aromatic rings **19** and **60g** were not transformed into the corresponding chlorides using chlorotrimethylsilane under catalyst-free and organic SFRC (entries 20 and 22).

Table 7.1: Chlorination of benzyl, allyl and tertiary alkyl alcohols with TMSCl[a)]



R = benzyl, allyl and alkyl up to 99% yield

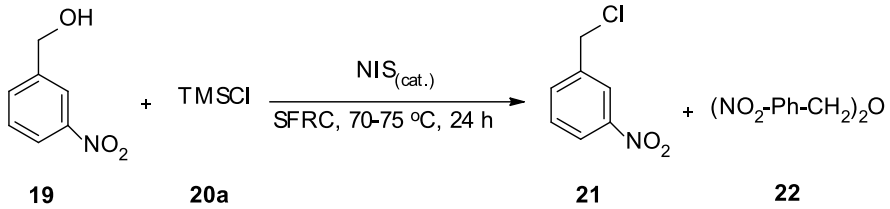
Entry	Chlorides			Conv.[b] [%]	Yield[c] [%]	Side product[d] [%]
1		R^1=Me	**23a**	100	100 (97)	/
2[e]		R^1=Me	**23a**	60	18	42
3		R^1=H	**27**	100	100 (96)	/
4[f]		R^1=H	**27**	/	/	/
5		R^2=H	**61a**	100	83 (79)	17
6		R^2=Me	**13a**	100	90	10
7[g]		**R^2=Me**	**13a**	**100**	**100 (98)**	/
8		R^2=F	**61b**	100	89 (85)	11
9		R^2=Cl	**61c**	100	86 (82)	14
10		*n=1*	**61d**	100	100 (99)	/
11		*n=2*	**61e**	100	100 (98)	/
12		R^3=H	**43d**	79	69	10
13[g]		**R^3=H**	**43d**	**100**	**92 (88)**	**8**
14		R^3=*p*-OMe	**49a**	100	100 (98)	**/**
15		R^3=*p*-Me	**62**	100	78 (74)	22
16		R^3=*p*-F	**61f**	89	68	21
17[g]		**R^3=*p*-F**	**61f**	**100**	**82 (78)**	**18**
18		R^3=*p*-Cl	**39a**	84	68	16
19[g]		**R^3=*p*-Cl**	**39a**	**100**	**91 (79)**	**9**
20		R^3=*m*-NO_2	**21**	**/**	/	/
21[g]		**R^3=*m*-NO_2**	**21**	**91**	**85 (76)**	**6**
22		R^3=*m*-CF_3	**61g**	/	/	**/**
23[g]		**R^3=*m*-CF_3**	**61g**	**91**	**79 (67)**	**12**
24			**61h**	95	69	26
25[g]			**61h**	**100**	**95 (87)**	**5**
26			**61i**	100	100 (98)	/
27			**61j**	100	100 (98)	/

28		**61k**	100	100 (98)	/
29		**63**	100	100 (99)	/
30		**61l**	100	100 (98)	/
31		**61m**	/	/	/
32		**61n**	/	/	/
33		**61o**	95	95 (90)	/

[a] Reaction conditions: alcohol (0.5 mmol), TMSCl **20a** (0.55 mmol), rt-(70-75 °C), 0.5-24 h.
[b] Determined from ^{1}H NMR spectra of isolated crude reaction mixture. [c] Yield calculated relative to alcohol; the values in parentheses refer to purified products. [d] Side product: R-O-R. [e] DCM (2 ml). [f] TMSCl (1 mmol), DCM (2.5 ml), 40 min. [g] In the presence of NIS (2-10 mol%).

Electron-donating substituents on the phenyl ring thus considerably enhanced the reaction efficiency, whereas nitro and trifluoromethyl groups, which are strongly electron withdrawing, suppressed the transformation. Thus, I studied the impact of *N*-halo organic compound as a catalyst on the course of reaction of 3-nitrobenzyl alcohol **19** with TMSCl under SFRC, and results are collected in Table 7.2. Gratifyingly, the addition of a substoichiometric amount of NIS was found to promote effectively and selectively the reaction of 3-nitrobenzyl alcohol **19** with TMSCl under SFRC. To increase the yield of 1-(chloromethyl)-3-nitrobenzene **21**, different concentrations of the catalyst were employed. It could be seen that using 3 mol% of the catalyst, provided the formation of the desired product in low yield **21**, accompanied with a small amount of dimeric ether **22** (entry 2). This reaction was more efficient when the catalyst loading was increased up to 5 mol% (entry 3). Similar results were achieved when the catalyst loading was increased up to 8 mol% (entry 4). Further optimization revealed that the reaction could be more efficient by increasing the catalyst loading up to 10 mol% (entry 5). I also checked the role of NFSi on this reaction course and I noticed that 5 mol% of NFSi provided a lower yield of **21** than 5 mol % of NIS.

Table 7.2: The effect of loading of NIS on the composition of crude reaction mixture under SFRC[a].



19 **20a** **21** **22**

Entry	NIS (Mol %)	Conv.[b] [%] of **19**	Relative distribution[c] [%]	
			21	**22**
1	/	/	/	/
2	3	43	39	4
3	5	74	70	4
4	8	88	82	6
5	10	91	85	6

[a] Reaction conditions: 3-nitrobenzyl alcohol **19** (0.5mmol), TMSCl **20a** (0.55 mmol). [b] Determined from ^{1}H NMR spectra of isolated crude reaction mixtures. [c] Yield calculated relative to alcohol.

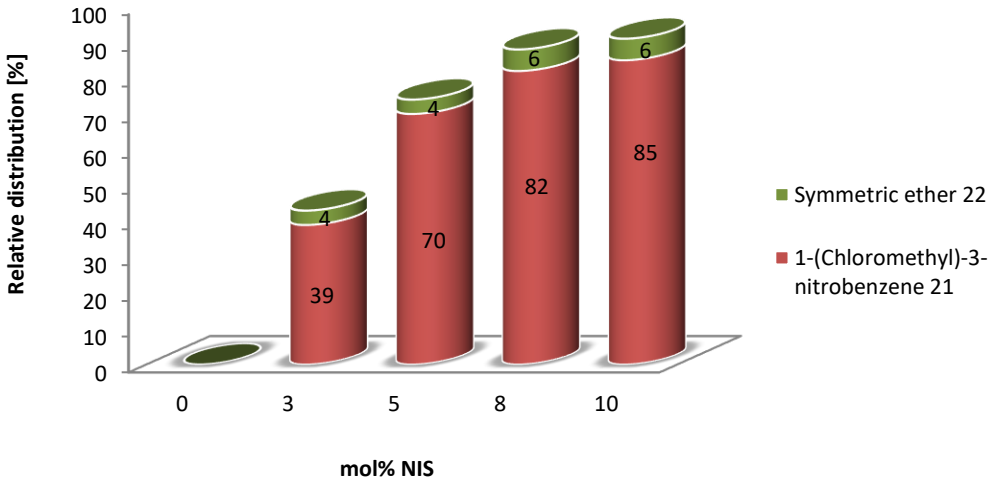
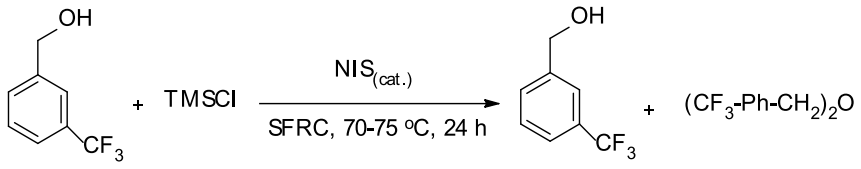


Figure 7.1 The effect of loading of NIS on the composition of crude reaction mixture under SFRC.

I further studied the impact of NIS as the catalyst on the course of reaction of 3-trifluoromethylbenzyl alcohol **60g** with TMSCl under SFRC. By adding 10 mol% of the catalyst I successfully accomplished the formation of chlorinated product **61g** in good yield, accompanied with the formation of a small amount of the symmetric ether **62**, which is known compound based on ^{1}H NMR spectra of isolated crude reaction mixture (Table 7.3, entry 4).

Table 7.3: The effect of loading of NIS on the composition of crude reaction mixture under SFRC[a].



60g **20a** **61g** **62**

Entry	NIS (Mol %)	Conv.[b] [%] of **60g**	Relative distribution[c] [%]	
			61g	**62**
1	/	/	/	/
2	3	38	32	6
3	8	81	69	12
4	10	91	79	12

[a] Reaction conditions: 3-trifluoromethylbenzyl alcohol **60g** (0.5mmol), TMSCl **20a** (0.55 mmol). [b] Determined from ^{1}H NMR spectra of isolated crude reaction mixtures. [c] Yield calculated relative to alcohol.

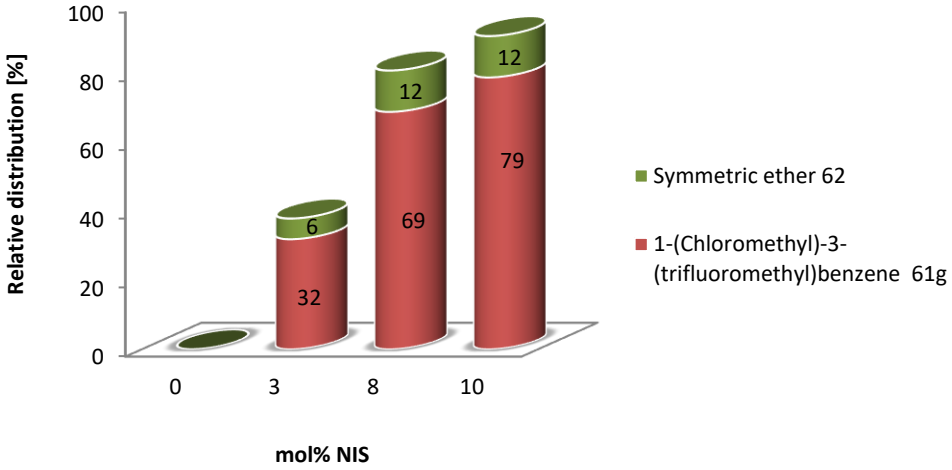


Figure 7.2: The effect of loading of NIS on the composition of crude reaction mixture under SFRC.

The role of NIS as the catalyst was further examined in the improvement of yields of the desired products **13a**, **43d**, **61f**, **39a**, and **61h (**entries **7, 13, 17, 19** and **25**). In the case of 1-(*p*-tolyl)ethanol **13**, the improvement of 98% yield without formation of the dimeric ether was attained by adding the NIS as the catalyst (entry 7). In the case of naphthalen-2-ylmethanol **60h** by adding NIS as the catalyst, quantitative conversion of the starting material into the corresponding chloride **61h** was observed, while only a small amount of dimer was noticed as the side product (entry 25). In the case of performing the reaction of benzyl alcohol **43** by adding NIS as the catalyst, quantitative conversion of the starting material into the corresponding chloride **43d** was observed, while only a small amount of dimer was detected as the side product (entry 13). In the case of 4-fluoro and 4-chlorobenzyl alcohols **60f** and **39**, where the conversion of the starting materials was high, it could be seen that the addition of NIS as the catalyst improved the conversion of the starting materials into the corresponding chlorides **61f** and **39a** (entries 17 and 19). I observed that by adding NIS as the catalyst, selectivity was improved, in some cases selectivity and efficiency. Furthermore, the chlorination method was also applied to

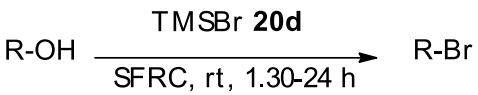
α-vinylbenzyl alcohol **60i** and cinnamyl alcohol **60j** transforming them into the corresponding chlorides **61i** and **61j** in quantitative yields (entries 26 and 27).

Similar to secondary and primary benzyl alcohols, effective transformations were observed in the reactions with tertiary benzyl and alkyl alcohols under the same conditions. 2-Phenylpropan-2-ol **29** was quantitatively and selectively converted into the (2-chloropropan-2-yl)benzene **61k** (entry 29), α,α-dimethylbenzenepropanol **32** and 3-ethylpentan-3-ol **60l** were converted into their corresponding chlorides **63** and **61l**, respectively; (entries 29 and 30). By contrast, the secondary and primary alkyl alcohols **60m** and **60n** were not transformed into their corresponding chlorides under the examined reaction conditions (entries 31 and 32).

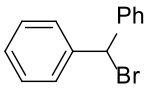
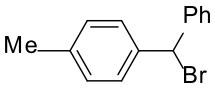
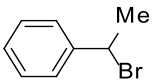
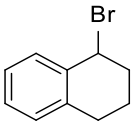
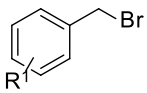
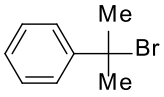
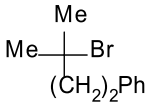
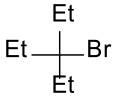
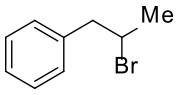
In the case of performing the reaction of 1,1-diphenylethanol **11** with TMSCl **20a** catalyzed by NIS, 1,1-diphenylethene **58** was the sole product. Since I found that primary and secondary alkyl alcohols were resistant towards transformations mediated with TMSCl, the S_N1 reaction course was found to be the most probable mechanistic characteristic of these valuable transformations.

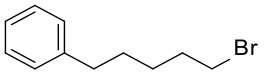
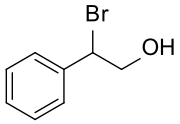
To expand the utility of the halosilane-mediated transformation of alcohols, I studied reactions of TMSBr with benzyl and tertiary alkyl alcohols under catalyst-free and organic SFRC; the results are reported in Table 7.4. In all cases, quantitative and chemoselective transformations were observed. TMSBr efficiently and selectively converted the secondary benzyl alcohols **1, 23, 60a** and **60e** into the corresponding bromides **28, 23b, 62a and 62e (**entries 1-4). The efficient and chemoselective transformation was observed, unlike the chlorotrimethylsilane-mediated transformations, in the cases of primary benzyl alcohols bearing electron-withdrawing or electron–donating substituents **43e, 64, 62f** and **65 (**entries 5-6 and 9-10). The corresponding reactions performed in CH_2Cl_2 gave good results (entry 7), whereas those performed in the greener solvent, 2-methyltetrahydrofuran (2-MeTHF), were unsuccessful (entry 8). Therefore, in the case of bromotrimethylsilane, the organic SFRC protocol was observed to be the best choice. Moreover, tertiary benzyl and alkyl alcohols **29, 32** and **60l** were efficiently and selectively converted under organic SFRC to the corresponding bromides **62k, 66** and **62l** (entries 11-13). By contrast, secondary and primary alkyl alcohols **67** and **60n** could not be transformed into the corresponding bromides under the examined reaction conditions (entries 14 and 15).

Table 7.4: Bromination of benzyl and tertiary alkyl alcohols with TMSBr[a].



R = benzyl and alkyl up to 99% yield

Entry	Bromides			Yield (%)[b]
1			**28**	100 (98)
2			**23b**	100 (98)
3			**62a**	100 (98)
4			**62e**	100 (98)
5		R^1=H	**43e**	100 (99)
6		R^1=*p*-Me	**64**	100 (98)
7[c]		R^1=*p*-Me	**64**	92
8[d]		R^1=*p*-Me	**64**	13
9		R^1=*p*-F	**62f**	100 (98)
10		R^1=*m*-NO_2	**65**	100 (99)
11			**62k**	100 (99)
12			**66**	100 (99)
13			**62l**	100 (98)
14			**68**	/

15		**62n**	/
16		**62o**	100 (99)

[a] Reaction conditions: alcohol (0.5 mmol), TMSBr **20d** (0.55 mmol), rt, 1.5-24 h. [b] Determined from ^{1}H NMR spectra of isolated crude reaction mixture. Yield calculated relative to alcohol; the values in parentheses refer to purified products. [c] DCM (2 ml). [d] 2-MeTHF (2 ml).

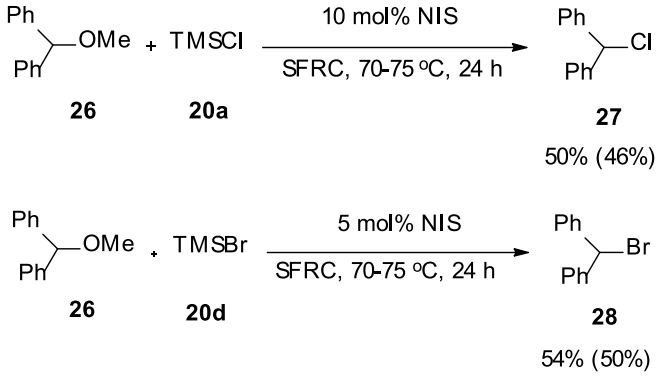
To improve the synthetic value of the reported methodology, the following reactions were performed on the 10-mmol scale: chlorination of 3-ethylpentan-3-ol **60l** and bromination of 4-methylbenzyl alcohol **4**. In both cases, the quantitative conversion of the starting materials into halides **61l** and **64** was achieved. NMR of the reaction mixtures revealed that they contained only halides and 1,1,1,3,3,3-hexamethyldisiloxane [$(TMS)_2$-O] in a 2:1 molar ratio. I could thus define the stoichiometry of the process as follows:

$$\underset{\mathbf{1}}{2R\text{-}OH} + 2TMS\text{-}X \longrightarrow \underset{\mathbf{2}\text{ or }\mathbf{3}}{2R\text{-}X} + \underset{\mathbf{4}}{(TMS)_2\text{-}O} + H_2O$$

The products were easily separated by distillation, where 1,1,1,3,3,3-hexamethyldisiloxane was collected as the first fraction and R-X as the second. 1,1,1,3,3,3-hexamethyldisiloxane could be further used as the reagent or regenerated to give trimethylhalosilane (TMSX) [224,225].

The results support the assumption that the reaction course is related to the stability of the carbocation intermediates formed after the dehydroxylation of alcohols; which is characteristic of S_N1-type nucleophilic substitution processes. To verify this assumption, I also examined 1-phenyl-1,2-ethanediol and observed the quantitative and chemoselective formation of 2-chloro-**61o** (entry 32, Table 7.1) or 2-bromo-2-phenylmethanol **62o** (entry 16, Table 7.4) after treatment with chlorotrimethylsilane or bromotrimethylsilane under organic SFRC, confirming that this substitution likely proceeds via a S_N1 reaction pathway. Because I also observed that primary and secondary alkyl alcohols were resistant to transformations under the aforementioned reaction conditions, the S_N1 reaction course was confirmed as the most likely reaction pathway. The formation of carbocation intermediates can be explained by at least two mechanisms. The first explanation assumes the initial hydrolysis of trimethylhalosilane with a small amount of water in the reaction system to produce HCl. In this process, an alcohol undergoes protonation by HX and then dehydration to form a carbocation that further reacts with the released chloride ion to produce the chlorinated product. The released water also reacts with the remaining trimethylhalosilane to form HX, and two molecules of the generated trimethylsilanol are easily condensed into the more stable molecules $(TMS)_2O$ and water [166]. The second explanation is related to catalysis caused by the 'halogen bonding' phenomenon, which is defined as 'non-covalent interaction of halogen atom X in one molecule with a negative site in another'. This phenomenon has been theoretically evaluated [226,227], and several organo-halogen compounds have been used as organo-Lewis acid catalysts in organic syntheses [167,170]. Therefore, in our case, trimethylhalosilane could play a dual role, acting as both a 'halogen bonding' catalyst, thereby accelerating the formation of carbocation intermediates, and as the halogen source.

In order to check if these transformations are limited only for alcohols, I performed the corresponding reactions with (methoxymethylene)dibenzene **26** under similar reaction conditions, the conversion of the starting material **1** into the corresponding chloride **27** or bromide **28** was found not to be as efficient as in the case of alcohols, accompanied with a small amount of dimer and benzophenone (Scheme 7.1). (Detailed experimental information and their spectroscopic and other identification data are given in the first chapter).



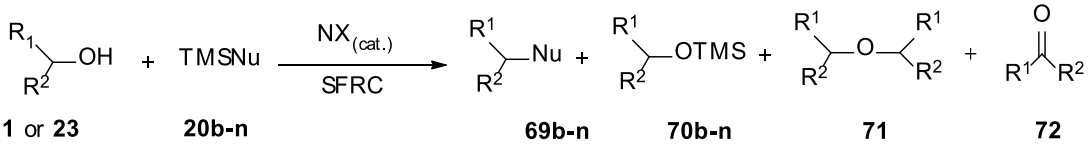
Scheme 7.1: Chlorination or bromination of (methoxymethylene)dibenzene **26** with TMSCl or TMSBr catalyzed by NIS under SFRC.

7.2 Various transformations of alcohols using trimethylsilyl derivatives

7.2.1 Results and discussion

Based on transformations of alcohols with TMSCl **20a** and TMSBr **20d**, I was curious to find out if it is possible to introduce in a similar way various other functional groups from the silane sources into organic molecules and results are collected in Table 33. I performed the reactions of phenyl(*p*-tolyl)methanol **23** as the model compound in the presence of *N*-halo organic compound as a catalyst, using (trimethylsilyl)isothiocyanate (TMSNCS) **20b**, ethoxytrimethylsilane (TMSOEt) **20c**, isopropioxytrimethylsilane (TMSO*i*Pr) **20e**, cyanotrimethylsilane (TMSCN) **20h**, *N*,*N*-dimethyltrimethylailylamine ($TMSN(CH_3)_2$) **20i**, trimethyl(trifluromethyl)silane ($TMSCF_3$) **20k**, ethynyltrimethylsilane ($HC{\equiv}CCH_2TMS$) **20k**, triphenylsilane (Ph_3SiH), **20l** triethylsilane ($(Et)_3SiH$ **20m**, and tris(trimethylsilyl)phosphate $[(CH_3)_3SiO]_3P(O)$ **20n** as the source of nucleophiles under SFRC. In the case of TMSNCS **20b** and TMSOEt **20c**, using NIS as the catalyst under SFRC, isothiocyanates and ethoxy were introduced into organic molecules in high to quantitative yield **69b-c** (entries 1-3). Using TMSO*i*Pr in the presence of NFSi as the catalyst, the introducing of an isopropioxy group into the target molecule **69e** was more successful than in the presence of NIS as the catalyst (entries 4 and 5), accompanied by the formation of dimeric ether **71** and a small amount of the oxidized alcohol **72** (entry 5). In the case of performing the reaction of diphenylmethanol **1** with trimethylsilylacetate (TMSOAc) **20f** and azidotrimethylsilane ($TMSN_3$) **20g**, catalyzed by NIS under SFRC, acetate and azido were introduced into the organic molecules in low yield **69f-g** (entries 6 and 7). The courses of reactions were found to be quite different in the case of TMSCN **20h** and $TMSN(CH_3)_2$ **20i** and the formation of trimethylsilylethers **70h-i** as sole products was observed (entries 8-10). Employing $TMSCF_3$ **20j**, $HC{\equiv}CCH_2TMS$ **20k**, Ph_3SiH **20l**, Et_3SiH **20m** and $[(CH_3)_3SiO]_3P(O)$ **20n** gave dimeric ether **71** as the main product (entries 11-16).

Table 7.5: Transformations of alcohols using trimethylsilyl derivatives under SFRC[a].



1 or **23** **20b-n** **69b-n** **70b-n** **71** **72**

1: $R^1 = R^2 = Ph$

23: $R^1 = MePh$, $R^2 = Ph$

Entry	Alcohol	TMS-Nu		NX (Mol %)	Relative distribution of alcohol and products in the reaction mixture[b] [%]				
					1 or **23**	**69b-n**	**70b-n**	**71**	**72**
1	**23**	-NCS	**20b**	NIS (3)	/	100 (97)	/	/	/
2	**23**	-OEt	**20c**	NIS (3)	/	85	/	/	15
3	**23**	-OEt	**20c**	NFSi (3)	/	82	/	13	5
4	**23**	-O*i*Pr	**20e**	NIS (3)	25	40	11	19	5
5	**23**	-O*i*Pr	**20e**	NFSi (3)	/	70	/	27	3
6	**1**	$-OOCCH_3$	**20f**	NIS (6)	/	46	/	47	7
7	**1**	$-N_3$	**20g**	NIS (3)	23	25	52	/	/
8	**23**	-CN	**20h**	NIS (4)	/	/	100 (98)	/	/
9[c]	**23**	-CN	**20h**	/	/	/	100	/	/
10	**1**	$-N(CH_3)_2$	**20i**	NIS (6)	/	/	100 (98)	/	/
11[d]	**23**	$-CF_3$	**20j**	NIS (3)	9	/	/	85	6
12	**1**	$HC{\equiv}CCH_2-$	**20k**	NIS (3)	24	/	/	62	14
13	**1**	Ph_3SiH	**20l**	NFSi (3)	6	/	/	83	11
14	**1**	Ph_3SiH	**20l**	NIS (3)	37	/	/	63	/
15	**1**	$(C_2H_5)_3SiH$	**20m**	NIS (3)	30	/	/	65	5
16	**23**	$[(CH_3)_3SiO]_3P(O)$	**20n**	NIS (3)	/	/	/	85	15

[a] Reaction conditions: alcohol **1** or **23** (0.5mmol), TMSNu **20b-n** (0.55 mmol), NIS (3-6 mol%) or NFSi (3 mol%), 70-75 °C, 24-25 h. [b] Determined from ^1H NMR spectra of isolated crude reaction mixtures. The values in parentheses refer to purified products. [c] 3 h, [d] 120 h.

7.3 Conclusion

In conclusion, I have demonstrated a chemoselective and scalable method for the direct conversion of a comprehensive type of alcohols into their corresponding chlorides or bromides *via* direct nucleophilic substitution of a hydroxyl group using trimethylhalosilanes as sources of halogen moiety under catalyst-free and solvent-free reaction conditions. *N*-iodosuccinimide was found as the convenient catalyst for improving the selectivity and efficiency of halofunctionalisation of some less reactive benzyl alcohols. So, the addition of substoichiometric amounts of *N*-iodosuccinimide in the case of reactions of 3-nitro **19** and 3-fluorobenzyl alcohols **60g** under solvent-free time being, this methodology was successful for primary, secondary and tertiary benzyl alcohols, allyl and tertiary alkyl alcohols. Furthermore, I have demonstrated that under similar reaction conditions, the conversion of methyl ether of corresponding benzyl alcohol **26** into the corresponding chloride **27** or bromide **28** was found not to be as efficient as in the case of alcohols. Under these reaction conditions, I investigated the method's limitations by studying benzyl alcohols with strongly deactivated aromatic rings and primary and secondary alkyl alcohols.

N-iodosuccinimide was also found to be a convenient catalyst for direct conversion of secondary benzyl alcohols into the corresponding benzyl-substituted isothiocyanate or ethers in quantitative yield, while in low yield to corresponding azido or acetyl products, by nucleophilic substitution of hydroxyl group using trimethyl substituted silanes, bearing the mentioned functional groups as sources of nucleophiles, while under similar reaction conditions using cyanotrimethylsilane **20h** and *N,N*-dimethyltrimethylsilylamine, trimethylsilylation of the hydroxyl group in target molecules was found as the sole reaction process. The courses of reactions were found to be quite different in the case of trimethyl(trifluromethyl)silane **20j**, ethynyltrimethylsilane **20k**, triphenylsilane **20l**, triethylsilane **20m** and tris(trimethylsilyl)phosphate **20n**, where dimeric ether was observed as the main product, accompanied with a small amount of oxidised alcohol.

Finally, I claimed, that the methodology presented in this chapter represents a new approach to the transformation of alcohols in a comprehensive kind of new derivatives, using silanes as desirable new functional group carriers. Additionally, the development of catalyst-free and organic solvent-free reaction conditions protocols will increase the green chemical profile of this type of organic transformation.

7.4 Experimental work

General procedure for the halo functionalization of organic compounds using NIS or NFSi on half mmol scale: A mixture of alcohol (0.5 mmol) and NIS or NFSi (3-10 mol%) which had been powdered in a mortar in the case of solid state reactants, was transferred to a 4 mL screw-capped vial, then added halosilane (0.55 mmol) and stirred at rt or heated at 70-75 °C for 0.5 h-24 h. The progress of the reaction mixture was monitored by TLC. Upon completion of the reaction, the crude reaction mixture was cooled down to room temperature, diluted with ethyl acetate (15 mL), washed with $Na_2S_2O_3$ (6 mL), $NaHCO_3$ (6 mL), and water (10 mL), and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the crude reaction mixture obtained was analysed by ^1H NMR. Finally, if necessary, the pure final products were obtained after flash chromatography or column chromatography on dried silica. Detailed experimental information such as catalyst loading, isolated yields, and spectroscopic and other identification data, are given below.

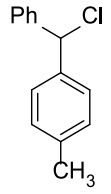
The isolated known compounds were identified by comparing the spectroscopic data with the literature.

The scale-up procedure for the synthesis of 3-chloro-3-ethylpentane 61l and 1-(bromomethyl)-4-methylbenzene 64 using NIS: A mixture of 3-ethyl-3-pentanol 60l (10 mmol, 1.15 g, 1.37 mL) and TMSCl 20a (11 mmol, 1.18 g, 1.39 mL) was transferred to a 4 mL screw-capped vial and stirred at rt for 24 h. Upon completion of the reaction, 1,1,1,3,3,3-hexamethyldisiloxane was distilled at 100 °C under reduced pressure from the crude reaction mixture and collected for further potential regeneration [224]; the remaining 3-chloro-3-ethylpentane 61l was defined as a pure product (colourless oil, 1.3 g; 95% yield).

A mixture of 4-methylbenzyl alcohol **4** (10 mmol, 1.22 g), which had been powdered in a mortar and TMSBr **20d** (11 mmol, 1.68 g, 1.45 mL) was transferred to a 20 mL round-bottom flask and stirred at rt for 1.30 h. Upon completion of the reaction, 1,1,1,3,3,3-hexamethyldisiloxane was distilled at 100 °C under reduced pressure from the crude reaction mixture and collected for further regeneration [225]; the remaining 1-(bromomethyl)-4-methylbenzene **64** was defined as a pure product (white solid, 1.8 g; 99% yield).

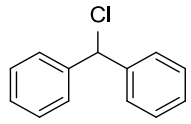
The isolated known compounds were identified by comparing the spectroscopic data with the literature.

1-(Chloro(phenyl)methyl)-4-methylbenzene (23a) [183]



	$C_{14}H_{13}Cl$ (Mr = 216.71);
Reaction conditions:	0.5 mmol phenyl(*p*-tolyl)methanol **23** (99.1 mg), 0.55 mmol TMSCl **20a** (69.8 μl), rt, stirring 400, 0.5 h – SFRC;
Purification:	Not necessary;
Yield:	105 mg (97%), colourless oil;
^{1}H NMR (300 MHz, $CDCl_3$):	δ (ppm) = 7.43 – 7.26 (m, 7H), 7.14 (d, *J* = 7.9 Hz, 2H), 6.10 (s, 1H), 2.33 (s, 3H);
^{13}C NMR (76 MHz, $CDCl_3$):	δ (ppm) = 141.3, 138.4, 138.0, 129.4, 128.6, 128.1, 127.9, 127.8, 64.4, 21.2.

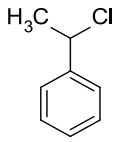
Diphenylmethyl chloride (27) [182] *from alcohol and TMSCl*



	$C_{13}H_{11}Cl$ (Mr = 202.68);
Reaction conditions:	0.5 mmol diphenylmethanol **1** (92.1 mg) 0.55 mmol TMSCl (69.8 μl), rt, stirring 400, 4 h – SFRC;
Purification:	Not necessary;
Yield:	97.3 mg (96%), colourless oil;

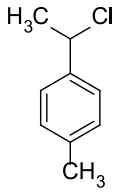
Spectroscopic data are given on page 54.

(1-Chloroethyl)benzene (61a) [228]



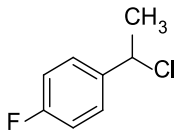
	C_8H_9Cl (Mr = 140.61);
Reaction conditions:	0.5 mmol 1-phenylethanol **60a** (60 μl) 0.55 mmol TMSCl (69.8 μl), rt, stirring 400, 4 h – SFRC;
Purification:	CC (SiO_2, CH_2Cl_2/hexane 1:1);
Yield:	54 mg (78%), colourless liquid;
^{1}H NMR (300 MHz, $CDCl_3$):	δ (ppm) = 7.45 – 7.21 (m, 5H), 5.08 (q, *J* = 6.8 Hz, 1H), 1.84 (d, *J* = 6.8 Hz, 3H).
^{13}C NMR (76 MHz, $CDCl_3$):	δ (ppm) = 142.9, 128.8, 128.4, 126.6, 58.9, 26.7.

1-(1-Chloroethyl)-4-methylbenzene (13a) [229]



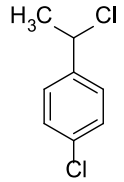
	$C_9H_{11}Cl$ (Mr = 154.64);
Reaction conditions:	0.5 mmol 1-(*p*-tolyl)ethanol **13** (68.9 μl), 0.55 mmol TMSCl (69.8 μl), 2 mol% NIS (2.2 mg, 0.02 mmol), rt, stirring 400, 6.5 h – SFRC;
Purification:	Not necessary;
Yield:	75 mg (98%), colourless oil;
^{1}H NMR (300 MHz, TMS):	δ (ppm) = 7.29 (d, *J* = 8.1 Hz, 2H), 7.14 (d, *J* = 7.9 Hz, 2H), 5.06 (q, *J* = 6.8 Hz, 1H), 2.33 (s, 3H), 1.82 (d, *J* = 6.8 Hz, 3H).
^{13}C NMR (76 MHz, $CDCl_3$):	δ (ppm) = 140.0, 138.2, 129.4, 126.5, 58.9, 26.6, 21.2.

1-(1-Chloroethyl)-4-fluorobenzene (61b) [230]



	C_8H_8ClF (Mr = 158.60);
Reaction conditions:	0.5 mmol 1-(4-fluorophenyl)ethanol **60b** (63 μl), 0.55 mmol TMSCl (69.8 μl), rt, stirring 400, 3.5 h – SFRC;
Purification:	CC (SiO_2, CH_2Cl_2/hexane 1:1);
Yield:	67 mg (85%), colourless oil;
^{1}H NMR (300 MHz, $CDCl_3$):	δ (ppm) = 7.42 – 7.34 (dd, 2H), 7.06 – 6.98 (dd, 2H), (J_1=J_2=8Hz, 2H) 5.07 (q, *J* = 6.8 Hz, 1H), 1.82 (d, *J* = 6.8 Hz, 3H);
^{13}C NMR (76 MHz, $CDCl_3$):	δ (ppm) = 162.5 (d, *J* = 247.0 Hz), 138.8 (d, *J* = 4Hz), 128.4 (d, *J* = 8.2 Hz), 115.6 (d, *J* = 21.7 Hz), 58.1, 26.7;
^{19}F NMR (285 MHz, $CDCl_3$):	δ (ppm) = -114.21 (tt, *J* = 8.6, 5.3 Hz).

1-Chloro-4-(1-chloroethyl)benzene (61c) [231]



$C_8H_8Cl_2$ (Mr = 175.06);

Reaction conditions: 0.5 mmol 1-(4-chlorophenyl)ethanol **60c** (66.8 μl), 0.55 mmol TMSCl (69.8 μl), rt, stirring 400, 17 h – SFRC;

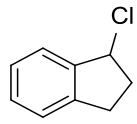
Purification: CC (SiO_2, CH_2Cl_2/hexane 1:1);

Yield: 71 mg (82%), colourless liquid;

^{1}H NMR (300 MHz, TMS): δ (ppm) = 7.38 – 7.28 (m, 4H), 5.05 (q, *J* = 6.8 Hz, 1H), 1.82 (d, *J* = 6.8 Hz, 3H);

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 141.5, 134.1, 128.9, 128.0, 57.9, 26.6.

1-Chloro-2,3-dihydro-1H-indene (61d) [162]



C_9H_9Cl (Mr = 152.62);

Reaction conditions: 0.5 mmol 1-indanol **60d** (67 mg), 0.55 mmol TMSCl (69.8 μl), rt, stirring 400, 24 h – SFRC;

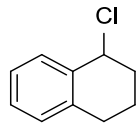
Purification: Not necessary;

Yield: 75 mg (99%), colourless oil;

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.45 – 7.39 (m, 1H), 7.27 – 7.19 (m, 3H), 5.45 – 5.38 (m, 1H), 3.23 – 3.12 (m, 1H), 2.92 – 2.82 (m, 1H), 2.64 – 2.51 (m, 1H), 2.41 – 2.31 (m, 1H);

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 143.4, 143.2, 129.0, 127.1, 125.1, 124.9, 63.3, 37.0, 30.4.

1-Chloro-1,2,3,4-tetrahydronaphthalene (61e) [162]



$C_{10}H_{11}Cl$ (Mr = 166.65);

Reaction conditions: 0.5 mmol 1,2,3,4-tetrahydronaphthalen-2-ol **60e** (74.1 mg), 0.55 mmol TMSCl (69.8 μl), rt, stirring 400, 23 h – SFRC;

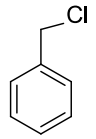
Purification: Not necessary;

Yield: 81 mg, (98%), colourless oil;

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.38 – 7.32 (m, 1H), 7.22 – 7.12 (m, 2H), 7.11 – 7.04 (m, 1H), 5.31 – 5.29 (m, 1H), 2.93 – 2.68 (m, 2H), 2.33 – 2.11 (m, 3H), 1.89 – 1.78 (m, 1H);

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 136.8, 136.4, 130.5, 129.4, 128.3, 126.3, 58.7, 33.1, 28.9, 18.4.

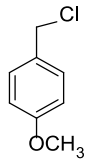
(Chloromethyl)benzene (43d) [162]



C_7H_7Cl (Mr = 126.58);

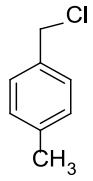
Reaction conditions: 0.5 mmol benzyl alcohol **43** (51.7 µl), 0.55 mmol TMSCl (69.8 µl), 3 mol% NIS (3.4 mg, 0.03 mmol), 70-75 °C, 24 h – SFRC;
Purification: CC (SiO_2, CH_2Cl_2/hexane 1:1);
Yield: 56 mg (88%), colourless oil;
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.39 – 7.29 (m, 5H), 4.56 (s, 2H);
^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 137.6, 128.8, 128.7, 128.5, 46.4.

1-(Chloromethyl)-4-methoxybenzene (49a) [163]



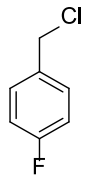
C_8H_9ClO (Mr = 156.61);
Reaction conditions: 0.5 mmol 4-methoxybenzyl alcohol **49** (62 µl), 0.55 mmol TMSCl (69.8 µl), rt, stirring 400, 4 h – SFRC;
Purification: Not necessary;
Yield: 77 mg (98%), colourless oil;
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.29 (d, *J* = 8.7 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 4.55 (s, 2H), 3.78 (s, 3H);
^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 159.8, 130.2, 129.8, 114.2, 55.4, 46.4.

1-(Chloromethyl)-4-methylbenzene (62) [232]



C_8H_9Cl (Mr = 140.61);
Reaction conditions: 0.5 mmol 4-methylbenzyl alcohol **4** (61 mg), 0.55 mmol TMSCl (69.8 µl), 70-75 °C, 2 h – SFRC;
Purification: CC (SiO_2, CH_2Cl_2/hexane 1:1);
Yield: 52 mg (74%), colourless oil;
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.27 (d, *J* = 8.1 Hz, 2H), 7.16 (d, *J* = 8.0 Hz, 2H), 4.55 (s, 2H), 2.34 (s, 3H);
^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 138.4, 134.7, 129.6, 128.7, 46.4, 21.3.

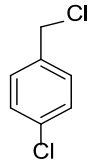
1-(Chloromethyl)-4-fluorobenzene (61f) [233]



C_7H_6ClF (Mr = 144.57);
Reaction conditions: 0.5 mmol 4-fluorobenzyl alcohol **60f** (54.5 µl), 0.55 mmol TMSCl (69.8 µl), 2 mol% NIS (2.2 mg, 0.02 mmol), 70-75 °C, 20 h – SFRC;
Purification: CC (SiO_2, CH_2Cl_2/hexane 1:1);
Yield: 56 mg (78%), colourless oil;
^{1}H NMR (300 MHz, TMS): δ (ppm) = 7.38 – 7.33 (m, 2H), 7.07 – 7.01 (m, 2H), 4.56 (s, 2H);

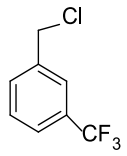
^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 162.8 (d, *J* = 248.4 Hz), 133.5 (d, *J* = 3.3 Hz), 130.6 (d, *J* = 8.3 Hz), 115.8 (d, *J* = 21.6 Hz), 45.6;
^{19}F NMR (285 MHz, $CDCl_3$): δ (ppm) = -113.8 (tt, *J* = 8.6, 5.3 Hz).

1-Chloro-4-(chloromethyl)benzene (39a) [232]



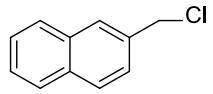
$C_7H_6Cl_2$ (Mr = 161.03);
Reaction conditions: 0.5 mmol 4-chlorobenzyl alcohol **39** (71.2 mg), 0.55 mmol TMSCl (69.8 μl), 3 mol% NIS (3.4 mg, 0.03 mmol), 70-75 °C, 6 h – SFRC;
Purification: CC (SiO_2, CH_2Cl_2/hexane 1:1);
Yield: 64 mg (79%), colourless oil;
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.32 (s, 4H), 4.54 (s, 2H);
^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 136.1, 134.4, 130.1, 129.1, 45.5.

1-(Chloromethyl)-3-(trifluoromethyl)benzene (61g) [234]



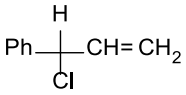
$C_8H_6ClF_3$ (Mr = 194.58);
Reaction conditions: 0.5 mmol 3-trifluoromethylbenzyl alcohol **60g** (68 μl) 0.55 mmol TMSCl (69.8 μl), 10 mol% NIS (11.2 mg, 0.1 mmol), 70-75 °C, 24 h – SFRC;
Purification: CC (SiO_2, CH_2Cl_2/hexane 1:1);
Yield: 65 mg (67%), colourless oil;
^{1}H NMR (300 MHz, TMS): δ (ppm) = 7.67 – 7.45 (m, 4H), 4.62 (s, 2H);
^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 139.1, 138.5, 132.0, 131.3 (q, *J* = 32.5 Hz), 129.4, 129.1, 125.5 (q, *J* = 3.9 Hz), 125.4 (q, *J* = 3.8 Hz), 124.0 (q, *J* = 272.4 Hz), 45.3.
^{19}F NMR (285 MHz, $CDCl_3$): δ (ppm) = -63.28 (s)

2-(Chloromethyl)naphthalene (61h) [235]



$C_{11}H_9Cl$ (Mr = 176.64);
Reaction conditions: 0.5 mmol naphthalen-2-ylmethanol **60h** (79.1 mg), 0.55 mmol TMSCl (69.8 μl), 2 mol% NIS (2.2 mg, 0.02 mmol), 70-75 °C, 3.5 h – SFRC;
Purification: CC (SiO_2, CH_2Cl_2/hexane 1:1);
Yield: 77 mg (87%), white solid;
Mp.: 49-51 °C, (lit.[236] 48-49 °C);
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.84 – 7.78 (m, 4H), 7.50 – 7.46 (m, 3H), 4.73 (s, 2H);
^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 134.9, 133.3, 133.2, 128.8, 128.1, 127.9, 127.7, 126.6, 126.6, 126.4, 46.8.

(1-Chloroallyl)benzene (61i) [237]



C_9H_9Cl (Mr = 152.62);

Reaction conditions: 0.5 mmol α-vinylbenzyl alcohol **60i** (65.7 μl), 0.55 mmol TMSCl (69.8 μl), 70-75 °C, 3 h – SFRC;

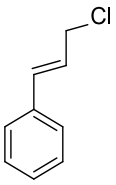
Purification: Not necessary;

Yield: 74 mg (98%), colourless oil;

^{1}H NMR (300 MHz, TMS): δ (ppm) = 7.40 – 7.22 (m, 5H), 6.64 (d, *J* = 15.6 Hz, 1H), 6.30 (dt, *J* = 15.6, 7.2 Hz, 1H), 4.22 (dd, *J* = 7.2, 1.2 Hz, 2H);

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 136.0, 134.3, 128.8, 128.4, 126.8, 125.0, 45.6.

(E)-(3-Chloroprop-1-en-1-yl)benzene (61j) [238]



C_9H_9Cl (Mr = 152.62);

Reaction conditions: 0.5 mmol cinnamyl alcohol **60j** (67.1 mg), 0.55 mmol TMSCl (69.8 μl), rt, stirring 400, 24 h – SFRC;

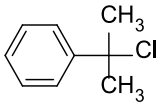
Purification: Not necessary;

Yield: 75 mg (98%), colourless oil;

^{1}H NMR (300 MHz, TMS): δ (ppm) = 7.40 – 7.23 (m, 5H), 6.65 (d, *J* = 15.6 Hz, 1H), 6.38 – 6.24 (m, 1H), 4.23 (dd, *J* = 7.2, 1.1 Hz, 2H);

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 136.0, 134.2, 128.8, 128.4, 126.8, 125.0, 45.6.

(2-Chloropropan-2-yl)benzene (61k) [239]



$C_9H_{11}Cl$ (Mr = 154.64);

Reaction conditions: 0.5 mmol 2-phenylpropan-2-ol **29** (68 mg), 0.55 mmol TMSCl (69.8 μl), rt, stirring 400, 6^{30} h – SFRC;

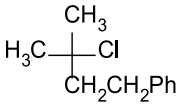
Purification: Not necessary;

Yield: 75 mg (98%), colourless oil;

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.60 – 7.55 (m, 2H), 7.37 – 7.21 (m, 3H), 1.99 (s, 6H);

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 146.4, 128.4, 127.7, 125.6, 69.7, 34.4.

(3-Chloro-3-methylbutyl)benzene (63) [240]



$C_{11}H_{15}Cl$ (Mr = 182.69);

Reaction conditions: 0.5 mmol α,α-dimethylbenzenepropanol **32** (85 μl), 0.55 mmol TMSCl (69.8 μl), 70-75 °C, 24 h – SFRC;

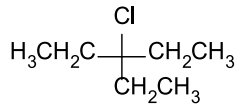
Purification: Not necessary;

Yield: 90 mg, (99%), colourless oil;

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.31 – 7.25 (m, 2H), 7.19 (d, *J* = 7.6 Hz, 3H), 2.86 – 2.77 (m, 2H), 2.06 – 2.00 (m, 2H), 1.63 (s, 6H);

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 141.9, 128.6, 128.5, 126.1, 70.6, 48.1, 32.6, 31.8.

3-Chloro-3-ethylpentane (61l) [241]



$C_7H_{15}Cl$ (Mr = 134.65);

Reaction conditions: 0.5 mmol 3-ethyl-3-pentanol **60l** (68.8 μl), 0.55 mmol TMSCl (69.8 μl), rt, stirring 400, 24 h – SFRC;

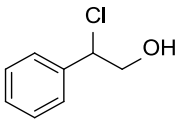
Purification: Not necessary;

Yield: 66 mg, (98%), colourless oil;

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.78 (q, *J* = 7.4 Hz, 6H), 0.95 (t, *J* = 14.7 Hz, 9H);

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 80.2, 33.0, 8.8.

2-Chloro-2-phenylethanol (61o) [242]



C_8H_9ClO (Mr = 156.61);

Reaction conditions: 0.5 mmol 1-phenylethane-1,2-diol **60o** (69 mg), 0.55 mmol TMSCl (69.8 μl), 70-75 °C, 24 h – SFRC;

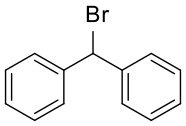
Purification: CC (SiO_2, CH_2Cl_2/hexane 1:1);

Yield: 71 mg (90%), colourless oil;

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.42 – 7.29 (m, 5H), 4.97 (t, *J* = 7.3, 5.8 Hz, 1H), 3.97 – 3.85 (m, 2H), 2.21 (s, 1H);

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 138.0, 128.9, 128.9, 127.6, 67.9, 64.8.

Diphenylmethyl bromide (28) [183] *from alcohol and TMSBr*



$C_{13}H_{11}Br$ (Mr = 247.13);

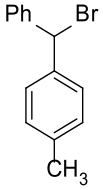
Reaction conditions: 0.5 mmol diphenylmethanol **1** (92.1 mg), 0.55 mmol TMSBr **20d** (72.6 μl), rt, stirring 400, 24 h – SFRC;

Purification: Not necessary;

Yield: 121 mg (98%), colourless oil;

Spectroscopic data are given on page 54.

1-(Bromo(phenyl)methyl)-4-methylbenzene (23b) [183]



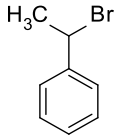
$C_{14}H_{13}Br$ (Mr = 261.16);

Reaction conditions: 0.5 mmol phenyl(*p*-tolyl)methanol **23** (99.1 mg), 0.55 mmol TMSBr (72.6 μl), rt, stirring 400, 4 h – SFRC;

Purification: Not necessary;

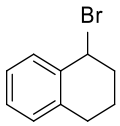
Yield: 128 mg (98%), colourless oil;
^{1}H NMR (300 MHz, TMS): δ (ppm) = 7.48 – 7.43 (m, 2H), 7.35 – 7.22 (m, 5H), 7.13 (d, *J* = 7.9 Hz, 2H), 6.27 (s, 1H), 2.33 (s, 3H).
^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 141.3, 138.3, 138.1, 129.4, 128.6, 128.5, 128.5, 128.1, 55.7, 21.2.

(1-Bromoethyl)benzene (62a) [243]



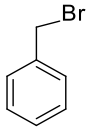
C_8H_9Br (Mr = 185.06);
Reaction conditions: 0.5 mmol 1-phenylethanol **60a** (60 µl) 0.55 mmol TMSBr (72.6 µl), rt, stirring 400, 3 h – SFRC;
Purification: Not necessary;
Yield: 91 mg (99%), pale yellow oil;
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.43 (dd, *J* = 8.3, 1.4 Hz, 2H), 7.36 – 7.22 (m, 3H), 5.20 (q, *J* = 6.9 Hz, 1H), 2.04 (d, *J* = 6.9 Hz, 3H).;
^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 143.3, 128.8, 128.5, 126.9, 49.7, 27.0.

1-Bromo-1,2,3,4-tetrahydronaphthalene (62e) [244]



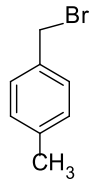
$C_{10}H_{11}Br$ (Mr = 211.10);
Reaction conditions: 0.5 mmol 1,2,3,4-tetrahydronaphthalen-2-ol **60e** (74.1 mg), TMSBr (72.6 µl), rt, stirring 400, 3 h – SFRC;
Purification: Not necessary;
Yield: 103 mg (98%), pale yellow oil;
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.39 – 6.96 (m, 4H), 5.58 (t, *J* = 3.3 Hz, 1H), 2.97 – 1.84 (m, 6H);
^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 137.0, 136.4, 130.9, 129.5, 128.4, 126.2, 52.1, 33.6, 28.8, 18.9.

(Bromomethyl)benzene (43e) [182]



C_7H_7Br (Mr = 171.03);
Reaction conditions: 0.5 mmol benzyl alcohol **43** (51.7 µl), 0.55 mmol TMSBr (72.6 µl), rt, stirring 400, 24 h – SFRC;
Purification: Not necessary;
Yield: 84 mg (99%), colourless oil;
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.40 – 7.27 (m, 5H), 4.48 (s, 2H);
^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 137.9, 129.1, 128.9, 128.5, 33.7.

1-(Bromomethyl)-4-methylbenzene (64) [230]



C_8H_9Br (Mr = 185.06);

Reaction conditions: 0.5 mmol 4-methylbenzyl alcohol **4** (61 mg), TMSBr (72.6 μl), rt, stirring 400, 1.5 h – SFRC;

Purification: Not necessary;

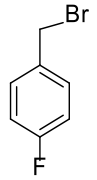
Yield: 90 mg (98%), white solid;

Mp.: 35-37 °C, (lit.[245] 34-36 °C);

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.27 (d, *J* = 8.1 Hz, 2H), 7.13 (d, *J* = 7.9 Hz, 2H), 4.47 (s, 2H), 2.33 (s, 3H);

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 138.5, 135.0, 129.6, 129.1, 33.9, 21.4.

1-(Bromomethyl)-4-fluorobenzene (62f) [246]



C_7H_6BrF (Mr = 189.02);

Reaction conditions: 0.5 mmol 4-fluorobenzyl alcohol **60f** (54.5 μl), TMSBr (72.6 μl), rt, stirring 400, 18 h – SFRC;

Purification: Not necessary;

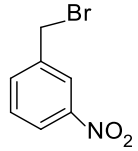
Yield: 92 mg (98%), pale yellow oil;

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.36 (dd, *J* = 8.5, 5.3 Hz, 2H), 7.02 (t, *J* = 8.6 Hz, 2H), 4.47 (s, 2H);

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 162.7 (d, *J* = 248.2 Hz), 133.8 (d), 131.0 (d, *J* = 8.5 Hz), 115.9 (d, *J* = 21.8 Hz), 32.7

^{19}F NMR (285 MHz, $CDCl_3$): δ (ppm) = -113.5 (tt, *J* = 8.7, 5.3 Hz).

1-(Bromomethyl)-3-nitrobenzene (65) [247]



$C_7H_6BrNO_2$ (Mr = 216.03);

Reaction conditions: 0.5 mmol 3-nitrobenzyl alcohol **19** (59 μl) 0.55 mmol TMSBr (72.6 μl), rt, stirring 400, 24 h – SFRC;

Purification: Not necessary;

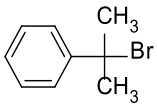
Yield: 106 mg (99%), pale yellow solid;

Mp.: 57-58 °C, (lit.[248] 57-58 °C);

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.26 (t, *J* = 1.8 Hz, 1H), 8.16 (ddd, *J* = 8.2, 2.2, 1.1 Hz, 1H), 7.74 (dt, *J* = 7.7, 1.4 Hz, 1H), 7.54 (t, *J* = 7.9 Hz, 1H), 4.54 (s, 2H);

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 148.5, 139.8, 135.1, 130.0, 124.0, 123.4, 31.2.

(2-Bromopropan-2-yl)benzene (62k) [239]



$C_9H_{11}Br$ (Mr = 199.09);

Reaction conditions: 0.5 mmol 2-phenylpropan-2-ol **29** (68 mg) 0.55 mmol TMSBr (72.6 μl), rt, stirring 400, 5 h – SFRC;

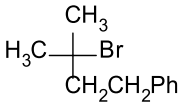
Purification: Not necessary;

Yield: 98 mg (99%), colourless oil;

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.64 – 7.59 (m, 2H), 7.36 – 7.22 (m, 3H), 2.19 (s, 6H);

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 146.9, 128.4, 127.9, 125.8, 64.2, 35.6.

(3-Bromo-3-methylbutyl)benzene (67) [240]



$C_{11}H_{15}Br$ (Mr = 227.14);

Reaction conditions: 0.5 mmol α,α-dimethylbenzenepropanol **32** (85 μl), TMSBr (72.6 μl), rt, stirring 400, 5 h – SFRC;

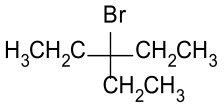
Purification: Not necessary;

Yield: 112 mg (99%), colourless oil;

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.32 – 7.24 (m, 2H), 7.20 (d, *J* = 7.2 Hz, 3H), 2.91 – 2.80 (m, 2H), 2.13 – 2.03 (m, 2H), 1.81 (s, 6H).;

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 141.7, 128.6, 128.5, 126.1, 67.6, 49.6, 34.4, 33.0.

3-Bromo-3-ethylpentane (62l) [241]



$C_7H_{15}Br$ (Mr = 179.10);

Reaction conditions: 0.5 mmol 3-ethyl-3-pentanol **60l** (68.8 μl), TMSBr (72.6 μl), rt, stirring 400, 24 h – SFRC;

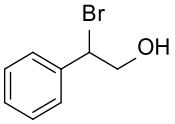
Purification: Not necessary;

Yield: 88 mg (98%), pale yellow oil;

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.88 (q, *J* = 7.3 Hz, 6H), 0.98 (t, *J* = 7.3 Hz, 9H);

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 81.6, 34.3, 9.9.

2-Bromo-2-phenylethanol (62o) [249]



C_8H_9BrO (Mr = 201.06);

Reaction conditions: 0.5 mmol 1-phenylethane-1,2-diol **60o** (69 mg), 0.55 mmol TMSBr (72.6 μl), rt, stirring 400, 24 h – SFRC;

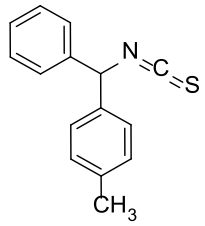
Purification: Not necessary;

Yield: 99 mg (99%), yellow oil;

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.43 – 7.29 (m, 5H), 5.05 (dd, *J* = 7.8, 5.8 Hz, 1H), 4.06 (dd, *J* = 12.2, 7.8 Hz, 1H), 3.95 (dd, *J* = 12.2, 5.8 Hz, 1H), 2.89 (s, 1H);

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 138.3, 129.1, 129.0, 128.0, 67.6, 56.9.

1-(Isothiocyanato(phenyl)methyl)-4-methylbenzene (24 or 69b) [179]

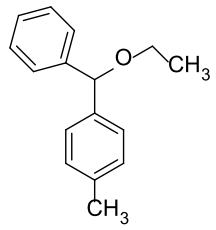


$C_{15}H_{13}NS$ (Mr = 239.34);

Reaction conditions: 0.5 mmol phenyl(p-tolyl)methanol (99.1 mg), 0.55 mmol TMSNCS (77.5 μl), 3 mol% NIS (3.4 mg, 0.03 mmol), 70-75 °C, 25 h – SFRC;

Spectroscopic and other identification data, are given on page 53.

1-(Ethoxy(phenyl)methyl)-4-methylbenzene (25 or 69c) [180]

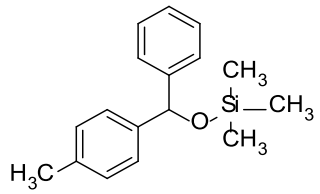


$C_{16}H_{18}O$ (Mr = 226.31);

Reaction conditions: 0.5 mmol phenyl(*p*-tolyl)methanol (99.1 mg), 0.55 mmol TMSOEt (85.9 μl), 3 mol% NIS (3.4 mg, 0.03 mmol), 70-75 °C, 25 h – SFRC;

Spectroscopic and other identification data, are given on page 53.

Trimethyl(phenyl(p-tolyl)methoxy)silane (69h) [250]



$C_{17}H_{22}OSi$ (Mr = 270.44);

Reaction conditions: 0.5 mmol phenyl(*p*-tolyl)methanol **23** (99.1 mg), 0.55 mmol TMSCN **20h** (68.8 μl), 3 mol% NIS (3.4 mg, 0.03 mmol), or without NIS, 70-75 °C, 3 h – SFRC;

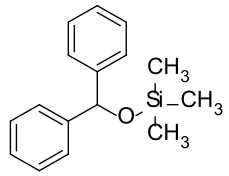
Purification: Not necessary;

Yield: 133 mg (98%), colourless liquid;

^{1}H NMR (300 MHz, TMS): δ (ppm) = 7.35 – 7.17 (m, 7H), 7.09 (d, *J* = 7.9 Hz, 2H), 5.73 (s, 1H), 2.30 (s, 3H), 0.07 (s, 9H);

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 145.2, 142.1, 136.7, 129.0, 128.3, 127.1, 126.6, 126.6, 76.5, 21.2, 0.3.

(Benzhydryloxy)trimethylsilane (69i) [153]



	$C_{16}H_{20}OSi$ (Mr = 256.41);
Reaction conditions:	0.5 mmol diphenylmethanol **1** (92.1 mg), 0.55 mmol $TMSN(Me)_2$ **20i** (88.1 μl), 6 mol% NIS (6.7 mg, 0.06 mmol), 70-75 °C, 24 h – SFRC;
Purification:	Not necessary;
Yield:	126 mg (98%), colourless liquid;
^{1}**H NMR** (300 MHz, TMS):	δ (ppm) = 7.35 – 7.17 (m, 10H), 5.76 (s, 1H), 0.07 (s, 9H);
^{13}**C NMR** (76 MHz, $CDCl_3$):	δ (ppm) = 144.9, 128.3, 127.1, 126.6, 76.5, 0.3.

Chapter 8

Transformation of tertiary alcohols to vicinal halo-substituted derivatives using *N*-halosuccinimides

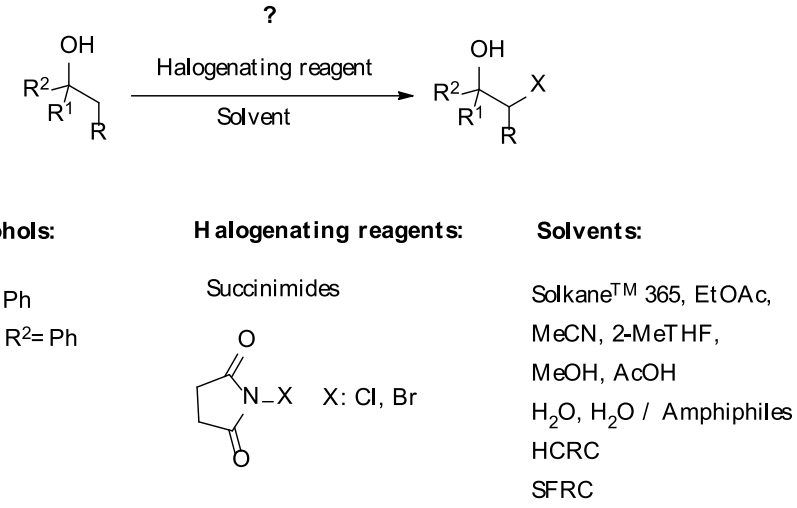
Vicinal halohydrins are versatile building blocks in organic, medicinal and industrial chemistry and widely used for transformation into epoxides [200] and ketones [251]. Halohydrins can be directly synthesized by functionalization of alkenes to *vic*-halohydrins using a variety of reagents: such as *N*-halosuccinimide with water in the presence of β-cyclodextrin[252], ionic liquid [253], thiourea [254], or ammonium acetate [255].

However, these synthetic procedures have several disadvantages, such as multiple step synthesis, toxic and expensive reagents, problematic manipulation, and long reaction time.

It is therefore important to develop an effective methodology for the different organic transformations that follow the principles of green chemistry to accomplish the desired chemical transformation.

The formation of bromohydrin from styrene using H_2O_2-HBr system or *N*-bromosuccinimde (NBS) in water as a reaction medium was shown [256]. Reactions of aryl-alkyl substituted tertiary alcohols with fluorinating agents have been already studied in our laboratory, and it has been shown that they could be directly converted into the vicinal fluorohydrins in high yields using 1-chloromethyl-4-fluoro-1,4diazobicyclo[2.2.2]octane bis(tetrafluoroborate) (Selectfluor™ F-Teda BF_4) in acetonitrile [171] and also in aqueous media in the presence of amphiphile [257]. It was found that introduction of an additional phenyl group *geminal* to the OH group even improved the yield of *vicinal* fluorohydrin formation[171]. Based on these facts, I was motivated to develop a new, efficient and selective methodology for the direct conversion of tertiary alcohols into the vicinal halohydrins — chlorohydrins and bromohydrins — under green reaction conditions, using *N*-halosuccinimides as very widely used halogen atom transfer reagents.

The general concept of our investigation is schematically presented in Scheme 8.1. Different structure types of tertiary benzyl alcohols will be treated with halogenating reagents in environmentally acceptable solvents as the reaction medium.



Scheme 8.1: Direct transformation of tertiary alcohols into chloro and bromohydrins: the concept and the work-plan of the research.

8.1 Halogenation of tertiary alcohols in organic solvents

8.1.1 Results and discussion

I chose 1,1-diphenylethanol (**11,** Table 8.1**)** as the model compound to investigate the best reaction conditions for its potential conversion to halohydrins. *N*-chloro- (NCS) and *N*-bromosuccinimide (NBS) were selected as halogen atoms transfer reagents, while the list of environmentally accepted solvents from aprotic Solkane™ 365 to 2-MeTHF, protic MeOH and AcOH, and finally water was chosen as reaction medium candidates under high concentration reaction conditions (HCRC) or under solvent–free reaction conditions (SFRC).

I found that 1,1,1,3,3-pentafluorobutane (*Solkane™ 365*) did not cause any transformation of starting material **11** (entries 1 and 2). However, in *ethyl acetate*, the reaction with NCS did not provide any conversion of starting material **11** (entry 3). Contrary, the reaction with NBS caused moderate conversion (32%) of starting material **11** where 1,1-diphenylethene was found as the main product **58** (entry 4).

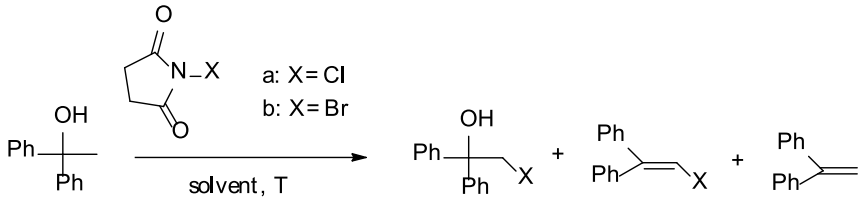
In *2-methyltetrahydrofuran* I observed a high conversion of starting material **11** in reaction with NCS and NBS, and also in these cases the elimination product was the main product **58** (entries 5 and 6).

Following the green chemical point view of acceptable solvents, I further checked the transformation of our model compound **11** in solvents such as *acetic acid* and *acetonitrile* and established that the reactions gave the mixture of products as follows: 2-halo-1,1-diphenylethanol **73a-b**, 1-halo-2,2-diphenylethene **74a-b** and 1,1-diphenylethene **58**.

In *acetonitrile*, using NCS, no transformation took place (entry 7), while by using NBS, moderate conversion of starting material **11** was observed, resulting in the formation of vicinal halohydrin as the sole product **73b** (entry 8).

In the case of performing the reactions in *acetic acid*, the quantitative conversion of **11** was observed, using NCS (entry 9), and the formation of addition-elimination product **74a** was established as the main product, accompanied with a small amount of the eliminated product **58**, after the shorter reaction time also accompanied with a small amount of the eliminated product **58** and vicinal halohydrin product **73a** (entry 11), while in the case of reaction using NBS, the formation of addition-elimination product **74b** was established as the sole product, also after the shorter reaction time (entries 10 and 12).

Table 8.1: Transformation of 1,1-diphenylethanol **11** with NCS and NBS in organic solvents[a].



11 **73a-b** **74a-b** **58**

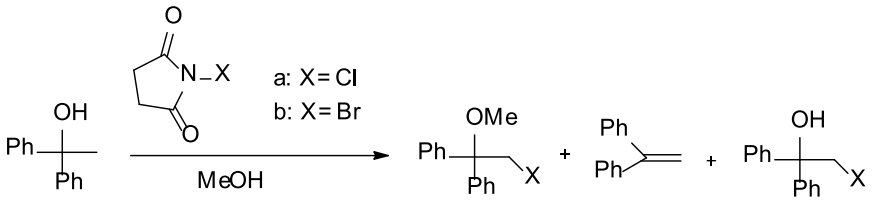
Entry	X	Solvent	Reaction conditions	Conv.[b] [%] of **11**	Yield[c] [%]		
					73a-b	**74a-b**	**58**
1	Cl	Solkane	40-45 °C, 18 h	/	/	/	/
2	Br	Solkane	40-45 °C, 18 h	/	/	/	/
3	Cl	EtOAc	75-80 °C, 18 h	/	/	/	/
4	Br	EtOAc	75-80 °C, 18 h	32	3	5	24
5	Cl	2-MeTHF	75-80 °C, 18 h	81	2	1	78
6	Br	2-MeTHF	75-80 °C, 18 h	89	7	/	82
7	Cl	MeCN	77-80 °C, 24 h	/	/	/	/
8	Br	MeCN	77-80 °C, 24 h	68	68	/	/
9	Cl	AcOH	115-117 °C, 24 h	100	/	98	2
10	Br	AcOH	115-117 °C, 24 h	100	/	100	/
11	Cl	AcOH	115-117 °C, 4 h	100	/	96	4
12	Br	AcOH	115-117 °C, 4 h	100	/	100	/

[a] Reaction conditions: 1,1-diphenylethanol **11** (0.5-1 mmol), NXS (0.55-1,1 mmol), solvent (5 mL). [b] Determined from ^{1}H NMR spectra of isolated crude reaction mixtures. [c] Yields calculated relative to alcohol **11**.

In the case of reactions using NCS in pure *methanol* I found quantitative conversion of starting material **11** resulting in the formation of halomethoxy **75a** (entry 1) as the main product, while in the case of the reaction using NBS eliminated product was the main product **58** (entry 2), (see Table 8.2)**.**

In the case of reaction with NCS and NBS in methanol with added water, I observed that the addition of water decreases the amount of the desired products **75a-b** (entries 3, 4, 5 and 6).

Table 8.2: Transformation of 1,1-diphenylethanol **11** with NCS and NBS in methanol[a].



11 **75a-b** **58** **73a-b**

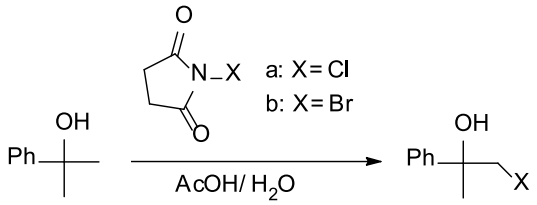
Entry	X	MeOH/H_2O	Conv.[b] [%] of **11**	Yield[c] [%]		
				75a-b	**58**	**73a-b**
1	Cl	MeOH	100	73	23	/[d]
2	Br	MeOH	100	40	60	/
3	Cl	MeOH/20 mmol	98	60	30	5[d]
4	Br	MeOH/20 mmol	100	13	84	3
5	Cl	2.5 mL/2.5 mL	100	43	25	29
6	Br	2.5 mL/2.5 mL	100	9	74	7[d]

[a] Reaction conditions: 1,1-diphenylethanol **11** (1 mmol), NXS (1.1 mmol), solvent (5 mL), 60-70 °C, 22 h. [b] Determined from ^{1}H NMR spectra of isolated crude reaction mixtures. [c] Yields calculated relative to alcohol **11**. [d] Other side products 3-10%.

In order to check such a transformation also in some other tertiary alcohols, I treated 2-phenyl-2-propanol **29** with NCS and NBS in *acetic acid* solution where a complex reaction mixture was observed.

In order to improve the selectivity of the reaction, I further studied how the addition of water to the acetic acid reaction media affects the course of the reaction of 2-phenyl-2-propanol **29** with NBS or NCS, and the results are given in Table 8.3. It could be seen that in the case when large amounts of water were added (entries 1 and 2), the formation of vicinal halohydrin products **76a-b** was exclusive, in both cases with NCS and NBS.

Table 8.3: The influence of addition of water to acetic acid reaction media on the course of the reaction of 2-phenyl-2-propanol **29** with NCS and NBS [a].



29 **76a-b**

Entry	X	AcOH/H_2O (vol ratio)	Reaction conditions	Conv.[b] [%] of **29**	Yield[c] [%] **76a-b**
1	Cl	1/1	115-117 °C, 4 h	100	95
2	Br	1/1	106-110 °C, 4 h	100	95

[a] Reaction conditions: 2-phenyl-2-propanol **29** (1 mmol), NXS (1.1 mmol), solvent (5 mL). [b] Determined from ^{1}H NMR spectra of isolated crude reaction mixtures. [c] Yields calculated relative to alcohol **29**.

8.2 Halogenation of tertiary alcohols in water in the presence of amphiphile

8.2.1 Results and discussion

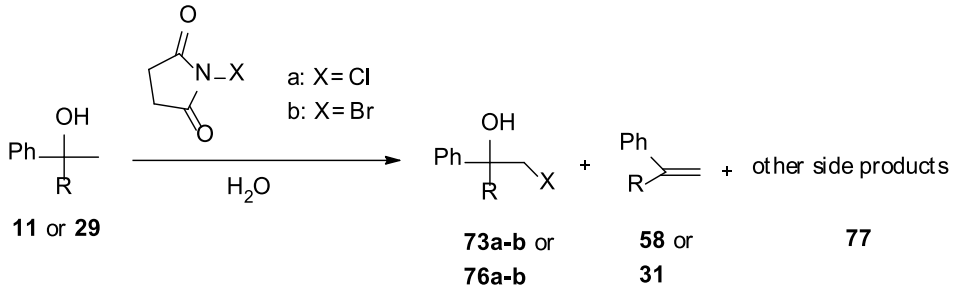
So far, the transformations were achieved by using *N*-chlorosuccinimide or *N*-bromosuccinimide in several organic solvents, and my final goal is to perform these transformations in aqueous media.

Water is one of the best alternatives to organic solvents [258]. It is naturally occurring, abundantly available, nontoxic, nonflammable and inexpensive. Although all natural processes occur in aqueous media, using water in the synthetic organic chemistry had not been popular even till three decades ago. The reasons for this are the limited solubility of organic molecules in water, leading to lower rates or/and yields and the hydrolytic instability of reagents, products and catalysts. The major breakthrough in using water as a medium for organic reactions occurred with the studies on the Diels–Alder reaction done by Breslow in 1980 [259].

These studies concluded that organic reactions proceed well, or even better, in aqueous media, in comparison with organic solvents.

Initially, I checked the course of the reaction of 1,1-diphenylethanole **11** with NXS in pure water and the results are given in Table 8.4. Since 1,1-diphenylethanole **11** nor NXS are soluble in water, the homogeneity of the reaction mixture was observed to be very low. The conversion of starting material **11** in the case of the reaction using NCS was thus found to be low (entry 1), while the NBS-mediated transformation gave considerably higher efficiency (entry 2), but I believe that in both cases better results could be obtained. I further preliminarily investigated the reactions of 2-phenyl-2-propanol **29** with *N*-halosucinimides in pure water and the results are collected in Table 8.4. The conversion of starting material **29** in the case of the reaction with NCS was found to be quantitative, resulting in the formation of the vicinal halohydrin as the sole product **76a** (entry 3), while in the case with NBS, quantitative conversion of starting material **29** was observed, providing vicinal halohydrin **76b** as the main product (due to unstability compound under chromatographic conditions, purification was unsuccessful), accompanied by the formation of eliminated product **31** (entry 4).

Table 8.4: Transformation of tertiary alcohols with NCS or NBS in water reaction media[a].

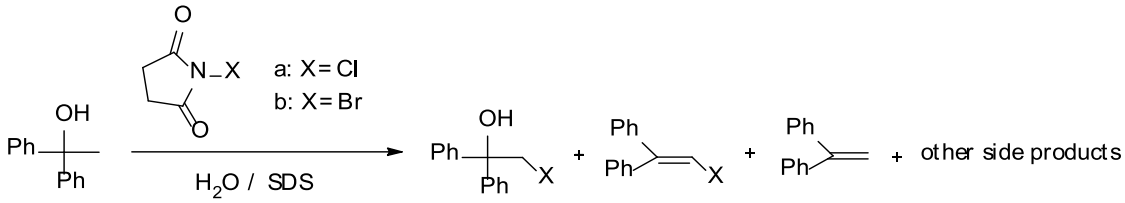


Entry	R	X	Conv.[b] [%] of **11** or **29**	Yield[c] [%]		
				73a-b or **76a-b**	**58** or **31**	**77**[d]
1	Ph	Cl	14	14	/	/
2	Ph	Br	72	54	/	18
3	Me	Cl	100	100	/	/
4	Me	Br	96	52	44	/

[a] Reaction conditions: alcohol **11** or **29** (1 mmol), NXS (1.1 mmol), solvent (5 mL), 100 °C, 7-20 h. [b] Determined from ^{1}H NMR spectra of isolated crude reaction mixtures. [c] Yields calculated relative to alcohol **11** or **29**. [d] Among side products, the main product is 2,2-dibromo-1,1-diphenylethanol.

In order to improve the efficiency of this transformation, in the continuation of my work I tested if the addition of a surfactant has an effect on the course of the reaction. I chose sodium dodecyl sulfate (SDS) as the amphiphilic surfactant and reactions were performed with its different concentrations in the aqueous media. Results are given in Table 8.5. The influence of the concentration of amphiphile on conversion of 1,1-diphenylethanol **11** in water with NCS and NBS is graphically presented in Figure 8.1 and it could be established that the catalytic effect of SDS amphiphile in the case of NCS and NBS-mediated reaction reached its maximum efficiency at its $3x10^{-3}$ molar concentration or higher. It was found that the choice of surfactant had a significant influence on the yield and the reaction time; namely, the addition of SDS increases the yields and reduces the reaction times.

Table 8.5: The course of the reaction of 1,1-diphenylethanol **11** with NXS in aqueous media in the presence of SDS amphiphile[a].



11 **73a-b** **74a-b** **58** **78**

Entry	X	H_2O/SDS	Conv.[b] [%] of **11**	Yield[c] [%]			
				73a-b	**74a-b**	**58**	**78**[d]
1	Cl	SDS (C=0.0008 M)	82	47	11	24	/
2	Br	SDS (C=0.0008 M)	95	53	12	24	6
3	Cl	SDS (C=0.001 M)	95	47	10	32	6
4	Br	SDS (C=0.001 M)	96	49	10	27	10
5	Cl	SDS (C=0.003 M)	100	72	8	20	/
6	Br	SDS (C=0.003 M)	100	56	5	28	12
7	**Cl**	**SDS (C=0.008 M)**	**100**	**86**	**7**	**7**	**/**
8	**Br**	**SDS (C=0.008 M)**	**100**	**67**	**5**	**17**	**11**
9	Cl	SDS (C=0.05 M)	100	89	4	7	/
10	Br	SDS (C=0.05 M)	100	70	/	23	7

[a] Reaction conditions: 1,1-diphenylethanol **11** (1 mmol), NXS (1.1 mmol), solvent (5 mL), 100 °C, 7 h. [b] Determined from ^{1}H NMR spectra of isolated crude reaction mixtures. [c] Yields calculated relative to alcohol **11**. [d] Among side products the main product is 2,2-dichloro-1,1-diphenylethanol in the case with NCS, 2,2-dibromo-1,1-diphenylethanol in the case with NBS.

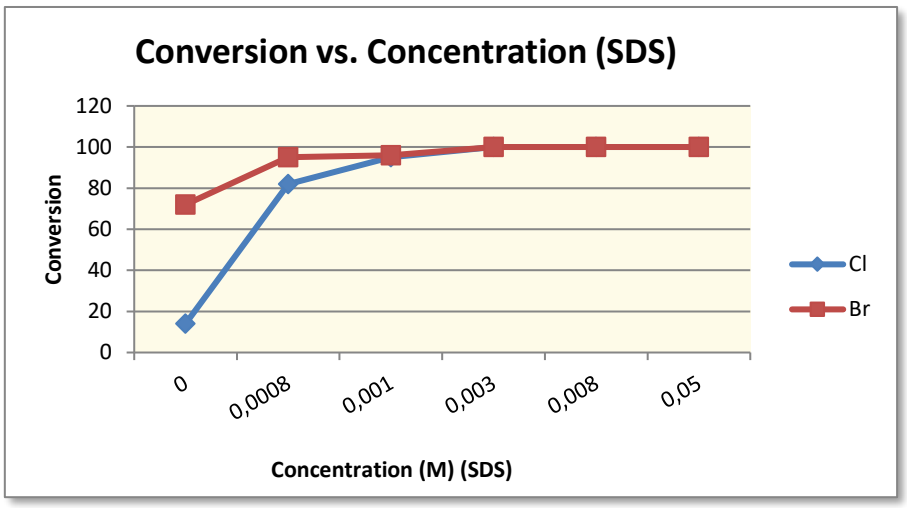
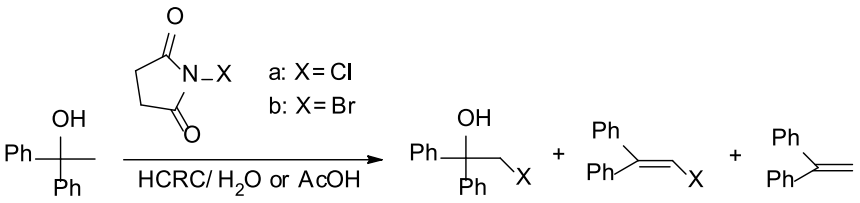


Figure 8.1: The effect of the added amount of SDS amphiphile on the efficiency of the reaction of 1,1-diphenylethanol **11** with NXS.

Moreover, to check the impact of SDS as the amphiphilic surfactant on the course of the reaction of 2-phenyl-2-propanol **29**, I performed with its different concentrations in the aqueous media, and no effect of SDS observed in both cases.

On the other hand, I performed these transformations under defined reaction conditions of HCRC and SFRC and the results are collected in Table 8.6. In the case of the reaction of 1,1-diphenylethanol **1** with NCS under water or acetic acid HCRC, I observed a low conversion of starting material **1** (entries 1 and 2). In the case of NBS under SFRC no reaction occurred (entry 3), while under water or acetic acid HCRC I observed quantitative to low conversion of starting material **11** (entries 4-7), but the selectivity was not good.

Table 8.6: Transformation of 1,1-diphenylethanol **11** with NCS and NBS under SFRC or HCRC.

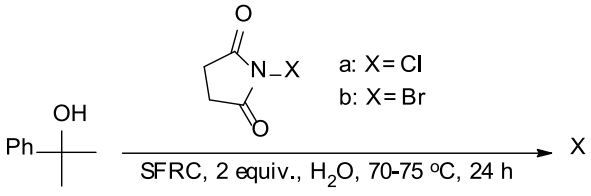


11 **73a-b** **74a-b** **58**

Entry	X	equiv. /H_2O or AcOH	Conv.[b] [%] of **11**	Yield[c] [%]		
				73a-b	**74a-b**	**58**
1	Cl	2/H_2O	5	5	/	/
2	Cl	2/AcOH	22	2	20	/
3	Br	1/H_2O	/	/	/	/
4	Br	2/H_2O	100	40	22	38
5	Br	4/H_2O	100	16	50	34
6	Br	10/H_2O	36	3	/	33
7	Br	2/AcOH	100	/	65	35

[a] Reaction conditions: 1,1-diphenylethanol **11** (0.5 mmol), NXS (0.55 mmol), 70-75 °C, 24 h. [b] Determined from ^{1}H NMR spectra of isolated crude reaction mixtures. [c] Yields calculated relative to alcohol **11**.

Moreover, I performed the reaction of 2-phenyl-2-propanol **29** with NCS and NBS under SFRC and in both cases no reaction took place (Scheme 8.2).

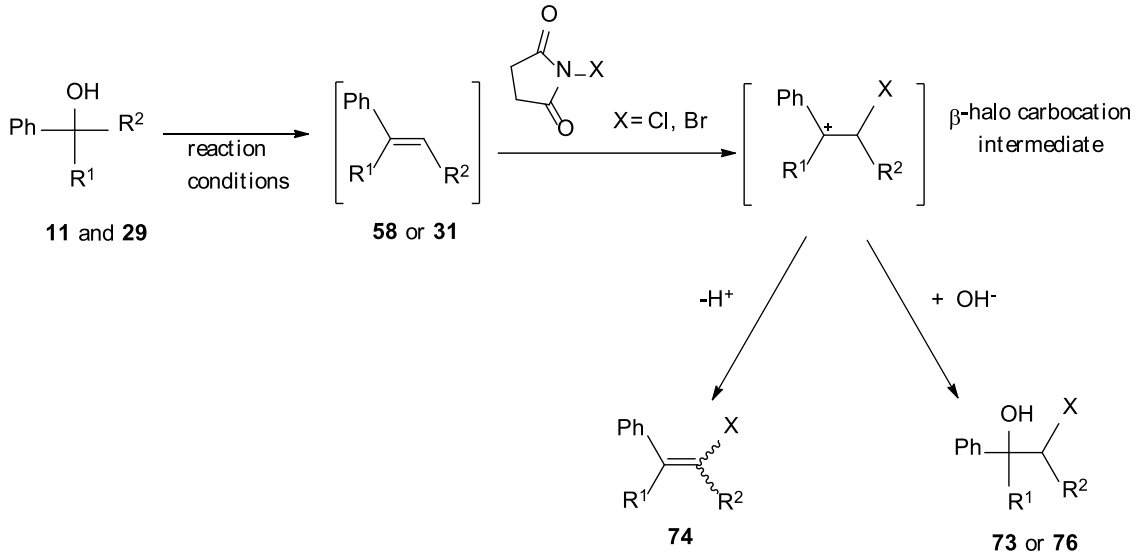


29

Scheme 8.2: Transformation of 2-phenyl-2-propanol **29** with NCS or NBS under SFRC.

On the basis of the results presented I could propose a plausible reaction pathway of the transformations of phenyl-alkyl substituted tertiary alcohols to vicinal halohydrins using *N*-halo succinimides as the halogenating reagents. I suppose that the first step of the reaction is the

dehydration of alcohol under actual reaction conditions thus forming the corresponding alkene, in our cases 1,1-diphenylethene **58** or 2-phenylpropyl-1-ene **31** observed among the products in the crude reaction mixtures isolated. The second step should be the halogenations of alkene with NXS reagents known as the halogene-transfer reagents to electron rich unsaturated organic compounds following the electrophilic process which includes the formation of the most stable ß-halo substituted carbocation intermediates. These intermediates could lose a proton and result in the formation of halogen-substituted alkenes in our cases compound **74**. In the presence of a sufficient concentration of hydroxyl nucleophile, it could collapse with it, thus forming vicinal halohydrins, in our cases compounds **73** and **76** (Scheme 8.3).



Scheme 8.3: Plausible reaction pathway for direct halogenation of phenyl-alkyl substituted tertiary alcohols to vicinal halohydrins using *N*-halo succinimides.

8.3 Conclusion

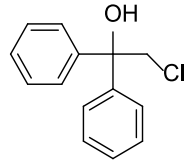
The assumption that tertiary benzyl alcohols bearing at least one vicinal hydrogen atom could be directly transformed to vicinal halohydrins **73a-b** or **76a-b** using N-halosuccinimides was verified on 1,1-diphenylethanol **11** and 2-phenyl-2-propanol **29** as the basic model compounds. In both cases the efficient and selective one pot synthesis to the corresponding vicinal chloro- **73a** or **76a** and bromo hydrins **73b** or **76b** was achieved using NCS or NBS, respectively, in aqueous reaction media, but in the case of more hydrophobic 1,1-diphenylethanol **11**, the addition of sodium dodecyl sulphate (SDS) in the amounts around its critical micelle concentration was found to be essential in order enhance considerably the yield of the transformation. When acetic acid was used as the reaction media, the addition-elimination **74a-b** process resulting in the selective formation of 2-chloro **74a** or 2-bromo-1-1-diphenylethene **74b** was observed, while under the same conditions a complex reaction course took place in the case of treatment of 2-phenyl-2-propanol **29**.

8.4 Experimental work

General procedure for vicinal halogenation of tertiary alcohols using NXS on mmol scale: A solvent (5 mL) was placed to a 10 mL round-bottom-flask equipped with a magnetic stirrer, under reflux at 40-117 °C , NXS (1.1 mmol) was then added, when NXS dissolved, the substrate **11** or **29** (1 mmol) was added and the solution was stirred for 4-24 h. The progress of the reaction mixture was monitored by TLC, while a consumption of NXS was tested by KI (0.1M). Upon completion of the reaction, the crude reaction mixture was cooled down to room temperature, diluted with EtOAc (15 mL), washed with $Na_2S_2O_3$ (6 mL), $NaHCO_3$ (6 mL), and water (10 mL), and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the crude reaction mixture obtained was analyzed by ^{1}H NMR. The pure final products were obtained after flash chromatography, column chromatography or preparative thin layer chromatography. Detailed experimental information, such as isolated yields and spectroscopic and other identification data, are given below.

The isolated known compounds were identified by comparing the spectroscopic data with the literature.

2-Chloro-1,1-diphenylethanol (73a) [260]



$C_{14}H_{13}ClO$ (Mr = 232.71);

Reaction conditions: 1 mmol 1,1-diphenylethanol **11** (198.1 mg), 1.1 mmol NCS (146.8 mg), 0.008M SDS (11.5 mg), H_2O (5 mL), 100 °C, 7 h stirring 1000;

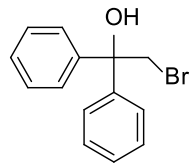
Purification: CC (SiO_2, EtOAc/hexane 9:1);

Yield: 186 mg (80%), colourless oil;

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.45 – 7.25 (m, 10H), 4.18 (s, 2H), 3.16 (s, 1H).

^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 143.4, 128.5, 127.8, 126.5, 78.0, 53.3.

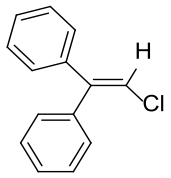
2-Bromo-1,1-diphenylethanol (73b) [261]



$C_{14}H_{13}BrO$ (Mr = 277.16);

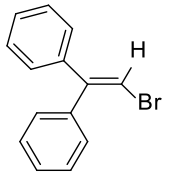
Reaction conditions: 1 mmol 1,1-diphenylethanol **11** (198.1 mg), 1.1 mmol NBS (195.6 mg), 0.05M SDS (72 mg), H_2O (5 mL), 95-100 °C, 7 h stirring 1000;
Purification: TLC-preparative (EtOAc/hexane 9:1)
Yield: 164 mg (59%), yellow oil;
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.54 – 7.20 (m, 10H), 4.11 (s, 2H), 3.10 (s, 1H);
^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 143.4, 128.5, 127.8, 126.4, 77.3, 44.1.

(2-Chloroethene-1,1-diyl)dibenzene (74a) [262]



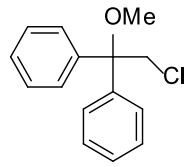
$C_{14}H_{11}Cl$ (Mr = 214.69);
Reaction conditions: 1 mmol 1,1-diphenylethanol **11** (198.1 mg), 1.1 mmol NCS (146.8 mg), CH_3COOH (5 mL), 115-117 °C, 4 h stirring 400;
Purification: Crystalization (hexane)
Yield: 173 mg (80%), white crystals;
Mp.: 39-40 °C, (lit.[262] 39-40 °C);
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.41 – 7.18 (m, 10H), 6.58 (s, 1H);
^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 144.0, 140.3, 137.7, 130.0, 128.6, 128.3, 128.2, 128.1, 127.9, 116.0

(2-Bromoethene-1,1-diyl)dibenzene (74b) [218]



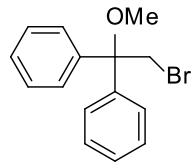
$C_{14}H_{11}Br$ (Mr = 259.14);
Reaction conditions: 1 mmol 1,1-diphenylethanol **11** (198.1 mg), 1.1 mmol NBS (195.6 mg), CH_3COOH (5 mL), 115-117 °C, 4 h stirring 400;
Purification: FCH (SiO_2, EtOAc);
Yield: 250 mg (97%), white crystals;
Mp.: 47-49 °C, (lit.[218] 48-50 °C);
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.42 – 7.18 (m, 10H), 6.77 (s, 1H);
^{13}C NMR (76 MHz, $CDCl_3$): δ (ppm) = 147.0, 140.9, 139.2, 129.8, 128.6, 128.4, 128.3, 128.1, 127.8, 105.3.

(2-Chloro-1-methoxyethane-1,1-diyl)dibenzene (75a) [263]



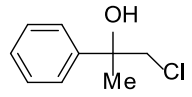
	$C_{15}H_{15}ClO$ (Mr = 246.73);
Reaction conditions:	1 mmol 1,1-diphenylethanol **11** (198.1 mg), 1.1 mmol NCS (146.8 mg), CH_3OH (5 mL), 60-70 °C, 22 h stirring 400;
Purification:	CC (SiO_2, EtOAc/hexane 9:1);
Yield:	160 mg (65%), white solid;
Mp.:	46-48 °C, (lit.[263] 47-49 °C);
^{1}H NMR (300 MHz, $CDCl_3$):	δ (ppm) = 7.38 – 7.25 (m, 10H), 4.34 (s, 2H), 3.18 (s, 3H);
^{13}C NMR (76 MHz, $CDCl_3$):	δ (ppm) = 142.6, 128.2, 127.6, 127.3, 82.0, 50.9, 48.8.

(2-Bromo-1-methoxyethane-1,1-diyl)dibenzene (75b) [264]



	$C_{15}H_{15}BrO$ (Mr = 291.18);
Reaction conditions:	1 mmol 1,1-diphenylethanol **11** (198.1 mg), 1.1 mmol NBS (195.6 mg), CH_3OH (5 mL), 60-70 °C, 22 h stirring 400;
Purification:	CC (SiO_2, EtOAc/hexane 9:1);
Yield:	102 mg (35%), colourless oil;
^{1}H NMR (300 MHz, $CDCl_3$):	δ (ppm) = 7.38 – 7.22 (m, 10H), 4.23 (s, 2H), 3.16 (s, 3H);
^{13}C NMR (76 MHz, $CDCl_3$):	δ (ppm) = 142.8, 128.2, 127.5, 127.2, 81.3, 50.7, 38.8.

1-Chloro-2-phenylpropan-2-ol (76a) [260]



	$C_9H_{11}ClO$ (Mr = 170.64);
Reaction conditions:	1 mmol 2-phenylpropan-2-ol **29** (136.1 mg), 1.1 mmol NCS (146.8 mg), CH_3COOH (5 mL), 115-117 °C, 4 h stirring 400;
Purification:	FCH (SiO_2, EtOAc);
Yield:	159 mg (93%), colourless oil;
^{1}H NMR (300 MHz, $CDCl_3$):	δ (ppm) = 7.50 – 7.25 (m, 5H), 3.86 – 3.73 (m, 2H), 2.60 (s, 1H), 1.64 (s, 3H);
^{13}C NMR (76 MHz, $CDCl_3$):	δ (ppm) = 144.3, 128.5, 127.6, 125.1, 73.9, 55.5, 27.4.

Chapter 9

Conclusions

A group of organic molecules bearing an active *N*-halogen bond: *N*-halosuccinimides (chloro, bromo or iodo, respectively), 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis-tetrafluoroborate (*Selectfluor™ F-TEDA-BF_4)* and *N*-fluorobenzenesulfonimide (*Accufluor™ NFSi*) was introduced, tested and applied as new, efficient, non-metal and non-acidic catalysts for reactions of a comprehensive range of alcohols with various types of electron rich organic molecules or reactive anionic species thus forming new carbon-carbon or carbon-heteroatom bonds in target alcohol molecules. Green chemical profiles of these valuable transformations were enhanced by leading reactions under solvent-free reaction conditions (SFRC) or high concentration reaction conditions (HCRC). The scope of the reaction was preliminarily tested by selecting a most convenient structural type of alcohol and electron rich organic molecule as reactants, and *N*-halo compound from the mentioned list as the most efficient catalyst for each of a particular transformation. After these general reaction parameters were determined, each type of transformation was studied and developed in details.

Diphenylmethanol **1** was chosen as the basic model compound and its dimerization to bis(diphenylmethyl)ether **3** was established in the presence of substoichiometric amounts (2 mol%) of named *N*-halo compounds under SFRC, *N*-iodosuccinimide (NIS) giving the highest efficiency. In the case when a two-molar excess of methanol was present in the reaction mixture, the formation of methyl diphenylmethyl ether **2** was observed. 4-Methylbenzyl alcohol **4** was further examined as aprimary benzyl alcohol target and under both mentioned reaction conditions, dimerization to the corresponding dibenzyl ether **6** or corresponding methyl benzyl ether **5** was established. 1,3-Dicarbonyl compound and phenyl substituted alkenes were selected as electron rich organic molecules and the formation of a new C-C bond between benzyl carbon atom and the most electron rich carbon atom on di-carbonyl or alkene target was formed. NIS was established as the most efficient catalyst in these cases, too. Additionally, the C-C bond formation could also be achieved by direct coupling of secondary benzyl alcohol and *in situ* formed electron rich alkenes derived from dehydration of tertiary alcohol bearing a vicinal hydrogen atom in the presence of NIS as the catalyst under SFRC. New C-N bond formation in target secondary benzyl alcohol was accomplished when the reactions were performed in the presence of acetonitrile and the corresponding Ritter-type *N*-acyl benzyl product was formed **14**, while aniline-type substrate afforded *N*-benzyl phenyl amine derivative **18**. Various trimethylsilyl derivatives were further used as potential sources of a nucleophilic species and corresponding chlorobenzyl derivative **21** was formed from primary benzyl alcohol bearing a deactivated ring, while the formation of the corresponding benzyl-substituted isothiocyanate **24** was established using (trimethylsilyl)isothiocyanate as the nucleophile source. (**Chapter 4**)

Direct transformation of primary, secondary and tertiary benzyl alcohols, tertiary alkyl and allyl alcohols into the corresponding ethers was discovered and developed using *N*-halosuccinimides and *N*-fluoro organic compounds in substoichiometric amounts in the presence of methanol, ethanol and isopropanol as nucleophile sources, under high concentration reaction conditions or in solution. In most cases NIS exhibited the best catalytic activity. The cross coupling of two different benzyl alcohols to ethers was achieved by NIS catalyzed reaction under SFRC. (**Chapter 5**)

Novel, efficient, selective and easily scalable methodology for C-C bond formation through the direct coupling of various ß-dicarbonyl compounds with various benzyl alcohols in one hand or through direct coupling of phenyl substituted alkenes or heteroatom benzo-cyclenes as their

analogues with benzyl alcohols on the other hand, employing NIS catalysis under SFRC, was developed. The reactivity of ß-dicarbonyl compounds was found to be the function of their enolisability, while primary benzyl alcohols targets needed strong activation of the ring. A comprehensive range of secondary benzyl alcohols gave efficient coupling, while tertiary benzyl alcohols were found as inconvenient targets. (**Chapter 6.1**)

In the case of 1,1-diphenyethene **58** as the electron rich moiety, benzylation of the position 2 took place, following the addition-elimination process resulting in the formation of 1,1-diphenyl-2-benzyl-ethene derivatives **12**. Benzylation of the position C-2 was observed in the case of 1,2-dihydronaphthalene **9** and 2,3-benzofuran **56b**, while C-3 was benzylated in the case of 1-acetylindole **56a**. (**Chapter 6.2**)

A chemoselective method for the direct halogenation of different types of alcohols with halosilanes under catalyst- and organic solvent-free reaction conditions (SFRC) was developed. Various primary, secondary and tertiary benzyl alcohols, allyl alcohols, and tertiary alkyl alcohols were directly transformed to the corresponding benzyl and alkyl halides, respectively, using chlorotrimethylsilane (TMSCl) **20a** and bromotrimethylsilane (TMSBr) **20d**. In the case of benzyl alcohols bearing a deactivated benzene ring, the catalytic support for the efficient halogenation is needed. So, the addition of substoichiometric amounts of *N*-iodosuccinimide in the case of reactions of 3-nitro **19** and 3-fluorobenzyl alcohols **60g** under solvent-free reaction conditions enabled the formation of the desired chlorinated products. Under similar reaction conditions using cyanotrimethylsilane **20h** and *N,N*-dimethyltrimethylsilylamine **20i**, trimethylsilylation of the hydroxyl group in target molecules was found as the sole reaction process. The courses of reactions were found to be quite different in the case of trimethyl(trifluromethyl)silane **20j**, ethynyltrimethylsilane **20k**, triphenylsilane **20l**, triethylsilane **20m** and tris(trimethylsilyl)phosphate **20n**, where dimeric ether was observed as the main product, accompanied with a small amount of oxidised alcohol. (**Chapter 7**)

The assumption that tertiary benzyl alcohols bearing at least one vicinal hydrogen atom could be directly transformed to vicinal halohydrins **73a-b** or **76a-b** using *N*-halosuccinimides was verified on 1,1-diphenylethanol **11** and 2-phenyl-2-propanol **29** as the basic model compounds. In both cases, the efficient and selective one pot synthesis to the corresponding vicinal chloro- **73a** or **76a** and bromohydrins **73b** or **76b** was achieved using NCS or NBS, respectively, in aqueous reaction media. In the case of a more hydrophobic 1,1-diphenylethanol **11**, the addition of sodium dodecyl sulphate (SDS) in the amounts around its critical micelle concentration was found to be essential in order to enhance considerably the yield of the transformation. When acetic acid was used as the reaction media, the addition-elimination process resulting in the selective formation of 2-chloro **74a** or 2-bromo-1-1-diphenylethene **74b** was observed, while under the same conditions a complex reaction course took place in the case of treatment of 2-phenyl-2-propanol **29**. (**Chapter 8**)

References

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AJVAZI, Njomza, STAVBER, Stojan. New method for C - C bond formation following *N* - halo compound catalysis under solvent-free reaction conditions. V: Slovenski kemijski dnevi 2015, Ljubljana, 24. - 25. September 2015 = Slovenian Chemical Days 2015, Ljubljana, September 24 - 25, 2015. KAUČIČ, Venčeslav (ur.), et al. *Zbornik referatov in povzetkov*. Ljubljana: Slovensko kemijsko društvo, 2015, 6 str. [COBISS.SI-ID 28891175]

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Biography

I was born on 20 March 1984 in Prishtina. On 21 September 2007 I completed the Basic University Studies in the Engineering Section at the Faculty of Mathematical-Natural Sciences at the University of Prishtina and obtained the title Bachelor of Chemistry. On 28 September 2009 I graduated with a Master degree in the field of Organic Chemistry with Biochemistry obtaining the title Master of Chemistry Sciences. In the 2011/2012 academic year I started my doctoral studies in the field of Nanosciences and Nanotechnologies at the Jožef Stefan International Postgraduate School under the supervision of Prof. Dr. Stojan Stavber.