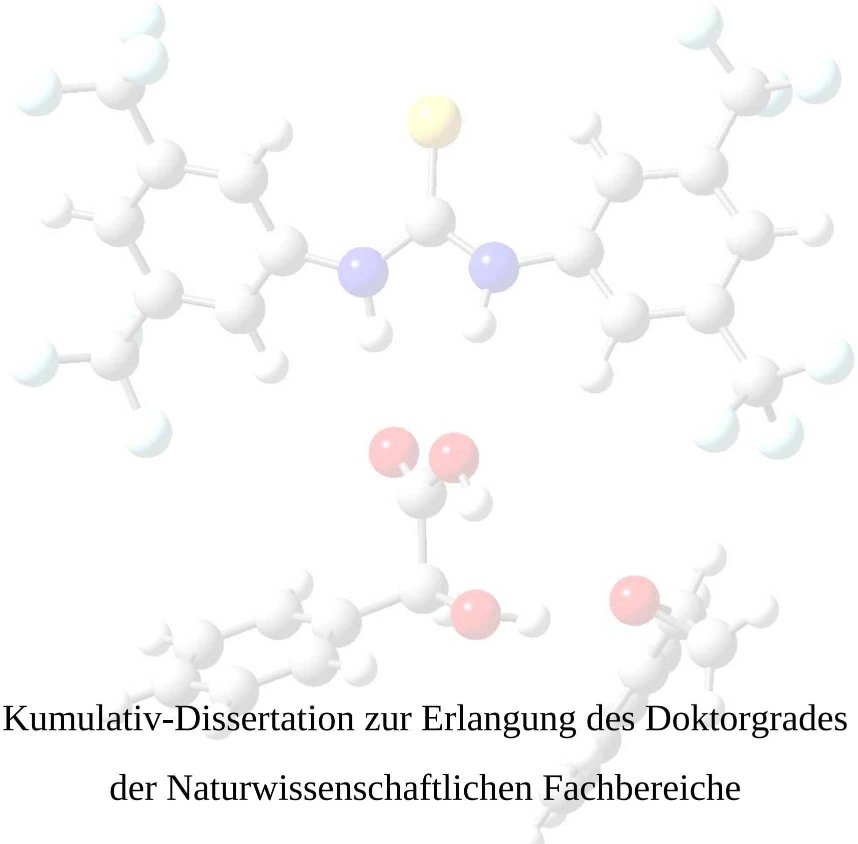
Organocatalytic Addition of Carbon and Oxygen Nucleophiles to C-O Electrophiles



Kumulativ-Dissertation zur Erlangung des Doktorgrades
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Ich möchte an dieser Stelle meinem Lehrer, Herrn Prof. Dr. P. R. Schreiner, ganz herzlich für die interessante Themenstellung, die vielen anregenden Diskussionen, sein stetes Interesse am Fortgang der Arbeit sowie die erwiesene Unterstützung und zugestandene forscherische Freiheit im Verlauf der Arbeit danken.

Für meine Familie

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Preface

The present doctoral thesis summarizes scientific papers written between 2004 and 2008 at the Institute for Organic Chemistry of the Justus-Liebig-University Giessen. The organocatalytic systems investigated range from simple phase-transfer catalytic alkynylation systems involving C–C bond formation to hydrogen bond activated additions of oxygen nucleophiles to C–O electrophiles.

Chapter 1 gives an overview over all established methodologies and state-of-the-art to transform aldehydes and ketones to the corresponding propargylic alcohols utilizing *in situ* generated acetylides. The following chapter summarizes methods to functionalize epoxides to get access to the versatile and important class of *ß*-alkoxy alcohols. Chapter 3 gives a short introduction to the class of 1,3-dioxolanes and their importance in organic chemistry with respect to protecting group chemistry and transformation of 1,2-epoxides to 1,2-diols. Chapter 4 comprises scientific papers discussing the phase-transfer catalytic transformation of aldehydes and ketones into propargylic alcohols as well as the organocatalytic functionalization of styrene oxides with alcohols and aldehydes, leading to *ß*-alkoxy alcohols and 1,3-dioxolanes (manuscript in preparation). Chapter 5 summarizes the corresponding experimental details as well as spectroscopic properties. References (Chapter 6), bibliography (Chapter 7), acknowledgement (Chapter 8), abbreviations (Appendix A) and chemical structures (Appendix B) are finally attached.

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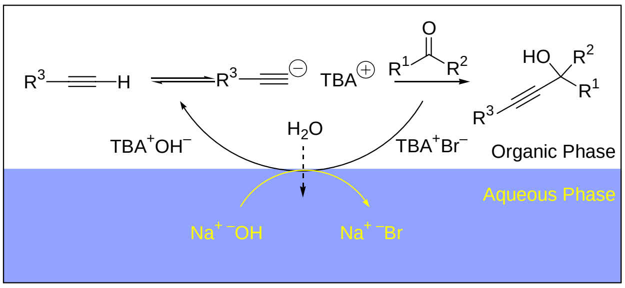
Abstract

Various methodologies utilizing alkyl metal compounds or metal salts in combination with a chiral ligand are used to transform aldehydes or ketones and terminal alkynes to propargylic alcohols. Virtually none of the established transition metal-catalyzed protocols are universally applicable to aliphatic as well as aromatic aldehydes and ketones. On the other hand simple procedures utilizing cheap and easy manageable alkaline bases are comparable concerning reactivity and tolerance but afford no chiral induction.



Scheme A. PTC alkynylation of aldehydes and ketones

We developed alkynylations of various aldehydes and ketones under practical phase-transfer conditions at room temperature (Scheme A). This straightforward methodology combines one-pot synthesis and simple workup with good to excellent yields for propargylic alcohols derived from aliphatic aldehydes and ketones. Even aromatic aldehydes and ketones could be transformed to the corresponding propargylic alcohols in slightly lower yields. As the coordination between the PT-catalyst and the *in situ* generated carbanion is implied in this and other PTC reactions, we also made efforts to develop stereoselective alkynylations utilizing chiral PT-catalysts.

The addition of alcohols to epoxides leads to the synthetically important class of β-alkoxy alcohols. As alcohols behave as poor nucleophiles in such substitution reactions the methodologies applied reach from simple Brønsted acid catalysis to SET involving redox processes. Due to the S_N2-akin reaction type, only racemic mixtures can be obtained from non-enantiopure material. Chiral Lewis acids lead to desymmetrizations in case of *meso*-epoxides and kinetic resolutions when unsymmetric racemic epoxides are implemented.

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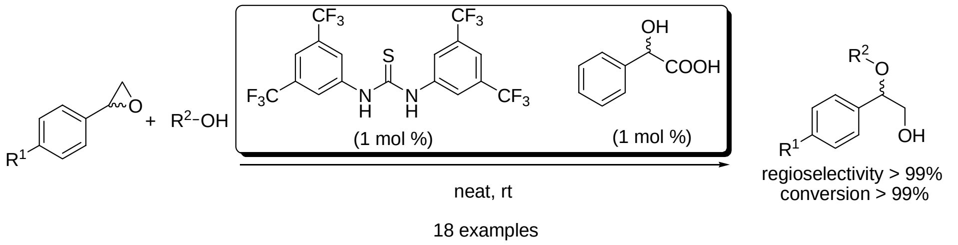
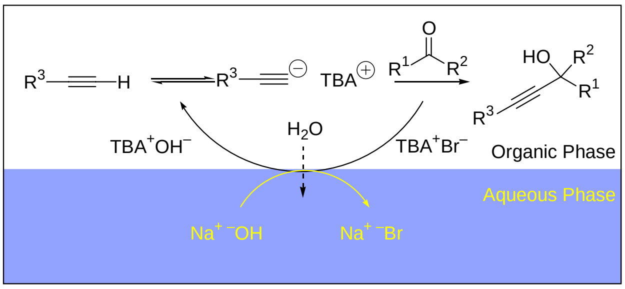


Scheme B. Cooperative Bronsted acid-type organocatalysis: alcoholysis of styrene oxide

We present a mild and efficient method for the completely regioselective alcoholysis of styrene oxides utilizing a cooperative Brønsted acid type organocatalytic system comprised of equimolar amounts of mandelic acid (1 mol%) and *N,N′*-bis-[3,5-bis-(trifluoromethyl)phenyl]-thiourea (1 mol%) (Scheme B). Various styrene oxides are readily transformed into their corresponding *β*-alkoxy alcohols in good to excellent yields at full conversion. Simple aliphatic, sterically demanding as well as unsaturated and acid sensitive alcohols can be employed. Utilizing mandelic acid as chiral catalyst stereoselective transformations of epoxides to the corresponding *β*-alkoxy alcohols are under investigation.

Zusammenfassung

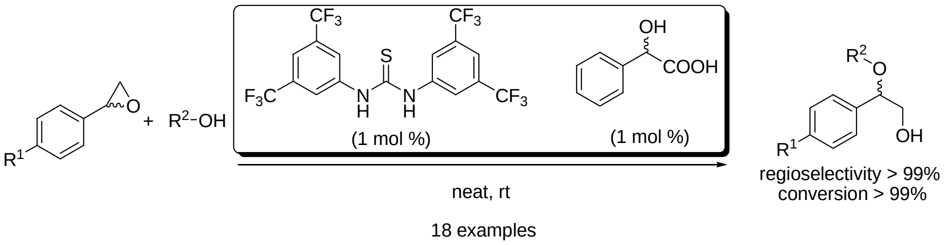
Zur Darstellung von Propargylalkoholen aus Aldehyden und Ketonen mit terminalen Alkinen existieren eine Reihe verschiedener Methoden, welche Alkyl-Metallverbindungen oder Metallsalze in Kombination mit chiralen Liganden benötigen. Keine der gängigen Übergangsmetall-katalysierten Methoden ist jedoch universell und auf aliphatische, sowie aromatische Aldehyde und Ketone anwendbar. Andererseits liefern einfache Prozeduren unter Verwendung kostengünstiger und einfach zu handhabender Alkalibasen vergleichbare Ergebnisse, bezogen auf Reaktivität und Toleranz, bieten aber nicht die Möglichkeit chiraler Induktion.



Schema A. PTC Alkinylierung von Aldehyden und Ketonen

Zu diesem Zweck wurde eine Methode entwickelt, welche Alkinylierungen von verschiedenen Aldehyden und Ketonen unter praktikablen Phasentransfer Bedingungen bei Raumtemperatur ermöglicht (Schema A). Die unkomplizierte Prozedur kombiniert Eintopfsynthese-Bedingungen mit einfacher Aufarbeitung der Produkte, welche in guten bis exzellenten Ausbeuten im Falle aliphatischer Aldehyde und Ketone erhalten werden können. Selbst aromatische Aldehyde und Ketone konnten zu den entsprechenden Propargylalkoholen mit etwas niedrigeren Ausbeuten umgesetzt werden. Da, wie im Falle anderer PT-Reaktionen auch, eine Koordination des *in situ* dargestellten Carbanions und des Phasentransfer-Katalysators angenommen wird, wurden erste Versuche zur stereoselektiven Darstellung von Propargylalkoholen mit chiralen PT-Katalysatoren unternommen.

Die nucleophile Addition von Alkoholen an Epoxide liefert *β*-Alkoxyalkohole, eine synthetisch wichtige Substanzklasse. Da Alkohole aber schlechte Nucleophile für solche Substitutionsprozesse darstellen, existieren unterschiedliche Methoden, von einfacher Brønsted-Säure-Katalyse bis hin zu Redox-Systemen mit Ein-Elektonen-Übertragungsprozessen, welche das eingesetzte Elektrophil (hier das Epoxid) zusätzlich aktivieren. Aufgrund des S_N2-artigen Verlaufs einer solchen Ringöffnung mit Inversion am elektrophilen Zentrum, liefern alle gängigen Reaktionsprotokolle ausschließlich racemische Gemische der entsprechenden *ß*-Alkoxyalkohole, für den Fall, dass das verwendete Epoxid ebenfalls als Racemat eingesetzt wurde. Chirale Lewis-Säuren führen im Falle von *meso*-Epoxiden zur Desymmetrisierung und im Falle unsymmetrischer Epoxide zu kinetischer Racematspaltung.



Schema B. Kooperative Brønsted Säure Katalyse: Alkoholyse von Styroloxid

Als Alternative zeigen wir ein mildes und effizientes Protokoll einer komplett regioselektiven Alkoholyse von Styroloxid mittels kooperativer Brønsted-Säure Katalyse, bestehend aus Mandelsäure (1 mol%) und N,N´-Bis-[3,5-bis-(trifluormethyl)phenyl]-thioharnstoff (1 mol%) (Schema B). Verschiedene Styroloxide konnten bequem zu den entsprechenden *ß*-Alkoxyalkoholen mit guten bis exzellenten Ausbeuten und vollem Umsatz umgewandelt werden. Einfache aliphatische und sterisch anspruchsvolle sowie ungesättigte und säurelabile Alkohole können hierzu eingesetzt werden. Die Verwendung von Mandelsäure als chirales Auxiliar eröffnet des Weiteren die Möglichkeit, stereoselektive Umsetzungen diesbezüglich zu untersuchen.

1. Transformations of Aldehydes and Ketones to Propargylic Alcohols

1.1 Introduction

Carbon–carbon bond formation as well as functionalization of hydrocarbons by ´simple´ C–H bond activation is still a highly desirable goal, leading to numerous classes of versatile intermediates for organic synthesis. The nucleophilic addition of C–H bond-activated terminal alkynes to aldehydes and ketones is an essential C–C bond coupling process that provides propargylic alcohols as synthetically useful components. Propargylic alcohols are often key intermediates in the synthesis of natural products such as prostaglandins, steroids, carotenoids, amino acids, novel histamine H_3-receptor antagonists, and nonnucleosidal HIV reverse transcriptase inhibitors.[1-13] Typically metal mediated additions of alkynes to carbonyl compounds are employed involving a stoichiometric amount of mostly air and moisture sensitive organometallic compounds (e.g., organolithium,[8, 9, 11, 12, 14-17] Grignard reagents,[9, 14, 18, 19] zinc derivatives). Because aldehydes can undergo nucleophilic additions or are themselves subject to deprotonation under such strongly basic conditions, generation of metal acetylides is conducted as a separate step before introduction of the electrophilic aldehyde coupling partner. Furthermore, reagents such as *n*-BuLi can also react as nucleophiles towards carbonyl compounds.[20] The use of Grignard reagents and *n*-BuLi furnishes the magnesium or lithium alkoxide that has to be hydrolyzed by water to free the corresponding alcohol. In case of the magnesium salts acidic conditions are necessary to facilitate this step. Only a few reports demonstrate the catalytic and specifically organocatalytic activation of an alkyne derivative and subsequent addition to a carbonyl compound with limitation to either aliphatic/aromatic aldehydes or aliphatic/aromatic ketones.[21-28]

In 1905 Favorskii reported an addition reaction of acetylene to aldehydes and ketones mediated by KOH that provided propargylic alcohols in good yields.[29] This simple approach has been the basis for several works, including the use of inexpensive and easy manageable alkaline bases such as KO*t*Bu and CsOH.[21, 22] In 2003 Saito and coworkers replaced the alkaline bases by a quaternary ammonium salt, namely Triton B™ and paved the way for the use of organocatalytic phase-transfer systems.[25, 30]

1.2 Representative and established alkynylation methods using stoichiometric amounts of metal acetylides

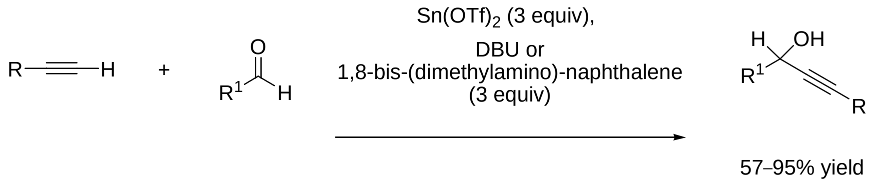
One advantage of alkynes is their easy metalation because of the relatively low pK_a (~ 25). Thus, a large variety of strong bases (e.g., Grignard reagents,[9, 14, 18] *n*-BuLi,[8, 9, 11, 12, 14-17] Me_2Zn), metalated amides (LDA,[31] LHMDS,[32] KHMDS,[33] KNH_2[34]), alkoxides (*t*BuOK[21]) as well as alkali hydroxides/carbonates (KOH,[29, 35] CsOH,[22] Cs_2CO_3[34]) are suitable for deprotonation and subsequent metalation of terminal alkynes. In general there are two methodologies for the (enantioselective) addition of metal acetylides to aldehydes and ketones:

1. Use of stoichiometric amounts of metal acetylides
2. *In situ* generation of substoichiometric amounts of metal acetylides

1.3 Alkynylation reactions using zinc derivatives as reaction promoters

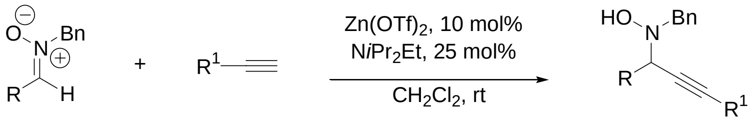
1.3.1 Stoichiometric alkynylation reactions using Zn(II) salts

It is well known that a dichotomy in reactivity of transition metal acetylides exists and species like Zn-, Ag- or Cu-acetylides fail to add to C=O or C=N electrophiles whereas simple alkali and alkaline earth metal acetylides readily participate in such processes. The preparation of active metal acetylides (B,[36] Al,[37, 38] Ce,[39] V,[40] etc.) is commonly implemented by transmetalation of simple Li, Na or Mg acetylides. Yamaguchi and co-workers found that such reactive metal acetylides could also be synthesized by the suitable selection of a metal salt in combination with an adequate amine under mild reaction conditions. It is known that for example Cu(I)[41] and Ag(I)[42, 43] salts form such designated metal acetylides. $Sn(OTf)_2$ formed under equal conditions the reactive acetylide in the presence of 1,8-bis-(dimethylamino)-naphthalene or DBU, which gave good isolated product yields in the addition reactions to aldehydes and ketones (Scheme 1).[44]



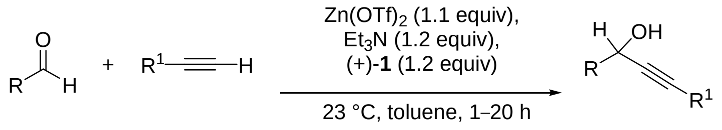
Scheme 1. *In situ* generation and subsequent addition of tin acetylide to aldehydes and ketones

Later, Huang et al. discovered a comparable reaction with gallium salts, primarily GaI_3, to form the desired acetylide in the presence of secondary and tertiary amines.[45] In 1999, Carreira et al. found that $Zn(OTf)_2$ in combination with a tertiary amine led to the *in situ* formation of the corresponding reactive zinc acetylides, which could be successfully added to nitrones (Scheme 2).[46] IR spectroscopic studies evidence a reversible *in situ* formation of zinc acetylides for this substoichiometric metal acetylide generation reaction.

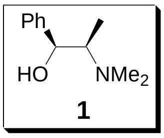


Scheme 2. Addition of alkynes to nitrones mediated by $Zn(OTf)_2$

Continuous work by the group of Carreira based on these mechanistic rationalizations led to a practical method that provided optically active secondary propargylic alcohols derived from aromatic/aliphatic aldehydes and terminal alkynes.[47] The utilized methodology involves *in situ* preparation of the required metal acetylide under mild reaction conditions (rt) without preclusion of oxygen or moisture. Even in the presence of 84–1000 ppm H_2O the enantioselectivity as well as the yield of the adducts were comparable to those when the reaction is conducted with rigorous exclusion of moisture and oxygen.[48] In the presence of a chiral amino alcohol as additive the desired alkynols could be isolated in good to excellent yields (52–99%) and high enantioselectivity (80–99% *ee*) (Scheme 3). Screening of several potential additives (+)-*N*-methylephedrine (**1**) has proven most effective.



aldehyde	alkyne	yield [%]	*ee* [%]
c-C_6H_{11}	Ph	99	96
t-Bu	Ph	99	94
Ph	Ph	53	94



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Scheme 3. Enantioselective additions of terminal alkynes to aldehydes

Propargylic alcohols based on ethyne were available by a practical method also described by Carreira and coworkers using the above mentioned reaction conditions. The addition reaction of 2-methyl-3-butyn-1-ol with aldehydes in the presence of

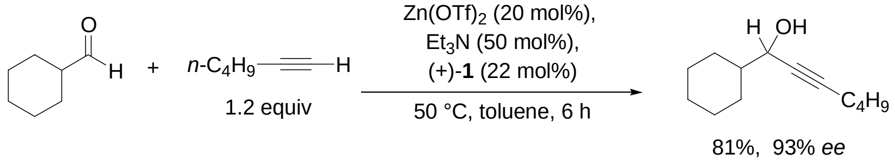
$Zn(OTf)_2$, NEt_3 and (*R*/*S*)-**1** and subsequent retro-Favorskii reaction using K_2CO_3/18-C-6 gave 3-hydroxy-1-butynes in 70–91% yield.[23]

In the course of optimizing the reaction conditions and to perfect the additive motif to assure highest possible chiral induction, Tyrell and coworkers examined the influence of electron-donating/electron-withdrawing substituents of functionalized benzaldehydes and salicylaldehyde derivatives on stereoselectivity and efficiency of the alkynylation reaction.[49] The resulting products are of interest for a novel variation of intramolecular Nicholas reaction.[50, 51] In general the efficiency and chiral induction highly depends on the nature and relative position of the substituent. Pure σ-acceptor groups like the trifluoromethyl group led to highest yields and enantioselectivities, whereas π-donor/acceptor groups in *o*- and *p*-position relative to the carbonyl group led to lower yields and enantioselectivities.

1.3.2 Catalytic zinc mediated alkynylation reactions

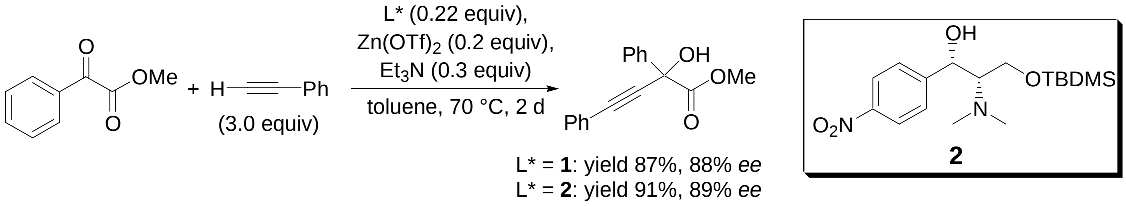
1.3.2.1 Alkynylation reactions using Zn(II) salts in substoichiometric amounts

Many addition processes of carbanions to carbonyl compounds mediated by metals mentioned in literature are described as catalytic, although they are only catalytic with respect to the active chiral complex (see **1.3.2.2**) that activates the nucleophilic/electrophilic reaction partner. After numerous investigations, Carreira and coworkers succeeded in developing a practical alkynylation method that is truly catalytic concerning to the amount of utilized metal derivative.[24] Propargylic alcohols derived from aliphatic aldehydes and various terminal alkynes could be prepared in good to excellent yields with excellent enantioselectivities (Scheme 4). Aromatic aldehydes undergo Canizzaro reactions and furnish only low yields of the desired alkynols. This is probably the result of the relatively high reaction temperatures (up to 60 °C) that are necessary to overcome the lack of turnover proposed to be the consequence of a kinetic barrier inhibiting protonation of the primarily formed Zn-alkoxide.



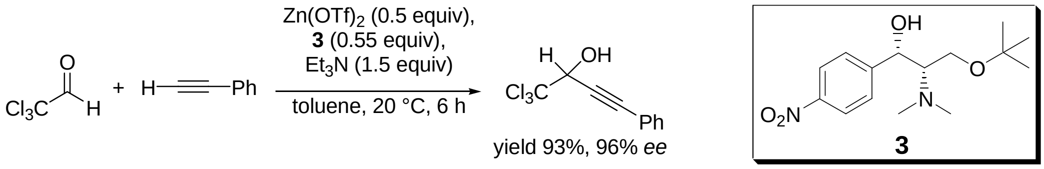
Scheme 4. Catalytic, enantioselective alkynylation of aliphatic aldehydes

A catalytic alkynylation protocol for the synthesis of α-hydroxy-β-ynyl esters was presented by Tan et al. utilizing the basics of the Carreira-methodology.[52] The delineated transformation of non–enolizable β-keto esters to the desired products was performed in the presence of $Zn(OTf)_2$, Et_3N, and the chiral amino alcohol **2** and provided the alkynols in good to excellent yields and high enantioselectivities (Scheme 5). Enolizable β-keto esters underwent significant by-product formation as a consequence of undesired aldol reactions.



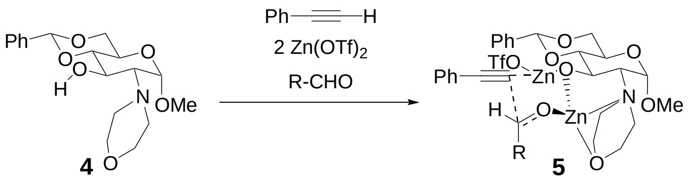
Scheme 5. Enantioselective addition of phenylacetylene to benzoylformate

Facile variation of the ligand motif **2** by Si and coworkers afforded an efficient catalytic method for synthesizing propargylic alcohols derived from chloral as versatile intermediates for transformations into homophenylalanine and 2-hydroxy-4-phenylbutanoate derivatives as pharmaceutically important building blocks.[53] The presented methodology afforded trichloromethylpropargylic alcohol adducts derived from various terminal alkynes in good to high yields and high enantioselectivities under mild reaction conditions (Scheme 6).[13]



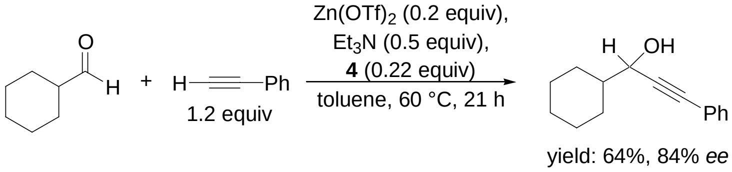
Scheme 6. Catalytic enantioselective alkynylation of chloral

A more complex and completely different ligand motif has been introduced by the group of Davis who used rigid carbohydrate-derived amino alcohols (**4**) as chiral



Scheme 7. Formation of tridentate transition structure **5** derived from **4**

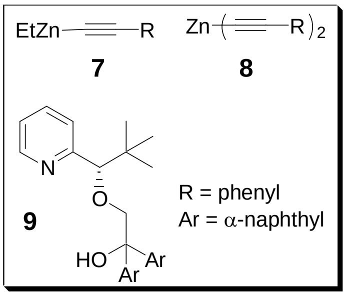
carriers.[54] Performing the reactions under established Carreira-conditions at 60 °C different aliphatic as well as aromatic aldehydes could be transformed to the corresponding alkynols in good yields and moderate to high *ee*´s (Scheme 8). Aromatic aldehydes bearing an electron-donating group in *para*-position furnished only low yields. This observation is consistent with the experimental findings discussed in **1.3.1**. The reaction was proposed to proceed through a tridentate transition structure with the morpholinyl oxygen playing an important role in coordinating the zinc center (Scheme 7). The predetermined steric constitution leads to stereoselective ´intramolecular´ alkynylide addition.



Scheme 8. Enantioselective alkynylation of aldehydes using carbohydrate-derived amino alcohols

1.3.2.2 Catalytic alkynylation reactions using dialkylzinc reagents

Besides the established protocols using substoichiometric amounts of metal derivatives, variations of alkynylation reactions employing dialkylzinc reagents have also been examined. The pioneering work in this area has been done by Niwa and Soai[55] in 1990 and Ishizaki and Hoshino in 1994,[56] who used Et_2Zn in combination with phenylacetylene (**6**) which formed initially a mixed organozinc agent (**7**) that transferred



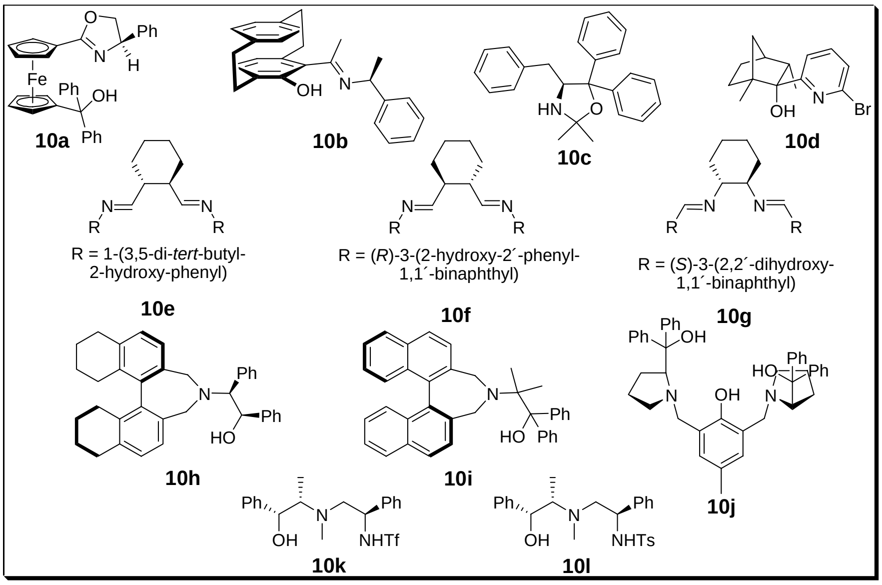


Figure 1. Chiral ligands used in asymmetric alkynylation reactions of aldehydes mediated by Alk_2Zn

the acetylide onto the aldehyde in the presence of 10 mol% tridentate **9**. The range of aldehydes examined included benzaldehyde and various aliphatic aldehydes. The corresponding products could be isolated in appreciable yields and *ee*´s. Reaction of **6** with benzaldehyde yielded 93% of product with 81% *ee*. Further investigations on this reaction outlined that the *in situ* prepared mixed organozinc reagent **7** is less reactive than the corresponding dialkynylzinc derivative **8** resulting in lower yields as a consequence of concurrent alkylation but gives higher *ee*-values.[55, 57]

Based on these findings several marginally diversified protocols have been designed using a methodology that can be depicted as shown in Scheme 9.[57-64]

The variety of used chiral ligands L* is shown in Figure 1. Almost all mentioned reaction protocols are limited to aromatic aldehydes. Aliphatic aldehydes generally give lower yields and enantioselectivities. A representative exception is the protocol introduced by Trost et al. that could also be utilized to transform *α,β*-unsaturated aliphatic aldehydes in the presence of **10j** to the corresponding propargylic alcohols (Figure 2).[60]

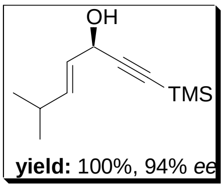
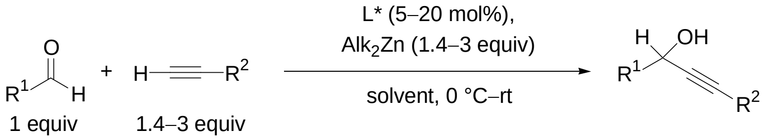
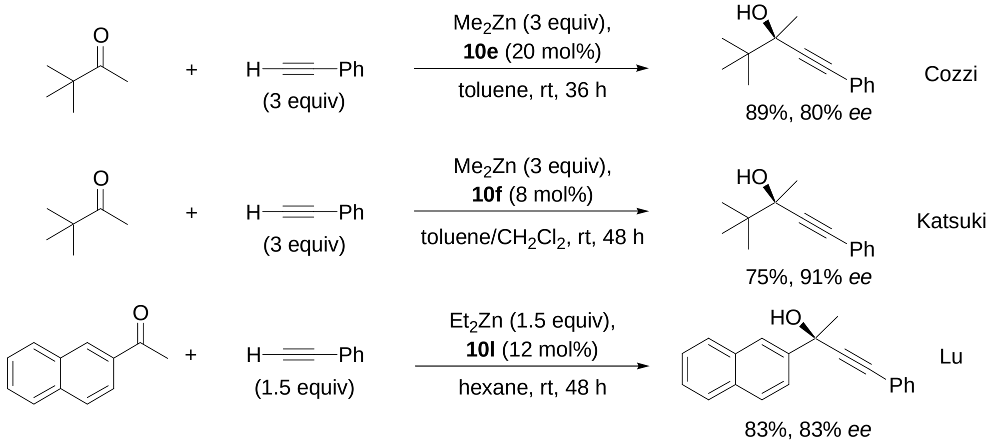


Figure 2.



Scheme 9. Generalized aldehyde-alkynylation protocol using dialkylzinc derivatives combined with chiral ligands L*

Less reactive ketones could also successfully be transformed to alkynols by using slightly modified reaction conditions (longer reaction times) and altered chiral ligands.



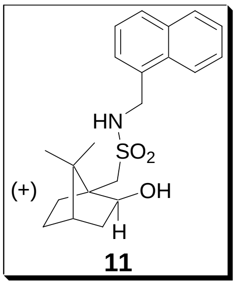
Scheme 10. Asymmetric alkynylation of ketones

Efforts in this direction have been made by the groups of Cozzi,[27] Katsuki,[28] and Lu,[65] who utilized **10e**, **10f**, and **10l** as chiral additives (Scheme 10).

1.4 Other transition metals as reaction promoters

1.4.1 Copper(II) and (I) mediated formation of chiral tertiary propargylic alcohols

The low reactivity of organozinc species towards less reactive ketones and the adherent stereoselectivities of these addition reactions (see **1.3.2.2**) motivated the group of Chan to modify the existent protocols using a stronger Lewis acid as reaction promoter.[26] They utilized copper triflate instead of zinc triflate in combination with a camphorsulfonamide ligand (**11**) to catalyze the alkynylation reactions of acetophenones with **6** in the presence of Me_2Zn. Various acetophenones were transformed to the corresponding tertiary alkynols with good product yields and moderate to excellent *ee´*s (Scheme 11). It appeared that electron-withdrawing or electron-donating substituents have no effect on the enantioselectivity of this reaction. Substituents in *ortho*-position of the substrate had a favorable effect on the stereoselectivity.



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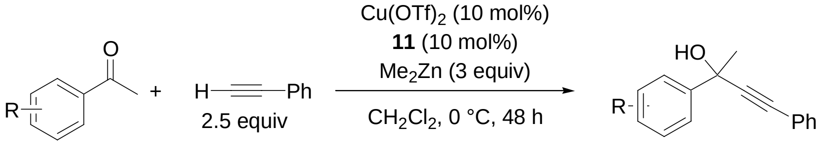
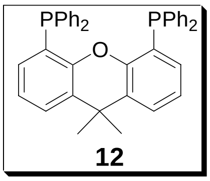


	yield [%]	*ee* [%]
R = H	92	88
R = *o*-Br	65	96
R = *o*-Cl	94	97
R = *p*-Br	75	91

Scheme 11. Enantioselective additions of phenylacetylene to acetophenons

A general method for direct alkynylation of trifluoromethyl ketones was developed by utilizing CuO*t*Bu–xantphos (**12**) complexes as catalysts by Shibasaki et al.[66] The desired alkynols could be isolated in good to excellent yields. Reaction of trifluoromethyl acetophenone with **6** yielded in 95% of product in the presence of 10 mol% of CuO*t*Bu and 10 mol% of **12** after 14 h at 100 °C in toluene. Reactions without the phosphine ligand gave the alkynols



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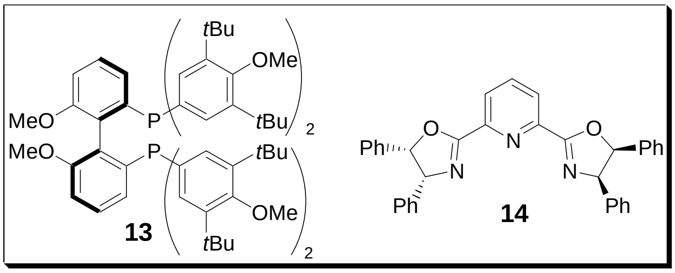
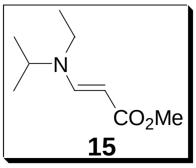


13 **14**

in very low yields. This observation is consistent with the conclusions described in **1.4.2**. First attempts to modify this methodology to get a stereoselective version are also presented. For this chiral phosphine **13** and pybox derivative **14** (2,6-bis[(4*R*,5*S*)-4,5-diphenyl-2-oxazolinyl]pyridine) were introduced as ligands. Up to 52% *ee* were reached when trifluoromethyl acetophenone was converted with **6** in the presence of **14**.

1.4.2 Silver(I) catalyzed aldehyde–alkyne (A^2) coupling reactions

Alkynylation reactions involving the *in situ* generation of a zinc acetylide, pioneered by Carreira and coworkers,[47] failed when utilizing electron-deficient acetylenic esters, due to formation of **15** as the major product; this prompted the group of Koide to develop an alternative method. They rationalized that silver(I) salts facilitate the coupling of ([$Cp_2(Cl)Zr$–R], R = CH_3, alkenyl) to aldehydes and ketones[67, 68] and described a method for transforming terminal acetylenic esters to the desired *γ*-hydroxy-*α*,*β*-acetylenic esters utilizing Ag(I) salts in combination with [Cp_2ZrCl_2, **37**] as reaction promoters. The reaction requires an excess of preliminarily prepared silver acetylide (1.6 equiv) and can therefore be carried out without further addition of a base. Utilizing this methodology, aliphatic as well as aromatic aldehydes could be transformed to the desired alkynols in good yields (Scheme 12). Mechanistic suggestions involve [$Cp_2(Cl)Zr$–C≡C–CO_2Me] as reactive species although the reaction intermediates could not be isolated and characterized.[69] Addition of substoichiometric amounts of AgOTf (0.2 equiv) accelerate the alkynylation reaction dramatically.



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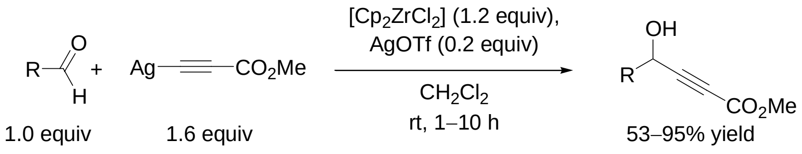
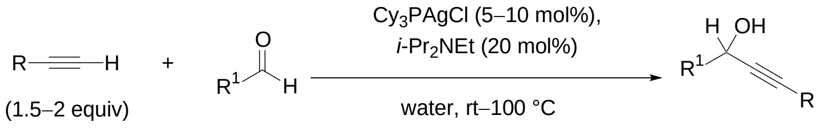


R =	yield [%]
m-nitrophenyl	95
E-2-phenylethenyl	93
n-pentyl	78

Scheme 12. [Cp_2ZrCl_2]/AgOTf-promoted alkynylation of aldehydes

A highly efficient catalytic alkynylation method for aldehydes was developed by the group of Li by using a combination of silver(I) salt, phosphine ligand and a sterically hindered tertiary amine.[42] This remarkable reaction allows coupling of various aldehydes with terminal alkynes in good to excellent yields to the corresponding alkynols in the presence of water (Scheme 13). Best results were obtained with *ortho*-substituted aromatic aldehydes in combination with phenylacetylene (**6**). Without the phosphine additive and a secondary amine as base, the reaction provides the corresponding propargylic amine with an imminium salt as intermediate. The use of aldehydes bearing an electron-withdrawing group led to higher yields but favored simultaneously the formation of chalcones.



R^1 =	yield [%]
c-hexyl	81
phenyl	69
2-chlorophenyl	98

Scheme 13. Silver(I) catalyzed alkynylation of aldehydes in water

Transition metal acetylides from Group 1B (Cu, Ag) do not add to C=O electrophiles in most cases due to the stability of the formed metal acetylide. Only stoichiometric amounts of deployed metal acetylides lead to the desired alkynylation products. The described methodology overcomes this hindrance by weakening and thus activating the silver–carbon bond via adding an electron-rich phosphine ligand. Further investigations led to the suggestion that the silver acetylide intermediate is doubly activated by the utilized phosphine ligand and water as well. This catalytic reaction can be described as heterogeneous due to the low solubility of substrates and the catalytically active compounds.

1.4.3 Rhodium-catalyzed aldehyde–alkyne coupling reactions

The fact that zinc catalyzed alkynylation reactions of 1,2-dicarbonyl compounds are limited to non enolizable systems[52] (see **1.3.2.1)** disposed Chisholm and coworkers to develop a rhodium based catalytic system that evades these known limitations.[70] Rhodium catalyzed addition reactions of alkynes are known to tolerate many functional groups, such as alcohols or carboxylic acids that are not tolerated by many other metal-catalyzed alkynylation reactions and rhodium acetylides are good nucleophiles in the presence of phosphine ligands.[71] With the use of

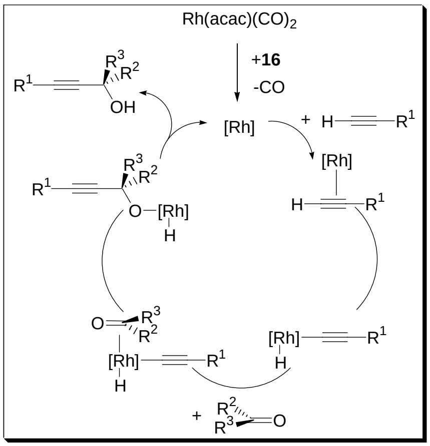
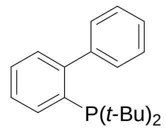


Figure 3. Proposed Rh-catalyzed alkynylation mechanism



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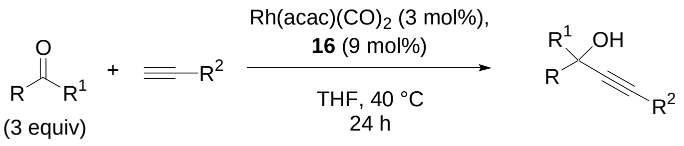
$Rh(acac)(CO)_2$ in combination with a phosphine ligand 2-(di-*tert*-butylphosphino)biphenyl (**16**) an effective method for alkynylation reactions of enolizable 1,2-diketones, 1,2-ketoesters, and aldehydes under mild reaction conditions was described. Various functionalized alkynes were used as coupling partners for *α*,*β*-dicarbonyl compounds and aldehydes with good to excellent yields for the desired tertiary or secondary propargylic alcohols (Scheme 14). The reaction is proposed to start with a ligand exchange[72] and proceeds with coordination of the alkyne to the newly assembled Rh complex followed by insertion of the metal into the alkyne C–H bond to form the nucleophilic Rh acetylide. Reductive elimination provides the alkynol and the regenerated catalyst (Figure 3).



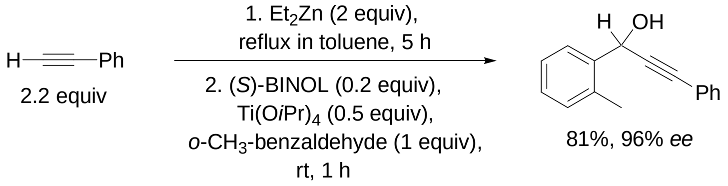
electrophile	**alkyne**	**yield [%]**
2,3-butanedione	phenylacetylene	82
ethyl pyruvate	4-pentyn-1-ol	94
c-hexylcarbaldehyde	4-pentyn-1-ol	80
p-nitrobenzaldehyde	4-pentyn-1-ol	94

selected examples

Scheme 14. Rh-catalyzed alkynylation of carbonyl compounds

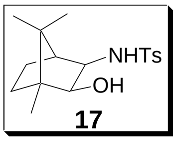
1.4.4 Alkynylations of aromatic aldehydes catalyzed by Titanium complexes

Zinc(II) mediated catalytic alkynylation reactions are known to form alkynols from aromatic aldehydes only in low yields (see **1.3.2.1**). Pu and coworkers developed a more tolerating catalytic system for such substrates by utilizing unmodified (*S*)-BINOL in combination with $Ti(OiPr)_4$ in catalytic amounts in the presence of Et_2Zn.[73] The reaction proceeded at room temperature with excellent stereocontrol when **6** in combination with *o*-, *m*-, or *p*-substituted benzaldehydes containing electron-donating or withdrawing substituents were utilized (Scheme 15). To avoid ethyl addition from the mixed organozinc compound **7** the reaction was performed in two steps with formation of **7** under reflux conditions and subsequent addition of aldehyde and catalyst precursors at room temperature.



Scheme 15. Addition of phenylacetylene to *o*-methyl benzaldehyde in the presence of (*S*)-BINOL and $Ti(OiPr)_4$

A simplified protocol was introduced by Wang et al. with variations of the reaction conditions.[74] The described protocol is a one-pot synthesis without previous formation of **7**. The use of a sulfonamide ligand leads to formation of a more Lewis-acidic Ti-complex which accelerates the addition reaction. Using camphorsulfonamide ligand **17** (10 mol%) and $Ti(OiPr)_4$ (40 mol%) in catalytic amounts aromatic aldehydes (1 equiv) were transformed to the propargylic alcohols with **6** (3 equiv) in the presence of Et_2Zn (3 equiv) in good product yields (71–93%) and high *ee*'s (75–98%). The reaction proceeds in dichloromethane at room temperature within 12–14 hours.



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1.5 Indium(III) salt-catalyzed carbonyl alkynylation

A catalytic alkynylation reaction of aldehydes and ketones promoted by the combination of indium(III) salts and *i*-Pr_2NEt has been presented by Shibasaki and coworkers in 2005.[75] The described methodology involves both activation of the soft nucleophile (alkyne) and the hard electrophile (carbonyl compound) (Figure 4). Validation for this mechanistic suggestion could be achieved by *in situ* IR and NMR experiments. Utilizing this catalytic system aromatic/aliphatic aldehydes as well as aliphatic ketones can be transformed to the corresponding propargylic alcohols in moderate to excellent yields (Scheme 16).

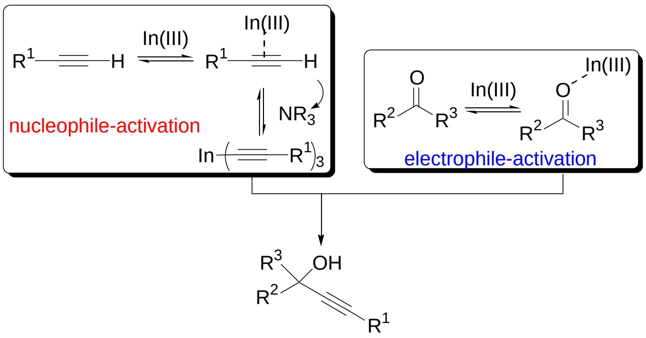
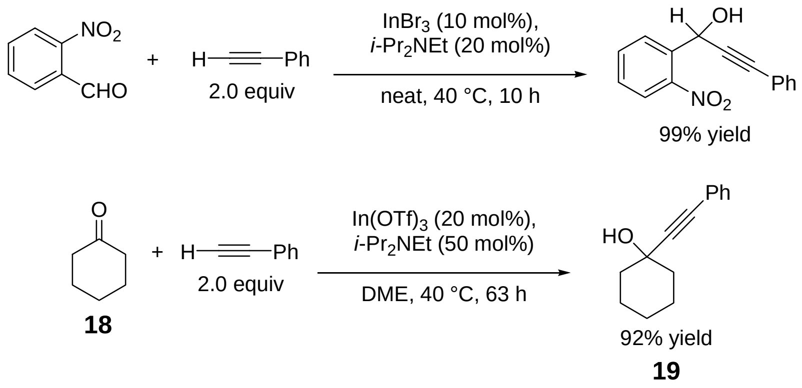


Figure 4. Dual activation of carbonyl and alkyne compound with catalytic amounts of In(III) salts



Scheme 16. InX_3 catalyzed alkynylation of aldehydes and ketones (X = Br, OTf)

A similar protocol was developed simultaneously by Konakahara and coworkers.[76] A slight increase of the amount of used $InBr_3$ (20 mol%) and the use of Et_3N instead of *i*-Pr_2NEt with diethyl ether as solvent led to shorter reaction times at room temperature. Reaction of *p*-cyanobenzaldehyde with **6** furnished 99% of product. Bulky aliphatic aldehydes could also be transformed whereas enolizable aldehydes gave low product yields (Figure 5).

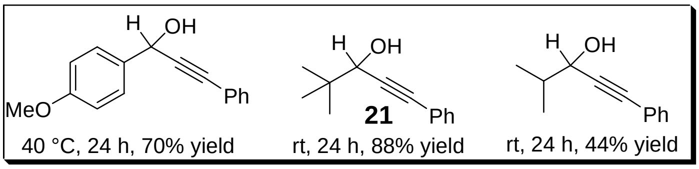
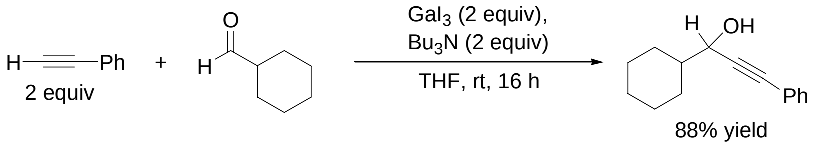


Figure 5. Representative alkynylation examples using $InBr_3$ as catalyst

1.6 Formation of propargylic alcohols mediated by Gallium(III) compounds

The pioneering work using gallium(III) compounds for alkynylations of aldehydes has been described by Huang et al. in 1995.[45] They used *in situ* generated GaI_3 in combination with an amine to convert aliphatic and aromatic aldehydes to the corresponding ynols at room temperature. The reaction is chemoselective in the presence of other functional groups such as olefin, esters, and nitro groups (Scheme 17), but not catalytic and requires overstoichiometric amounts of gallium salt and shows a remarkable solvent effect; in the presence of CH_2Cl_2 as solvent only enones could be isolated as reaction products.



Scheme 17. Alkynylation of cyclohexyl carbaldehyde utilizing GaI_3

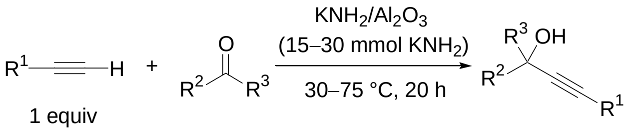
In 2008 Zhu and coworkers described an efficient and facile addition reaction of **6** to aldehydes using trimethylgallium.[77] At room temperature various aromatic and aliphatic aldehydes could be converted to the corresponding alkynols in good to excellent yields up to 98%. The reaction is also not catalytic and requires 3 equivalents of the gallium compound.

1.7 Alkaline bases as reaction promoters

The use of common bases like alkaline hydroxides as activating reagents for alkynylation reactions was primarily introduced by Favorskii in 1905.[29, 35] In general, such moderately strong bases like alkaline hydroxides and comparable alkoxides should not be able to form an acetylide anion from an alkyne (pK_a~25). Surprisingly, the observed reaction of ethyne with various aldehydes and ketones mediated by KOH in liquid ammonia, resulted in the formation of propargylic alcohols. Exploratory mechanistic suggestions by Favorskii implied addition of potassium hydroxide to the carbonyl compound and subsequent reaction with the terminal acetylene and libration of the free base. This proposed mechanism could not be validated because the postulated intermediate composed of KOH and carbonyl compound could not be isolated. Later on Bergmann favored an alkynylation route involving formation of potassium acetylide and subsequent reaction with the carbonyl compound.[78] 50% aq. KOH for example is able to deprotonate even allyl benzene with a pK_a of about 34 in a two phase system where the hydration sheath is nearly lost.[79-81] Nevertheless, this proposed mechanism did not explain the failure of NaOH to catalyze this reaction, although sodium acetylide was known to react easily with various carbonyl compounds. Indeed, this reaction does not involve an acid–base equilibrium forming a potassium acetylide; rather, the reaction is assumed to proceed through the formation of a potassium hydroxide-acetylene complex.[35] To date, several methods exploit these mechanistic findings by using simple, alkaline bases. Even though applicability and deployment of simple alkaline bases have useful practical advantages concerning safety, cost and complexity, asymmetric synthesis with such reagents performing addition reactions to C=O electrophiles has been, to date, elusive.

1.7.1 Solid base catalyzed reactions

In 1999 Baba et al. introduced a two phase system consisting of substoichiometric amounts of alkaline bases (KNH_2, $CsOH\cdot H_2O$, KOH, Cs_2CO_3) on Al_2O_3 as solid phase and the reactants (carbonyl compound/alkyne) as liquid phase. It emerged that the catalytic system KNH_2/Al_2O_3 is the most effective. In the presence of the strong solid base aliphatic ketones could be transformed to the corresponding propargylic alcohols (Scheme 18). Representative is the reaction of phenylacetylene (**6**) with cyclohexanone (**18**) to give 1-(phenylethynyl)-cyclohexan-1-ol (**19**) in 87% yield. The reaction is limited to aliphatic ketones; alcohols derived from aromatic aldehydes, for example, undergo rearrangements to the corresponding *α,β*-unsaturated ketones under the presented reaction conditions. When phenylacetylene (**6**) was used chalcones were the final products. Reactions using aliphatic aldehydes as electrophiles were not shown.

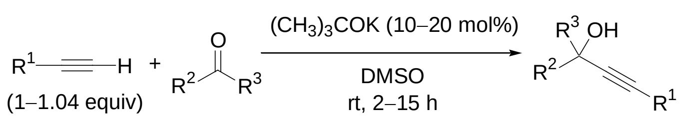


	ketone	yield [%]
R^1= Ph	cyclohexanone	87
R^1= Ph	pentane-3-one	36
R^1= Ph	cyclopentanone	1
R^1= C_4H_9	cyclohexanone	51
R^1= $Si(CH_3)_3$	cyclohexanone	27
R^1= *t*Bu	cyclohexanone	7

Scheme 18. Reactions of terminal alkynes with ketones catalyzed by KNH_2/Al_2O_3

1.7.2 Alkoxide-catalyzed alkynylation reactions

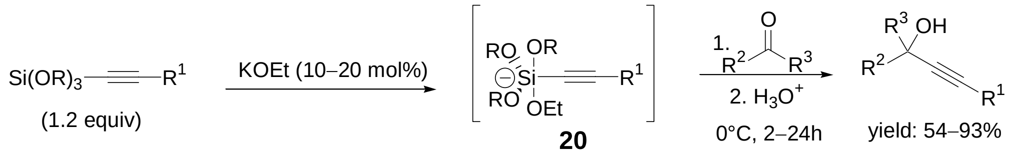
The use of *t*BuOK as base was reported by Babler et al. in 1996. The economical and simple method is based on the known equilibrium acidities of **6**, **18** and *tert*-butyl alcohol measured in DMSO as reaction medium.[21, 82] Similar to the methodology described in **1.7.1** only ketones could be transformed to the desired alkynols (Scheme 19). Attempts to functionalize enolizable aldehydes led to complex mixtures of products.



	ketone	yield [%]
R^1=$CH_3(CH_2)_5$	*c*-hexanone	80
R^1=$HO(CH_3)_2$	3-pentanone	70
R^1=CH_2OTHP	*c*-hexanone	91

Scheme 19. Alkoxide catalyzed alkynylation reaction

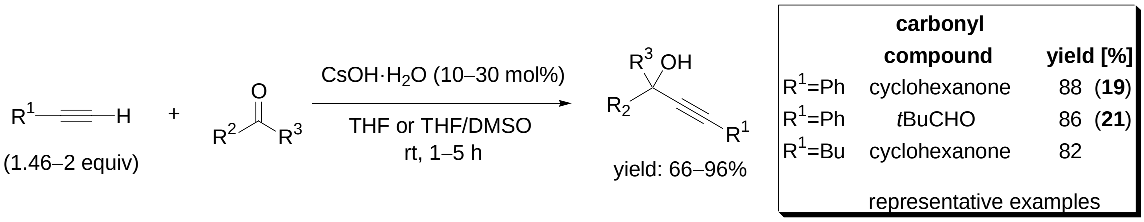
In 2005 Scheidt et al. introduced a different, very effective route for alkynylation reactions of aliphatic/aromatic aldehydes and ketones using simple alkoxides as Lewis bases in combination with trialkoxysilylalkynes (Scheme 20).[83] The described reaction was proposed to run through a reactive hypervalent silicate intermediate (**20**) with formation of an activated carbon nucleophile that subsequently undergoes addition to the carbonyl compound. Utilizing this methodology no undesired aldol by-products were observed with enolizable ketones or aldehydes, indicating the relatively mild reaction conditions compared to standard metallated alkynes.



Scheme 20. Lewis base-catalyzed additions of trialkoxysilylalkynes to carbonyl compounds

1.7.3 Alkynylation reactions using cesium hydroxide as catalyst

The use of catalytic quantities of $CsOH{\cdot}H_2O$ to effect addition reactions of terminal alkynes to carbonyl compounds was described by Knochel et al. in 1999.[22] Herein secondary and tertiary aliphatic aldehydes as well as aliphatic ketones could be successfully converted to the corresponding propargylic alcohols in good to excellent yields at appropriate reaction times. Reactions were carried out either in THF or THF/DMSO as solvent (Scheme 21). Whereas more acidic alkynes react in the presence of less polar THF, less acidic alkynes need a more polar medium for the desired addition reactions. The reaction product of pivalic aldehyde with **6**, **21** was isolated in 86% yield and **19** in 88% yield. To avoid formation of aldol products, slow addition of the aldehyde was performed (syringe pump, 0.5 mL/h). Under these conditions the deployed alkynes underwent clean additions to secondary or tertiary aliphatic carbonyl compounds. Functionalizations of aromatic carbonyl compounds were not reported.



carbonyl compound		yield [%]
R^1=Ph	cyclohexanone	88 (**19**)
R^1=Ph	*t*BuCHO	86 (**21**)
R^1=Bu	cyclohexanone	82

representative examples

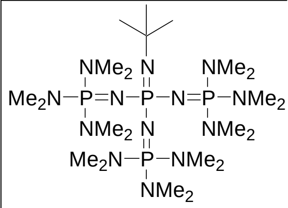
Scheme 21. Functionalization of aliphatic aldehydes and ketones using $CsOH{\cdot}H_2O$

1.8 Alkynylation reactions using non-metal catalytic systems

Only few efforts have been made to develop alkynylation methodologies with C–C bond formation utilizing non-metallic catalysts. Suitable organic molecules are quaternary ammonium hydroxide salts as well as phosphorus containing compounds that have been successfully used in organic synthesis.[84-92] Contrary to the above presented reactions using simple alkaline bases, such more specified molecules/salts are predestined to introduce chiral information due to their versatile structures with smooth generation of an asymmetric ammonium species.

1.8.1 Phosphazene bases as reaction promoters

In 1996 Schwesinger et al. introduced a new kind of extremely strong, uncharged, metal free polyaminophoasphazene bases with high sterical hindrance.[93] Kondo and coworkers adopted this concept in 2004 and developed an alkynylation protocol using *t*-Bu-P4 Base (3-(*tert*-butylamino) -1,1,1,5,5,5-hexakis (dimethylamino)-3-{[tris-(dimethylamino)phosphoranylidene]amino}-1λ^5-5λ^5-tri phosphazadien) (**22**) as catalyst.[94] However, no isolated product yields were presented and only acetone and pivalic aldehyde were utilized in combination with phenylacetylene (**6**).



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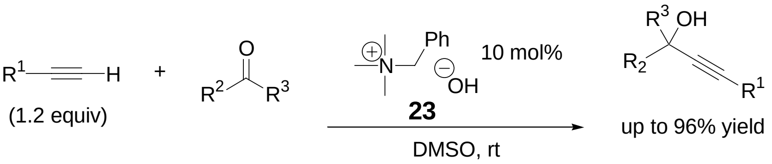
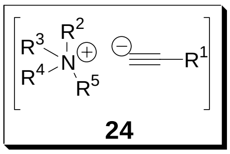
1.8.2 Quaternary ammonium hydroxide base-catalysts

Saito and coworkers showed that tetraalkylammonium hydroxides (namely Triton B™, [**23**]) in DMSO permitted the addition of terminal acetylenes to aldehydes and ketones in yields up to 96% (Scheme 22) at room temperature.[25] Formation of propargylic alcohols derived from cyclic/linear aliphatic ketones, as well as aliphatic aldehydes were reported.

Representative examples are the formation of **19** in 95% or **21** in 96% yield. Although the selected reaction conditions are comparably mild and tolerable to enolizable carbonyl compounds, propargylic alcohols derived from aromatic aldehydes could only be isolated in low to moderate yields (26–38%) when catalytic amounts of **23** (10 mol%) were used. Instead *E*-chalcones were formed after long reaction times in low to good yields (12–85%). The relevant rearrangement is postulated to be catalyzed by the deployed Lewis base (Scheme 23). The alkynylation reaction is proposed to run via formation of an ammonium acetylide as reactive intermediate (**24**) at which the large soft cation stabilizes the formed tight ion pair. In general, ammonium hydroxide salts are not air stable and cannot be educed. So the utilized catalyst has to be synthesized *in situ* or a formerly prepared solution of the adequate ammonium salt must be on-hand.



Scheme 22. Alkynylation reactions permitted by Triton B™



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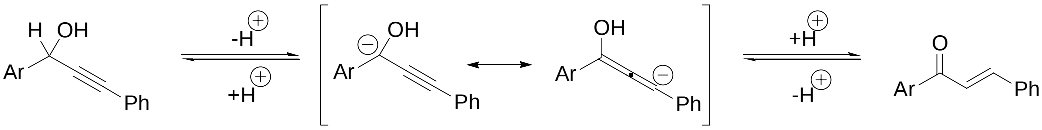


Scheme 23. Formation of chalcones from phenylacetylene (**6**) and aromatic aldehydes

1.9 Summary and Outlook

Recent and established developments in the area of alkynylation reactions of aldehydes and ketones have been presented. The inherent ability of terminal alkynes to undergo metalation under mild, controlled reaction conditions compatible with a host of electrophiles renders this functional group an alluring target for organic synthesis. Various methodologies utilizing alkyl metal compounds or metal salts in combination with a chiral ligand are used to transform aldehydes and ketones to the desired propargylic alcohols. Modulations of these methods to effect ligand-accelerated stereoselective additions to C=O offer new potentials for the synthesis of enantiopure alkynols. Virtually none of the established transition metal-catalyzed protocols are universally applicable to aliphatic as well as aromatic aldehydes and ketones. On the other hand simple procedures utilizing cheap and easy manageable alkaline bases are comparable concerning reactivity and tolerance but afford no chiral induction. Chiral ammonium salts could be the solution to overcome this limitation by using a phase-transfer catalytic system generating the active ammonium hydroxide *in situ* and get rid of metal-containing catalytic systems.

2. Alcoholysis of Epoxides

2.1 Introduction

Epoxides are among the most versatile compounds in organic chemistry. They are not only important synthetic products,[95-99] but also key intermediates for further transformations.[100] The high ring strain of epoxides (~27 kcal/mol)[101] allows ring-opening reactions with a variety of neutral[102-109] and charged nucleophiles[102-104, 110-120] and provides access to a broad spectrum of valuable intermediates; the addition of alcohols leads to the synthetically important class of β-alkoxy alcohols[103, 104, 110, 121-130] and is a widely studied reaction. Due to the poor nucleophilicity of alcohols activation of the epoxide functionality is necessary. Classical methods are the utilization of Brønsted[131-135] or Lewis acids[103, 104, 121-126, 136, 137] with activation of the basic epoxide oxygen and subsequent ring opening with the nucleophile or Lewis bases that add in the first step to the electrophilic ring-carbon center with formation of an opened alkoxide and adjacent substitution with the nucleophile. The use of strong mineral acids is naturally limited to acid-stable compounds and Lewis acids require stoichiometric quantities. Nature, however, uses an entirely different path for oxirane hydrolysis, which is key for removing unsaturated toxic organic compounds through epoxidation and subsequent hydrolysis.[138] There are numerous enzymes that catalyze this reaction,[139-144] and a common motif is the activation of the epoxide through double hydrogen bonding to, e.g., tyrosine residues (Figure 6).[145] Such enzymatic ring opening reactions are mild but also often sensitive towards p*H* and solvent.[146-149]

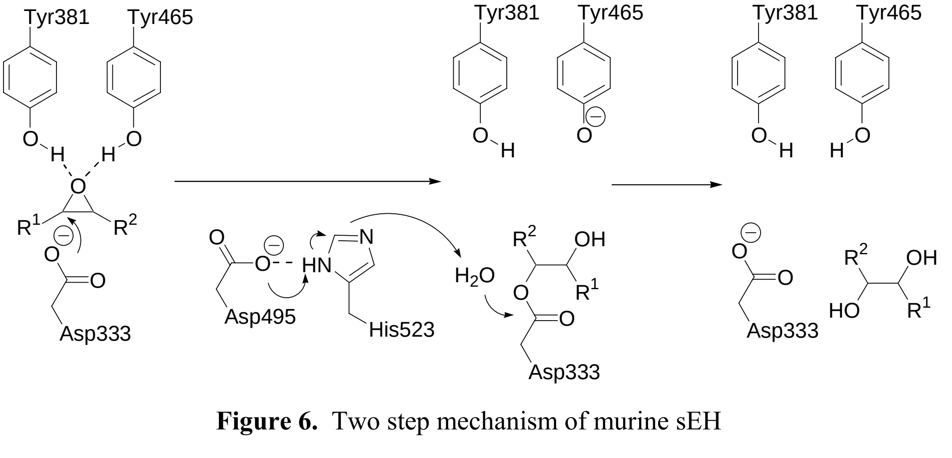


Figure 6. Two step mechanism of murine sEH

Recent developments in the field of organocatalysis in particular hydrogen-bonding organocatalysis describe the use of a *cooperative* system for epoxide ring openings with strong nucleophiles in the presence of water with approximately neutral p*H*.[150] Such reaction conditions are also key factors in THP-templated epoxide openings in cascade reactions leading to structures akin to Brevetoxin A.[149] Based on these findings an alternative approach for organocatalytic alcoholysis of styrene oxides that relies on using *two* cooperative hydrogen-bonding catalysts was developed.[151]

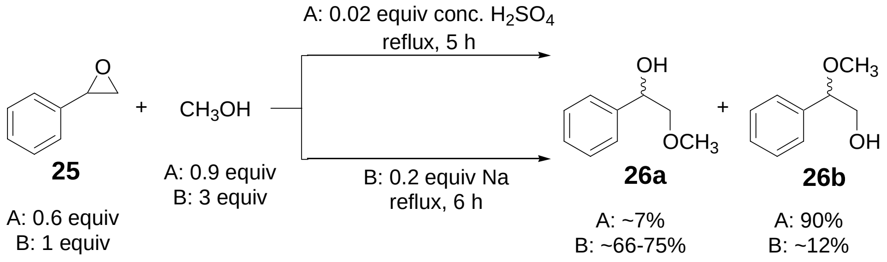
Despite the resounding achievements of these catalytic processes, important limitations are caused by the mechanistic key aspects of the S_N2-type (sometimes called a borderline S_N2 reaction) [152] ring opening reactions. Besides desymmetrizations of *meso*-epoxides and kinetic resolutions[100, 153, 154] it is difficult to obtain enantiopure products by simple addition reactions of nucleophiles to unsymmetric racemic epoxides.

2.2 Established methods for alcoholysis of epoxides

Nucleophilic additions to unsymmetric epoxides, e.g. styrene oxide can afford two regioisomers as reaction products. As the alcoholysis of epoxides requires an acid catalyst for efficient ring opening processes due to the weak nucleophilicity of alcohols the preferred site of attack utilizing unsymmetric epoxides is the carbon center which best can accommodate a positive charge, i.e., the benzylic position in case of styrene oxides. In most cases higher temperatures were required for such alcoholysis reactions including extensive polymerization reactions. Besides simple Brønsted acids including protonation of the basic epoxide oxygen Lewis acids are commonly utilized.

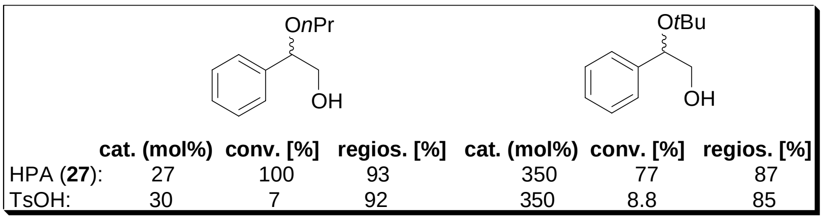
2.3 Epoxide ring opening reactions mediated by Brønsted acids

Classical Brønsted acid catalyzed alcoholysis of epoxides in particular alcoholysis of styrene oxide (**25**) was first studied by Emerson et al. in 1945.[155] In 1950 Reeve and Christoffel examined the reaction of **25** with methanol in the presence of sulfuric acid and in the presence of sodium methoxide.[133] Dependent on the utilized method either regioisomer **26a** or **26b** was the major product (Scheme 24). Acid catalyzed reaction provides mainly the 2-methoxy-2-phenylethanol (**26b**) whereas the methoxide promoted reaction furnishes the regioisomer **26a**. Further investigations using other aliphatic alcohols gave the same results. Surprisingly the acid catalyzed conversion of allyl alcohol with **25** furnished the 2° alcohol.



Scheme 24. Methanolysis of styrene oxide utilizing sulfuric acid and sodium methoxide as catalysts

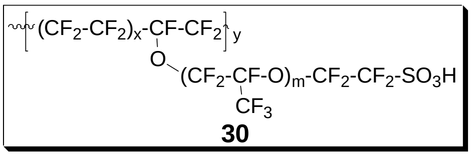
The disadvantages of conventionally utilized acids like sulfuric acid, perchloric acid and *p*-toluenesulfonic acid are the required harsh reaction conditions (reflux) and the resulting polymerization. Furthermore, the reaction rates are slow and decrease rapidly with the elapse of time. On this account Hayashi and coworkers introduced heteropoly acids (HPA) as catalysts for the alcoholysis of epoxides.[135] The HPA catalysts employed were 12-tungstophosphoric acid ($H_3PW_{12}O_{40}$, **27**), 12-molybdophosphoric acid ($H_3PMo_{12}O_{40}$, **28**) and 12-tungstosilicic acid ($H_4SiW_{12}O_{40}$, **29**). Those were found to catalyze the alcoholysis of epoxides more efficiently than the conventional acid catalysts at 45 °C in a homogeneous liquid phase at similar catalyst loadings (Figure 6). Conversions of aliphatic epoxides like 1,2- epoxybutane or 2-methylpropene oxide with 1-propanol and *tert*-butanol afforded the other regioisomer with terminal addition of the alcohol and formation of the 2° alcohol with 64–99% regioselectivity. An exception was the reaction of 1-propanol with 2-methylpropene oxide with formation of the 1° alcohol (84% selectivity).



	cat. (mol%)	conv. [%]	regios. [%]	cat. (mol%)	conv. [%]	regios. [%]
HPA (**27**):	27	100	93	350	77	87
TsOH:	30	7	92	350	8.8	85

Figure 6. Alcoholysis of styrene oxide catalyzed by HPA and TsOH

In 1981, Olah and coworkers presented a methodology that utilized Nafion-H (perfluoralkanesulfonic acid resin, **30**) as an effective catalyst for hydration and methanolysis of epoxides.[134] Aliphatic as well as aromatic epoxides were successfully converted to the corresponding *ß*-methoxy alcohols in good yields and moderate regioselectivities. Conversion of **25** with methanol afforded 81% yield of the primary *ß*-methoxy alcohol (**26b)** (Scheme 24). This methodology provides



$$\left[(CF_2\text{-}CF_2)_x\text{-}CF(O\text{-}(CF_2\text{-}CF(CF_3)\text{-}O)_m\text{-}CF_2\text{-}CF_2\text{-}SO_3H)\text{-}CF_2\right]_y$$

30

mild reaction conditions (rt) and a simple workup; the catalyst could be readily regenerated for further utilization without loss of activity.

2.4 Lewis acid catalyzed alcoholysis of epoxides

Besides BrØnsted acids Lewis acids are often utilized to transform epoxides to the corresponding *ß*-alkoxy alcohols. Simple metal salts (**31**, **32**, **35**), HPA-salts (**36**), boron compounds (**33**, **34**) as well as transition metal complexes (**37**, **38a**, **38b**, **39**) are commonly implemented (Figure 7). The methanolysis of (*R*)-**25** catalyzed by **31** afforded complete regioselectivity with nucleophilic attack at the benzylic position with inversion of the configuration at the benzylic carbon due to S_N2-type stereochemical course, affording (*S*)-**26b** in 88% yield and 95% *ee*.[137]

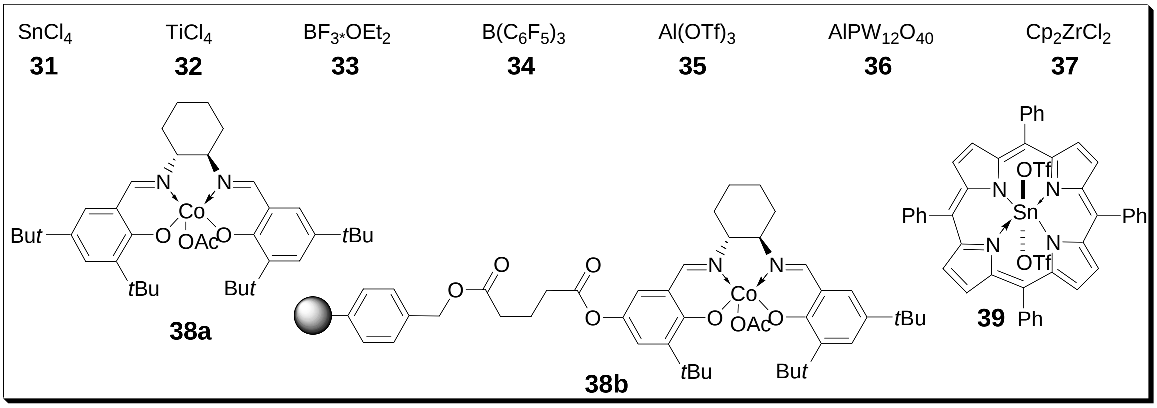
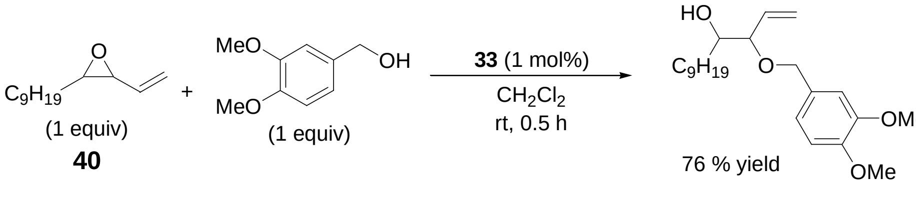


Figure 7. Established Lewis acids for alcoholysis reactions of epoxides

Boron trifluoride (**33**) has been utilized by Heck and coworkers to convert 3,4-epoxy-tridec-1-ene (**40**) to *ß*-hydroxy allyl-ethers.[121] The reaction was carried out at room temperature with 1 mol% of catalyst **33** in dichloromethane (Scheme 25). The reaction is stereospecific and leads in all cases to nucleophilic addition at C3. Utilization of other Lewis acids, such as $MgBr_2$ or Ti(O*i*Pr)$_4$ gave a rapid and complete degradation of the vinyl epoxide.



Scheme 25. Lewis acid-catalyzed regiospecific opening of 3,4-epoxy-tridec-1-ene with 3,4-dimethoxybenzyl alcohol

Variations of the regioselectivity for methanolysis reactions utilizing **33** as catalyst were obtained by Engel et al. when terminal epoxides were used that bear different functional groups.[136] Epoxide systems with a substituent providing particular stabilization of positive charge by delocalization, e.g. **25**, form exclusively the 1° alcohol (**26b**) with nucleophilic attack at the internal position. Alkyl groups lead to a mixture of both regioisomeres whereas epoxides with a substituent disfavoring a positive charge lead to formation of the 2° alcohol by attack on the terminal site of the epoxide ring (Figure 8).

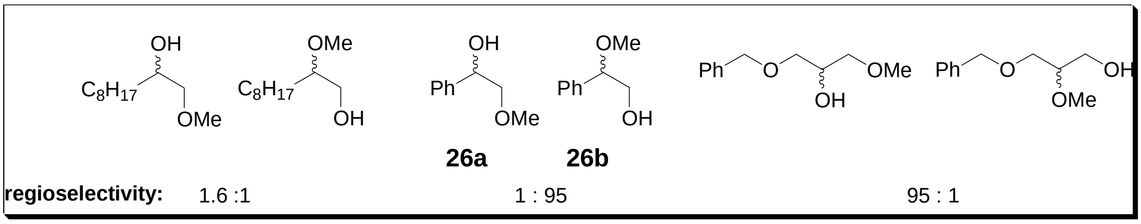


Figure 8. Substrate depending regioselectivity of terminal epoxide methanolysis utilizing boron trifluoride as catalyst

An effective protocol for epoxide cleavage with allyl and propargylic alcohols utilizing tris-(pentafluorophenyl)-borane (**34**) as catalytic additive (5 mol%) was developed by Chandrasekhar and coworkers.[122] Various epoxides including acid labile substrates with, e.g. THP-protected alcohol functionalities underwent alcoholysis under mild reaction conditions in high yields (Figure 9). Regioselectivities observed were similar to those shown in Figure 7 when **33** was used.

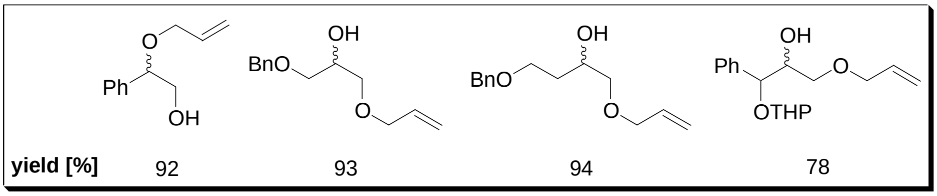


Figure 9. Representative examples for epoxide cleavage reactions using allyl alcohol as nucleophile and tris-(pentafluorphenyl)-borane as catalyst

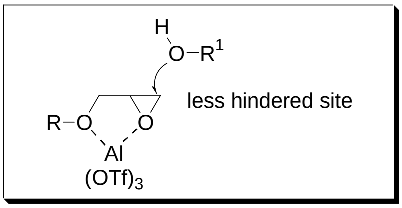


Figure 10. Chelate complex of glycidyl ether and catalyst $Al(OTf)_3$

Another very effective Lewis acid catalyst for ring opening reactions of epoxides with alcohols, $Al(OTf)_3$ (**35**), was found by Williams and coworkers.[124] A variety of epoxides were transformed to the anticipated products in good yields utilizing a range of alcohols and very low catalyst loadings (0.05–0.04 mol%). Transformation of glycidyl ethers to the corresponding *β*-alkoxy alcohols formed exclusively the 2° alcohol with nucleophilic attack at the less hindered carbon center. Proposed explanation for this regioselectivity is a formed bidentate chelate complex (Figure 10) formed by **35** and the glycidyl ether with decrease of Lewis acidity of the metal and thus allowing steric effects to get more dominant.

HPA compounds have given proof of being effective Brønsted acid catalysts for ring opening reactions of epoxides with alcohols (see **2.3**). The use of HPA salts (**36**) as Lewis acid catalysts for this type of reaction has been introduced by Firouzabadi and coworkers in 2006.[104] This heterogeneous reaction variation afforded high yields for the alcoholysis of, e.g. **25** with various alcohols with high regioselectivity at room temperature. 1–13 mol% of catalyst was used depending on the nature of the epoxide and the alcohol. Bulky alcohols like 2-propanol or *tert*-butanol required 2 mol% of **36**, whereas in case of methanol only 1 mol% was needed when **25**, simple aliphatic or cyclic aliphatic epoxides were transformed (Figure 11). Reaction of *R*-(+)-**25** with methanol in the presence of 1 mol% **36** at 0 °C afforded the product (*S*)-**26b** with 89% *ee* and affirms the S_N2-type course of reaction. The catalyst **36** could be quantitatively recovered and reused after drying.

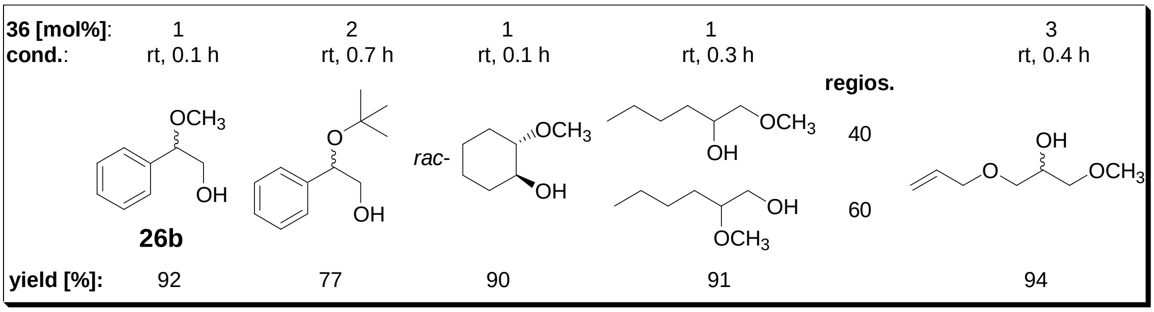
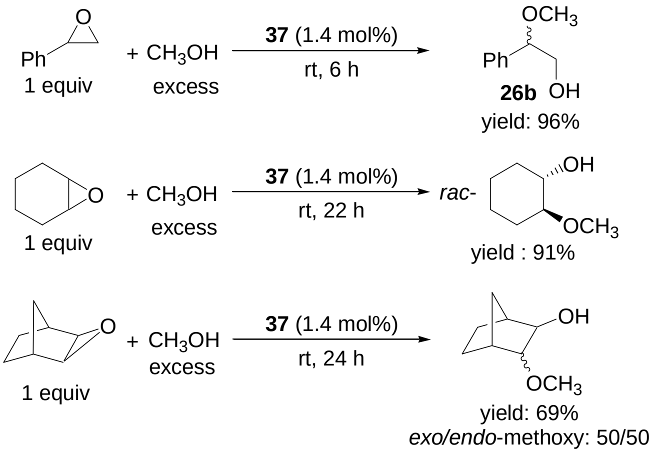


Figure 11. $AlPW_{12}O_{40}$ (**36**) as reusable Lewis acid catalyst: selected examples

Zirconocenes such as **37** (see **1.4.2**) are universally applicable compounds and have been used inter alia for polymerization reactions.[156, 157] In 2003 Kantam et al. reported a highly efficient **37**-catalyzed ring opening reaction of 1,2-epoxides based on styrene, cyclohexene, norbornene, and *trans*-stilbene, in the presence of a variety of alcohols.[123] The reaction proceeded with very small amounts of the catalytically active species **37** and afforded good to excellent yields with high regio- and stereoselectivity (Scheme 26). In case of *exo*-norbornene oxide a mixture of *exo*- and *endo*-methoxy isomers in the ratio 50:50 was obtained as a consequence of this reaction following an S_N1 mechanism.



Scheme 26. Cp_2ZrCl_2-catalyzed reaction of 1,2-epoxides with methanol

Metalloporphyrins are known to act as effective Lewis acids and have been successfully used for different transformation reactions.[158-160] Moghadam and coworkers utilized **39** for rapid and efficient alcoholysis of various epoxides with primary, secondary and tertiary alcohols, affording the corresponding *ß*-alkoxy alcohols.[103] The reactions of cyclohexene oxide gave the *trans*-product exclusively with yields from 98–99% within 5–20 minutes (rt to reflux) and a catalyst loading of 1.9 mol%. **25** gave the 1° alcohol with 85–99% yield under equal reaction conditions. Regioselectivities obtained for transformations of glycidyl ethers and simple aliphatic 1,2-epoxides were identical to those observed by other groups (Figures 8, 9, 11).

Kinetic resolutions of terminal epoxides have been observed when Jacobsen´s cobalt-salen complex (**38a**) or an immobilized variation of this catalyst ((*R,R*)-**38b**)[161, 162] was utilized as reaction promoter.[126, 163] A series of terminal epoxides were screened in the kinetic resolution with phenol. Both electron rich and electron poor epoxides as well as

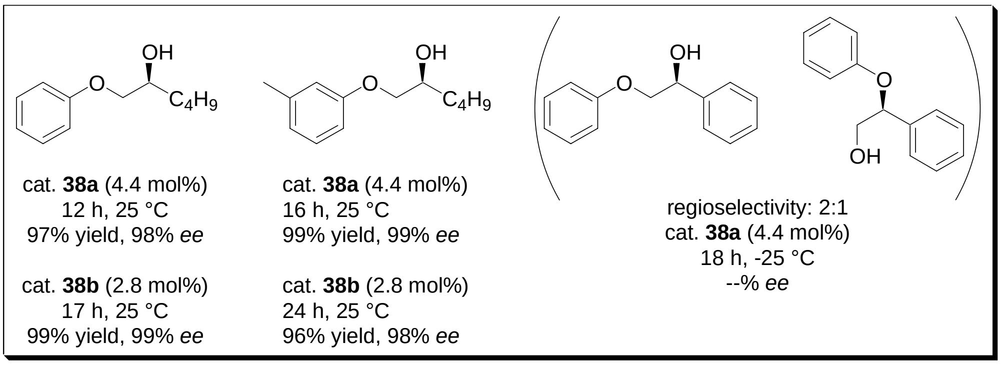


Figure 12. Kinetic resolution of 1,2-epoxides with phenols catalyzed by Co(III)-salen complexes

epoxides with a range of steric properties reacted with complete regioselectivity to provide the desired *α*-aryloxy alcohols in high yields and *ee*'s (Figure 12). Mechanistic investigations indicated a rare example of a five-coordinate square pyramidal cobalt-aryloxide complex with a molecule of phenol hydrogen-bonded to the alkoxide oxygen (Figure 13). Stoichiometric aryloxide transfer from this complex to the epoxide provided the corresponding *α*-aryloxy alcohol as the sole product.

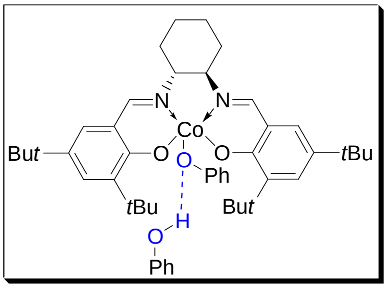
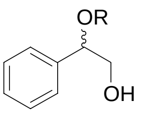


Figure 13. Hydrogen-bonded phenol

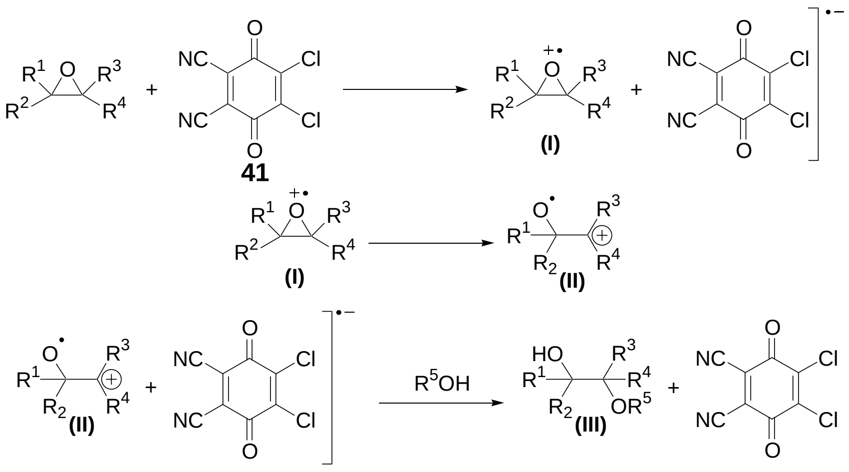
2.5 "*π*-Acids" as catalysts for alcoholysis of epoxides

Concerning the limitations of early reaction protocols utilizing simple Brønsted acids to convert only primary alcohols with epoxides to the corresponding *β*-alkoxy alcohols a completely different kind of catalysts, so called *π*-acids, were introduced. In 1990 Iranpoor and coworkers utilized DDQ (1,3-dichloro-5,6-dicyano-*p*-benzoquinone, **41**) as one-electron acceptor for ring opening reactions of epoxides with primary, secondary, and tertiary alcohols as nucleophiles.[127] The methodology is highly regioselective, involves neutral reaction conditions and was carried out without additional solvent and catalyst loadings of 20–60 mol% at room temperature or reflux (Figure 14). The proposed mechanism starts with an initial SET to form an epoxonium radical cation (**I**) and a DDQ radical anion followed by ring opening and subsequent addition of the nucleophile (R^5OH) to the carbenium ion. Adjacent electron transfer regenerates the catalyst (**41**) and forms the desired alkoxy alcohol (Scheme 27).



R	cat. [mol%]	yield [%]	reaction time [h]	cond.
CH_3	20	94	0.5	rt
C_2H_5	20	91	1	rt
$(CH_3)_3C$	20	80	6	reflux

Figure 14. Representative examples for alcoholysis products of styrene oxide utilizing DDQ as catalyst



Scheme 27. Proposed mechanism for alcoholysis of epoxides using DDQ as catalyst

The same principle was deployed by Masaki in 1993 by utilizing TCNE (tetracyanoethylene, **42**) as *π*-acid catalyst.[164] The reaction allowed alcoholysis reactions of epoxides at ambient temperatures to 40 °C in good yields and tolerance towards acid labile substrates combined with high regioselectivity (Figure 15). In case of **25** only primary alcohols were obtained whereas aliphatic epoxides gave both regioisomers (**43a**, **43b**). Epoxides bearing an etheric oxygen function at the remote position on the side chain by three methylene units from the epoxide part afforded mainly the primary alcohol due to anchimeric assistance (**44a**, **44b**).[165-167]

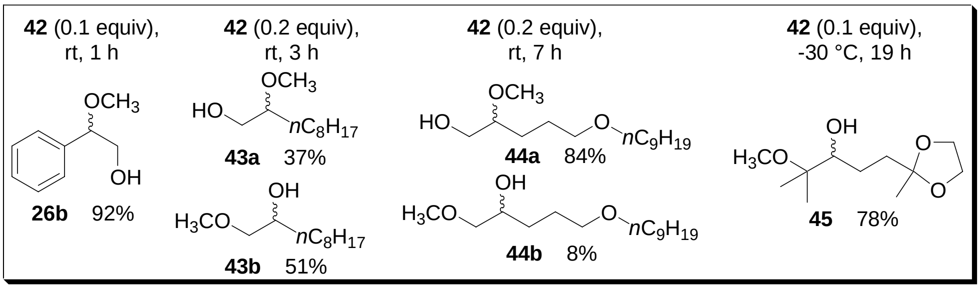


Figure 15. Selected examples for TCNE catalyzed epoxide alcoholysis

2.6 Summary and Outlook

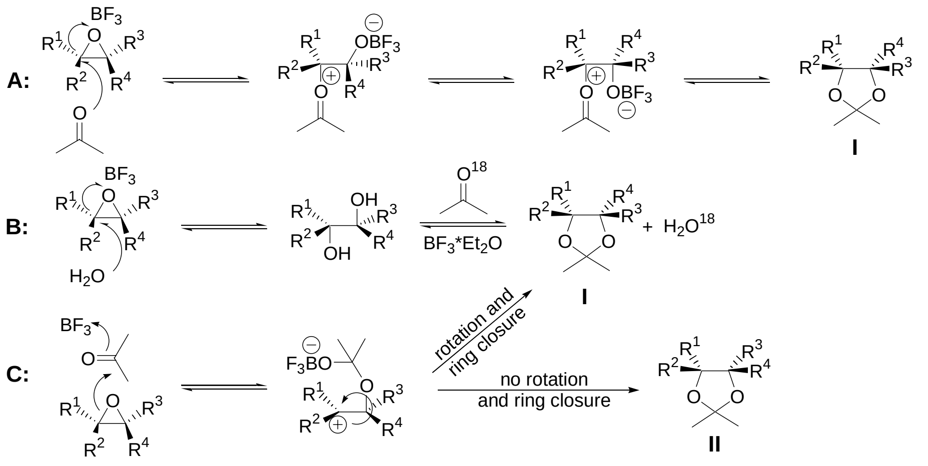
A variety of established methodologies for the alcoholysis reactions of epoxides have been presented. This reaction depicts an important transformation reaction that provides *ß*-alkoxy alcohols as versatile reaction intermediates with a free hydroxy group as a handle for further manipulations. As alcohols behave as poor nucleophiles in such substitution processes the methodologies applied reach from simple BrØnsted acid catalysis to SET involving redox processes. Strongly acidic conditions provide a powerful entry to the desired products but limit the palette of substrates due to harsh reaction conditions. Lewis acids are more tolerant towards acid labile substrates and minimize side reactions such as polymerizations of the applied epoxide. Metal free π-acid catalyzed reactions with an initial SET process are highly tolerant towards acid labile substrates but require higher amounts of the utilized catalyst and are less effective. All established reaction methodologies afforded high regioselectivities for the alcoholysis reactions of **25** or glycidyl ethers with formation of one privileged regioisomer, whereas transformation of simple unsymmetric aliphatic epoxides gave mixtures of both isomers.

Besides regioselectivity stereochemical aspects for this alcoholysis reaction are of great interest. Due to the S_N2-akin reaction type with inversion at the attacked carbon center, all presented protocols afforded only racemic mixtures of the formed products. Chiral Lewis acids led to desymmetrizations in case of *meso*-epoxides and kinetic resolutions when unsymmetric racemic epoxides were implemented. On this account a methodology is desirable that combines highly effective regioselective alcoholysis with enantioselective conversion under mild reaction conditions. Recent developments in organocatalysis using (double) hydrogen bonding for activation of electrophiles are promising alternatives.

3. Formation of 1,3-Dioxolanes

3.1 Introduction

1,3-dioxolanes are known transformation products of epoxy compounds, which are formed in the presence of Lewis acids.[103, 168-183] Formation of such acetals is a commonly used method for protecting carbonyl groups during the course of organic synthesis. Furthermore 1,3-dioxolanes are useful building blocks in synthetic chemistry as equivalents for 1,2-diols and have been applied for synthesis of complex natural compounds.[184-191] First investigations on this remarkable reaction by Yandovskii et al. and the group of Blackett offered three possible mechanistic ways to form the desired 1,3-dioxolanes (Scheme 28)[168, 192]. Mechanism B could be excluded by the use of ^{18}O-labeled acetone and mechanism C should involve formation of the two possible isomers **I** and **II**. Since the transformation of *cis*-but-2-ene-oxide gave the corresponding *trans*-dioxolane and *trans*-but-2-ene-oxide afforded the *cis*-isomer, mechanism C could also be excluded.



Scheme 28. Mechanistic proposals for the formation of 1,3-dioxolanes

Formation of 1,3-dioxolanes is proposed to start with an activation process of the basic epoxide oxygen by the present Lewis acid followed by a nucleophilic addition of the utilized carbonyl compound. Subsequent rotation and ring closure combined with exit of the Lewis acid-catalyst leads to the expected isomer **I** (mechanism A). Many of the utilized Lewis acids are strong and therefore not suitable for the transformation of compounds bearing acid sensitive functional groups. On this account a more tolerant methodology is necessary to expand the spectrum of substrates.

4. Publications

4.1. Organocatalytic Alkynylation of Aldehydes and Ketones under Phase-Transfer Catalytic Conditions[A]

Torsten Weil[a] and Peter R. Schreiner*[a]

[A]Torsten Weil and Peter R. Schreiner: Organocatalytic Alkynylation of Aldehydes and Ketones under Phase-Transfer Catalytic Conditions, *Eur. J. Org. Chem.* **2005**, 2213-2217. Copyright WILEY-VCH Verlag GmbH & Co. KGaA. Reproduced with permission.

Keywords: Alkynylation / C–C coupling / Organocatalysis / Phase-transfer catalysis / Propargylic alcohols

We developed alkynylations of various aldehydes and ketones under practical phase-transfer conditions at room temperature. The straightforward methodology combines one-pot synthesis and simple workup with good to excellent yields for propargylic alcohols derived from aliphatic aldehydes and ketones. Even aromatic aldehydes and ketones could be transformed to the corresponding propargylic alcohols in somewhat lower yields. The yield depending on the amount of PT catalyst and NaOH concentration was also determined.

Introduction

The nucleophilic addition of alkynes to aldehydes and ketones is an essential organic C–C coupling reaction that provides propargylic alcohols as versatile intermediates for organic synthesis.[1, 2] Metal-catalyzed additions of alkynes to carbonyl compounds with stoichiometric amounts of organometallics (e.g., organolithium, Grignard reagents) are typically employed. Only a few reports demonstrate the catalytic activation of an alkyne derivative and subsequent addition to a carbonyl compound.[3-7] These alternative routes involve either acid-base reactions of strong alkaline bases, or transition metal complexes

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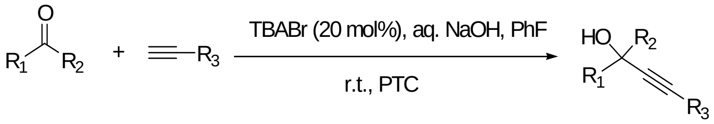
with the deployed alkyne. Virtually none of the published protocols are universally applicable to aliphatic as well as aromatic aldehydes and ketones. Using potassium *tert*-butoxide, only aliphatic ketones can be transformed to the corresponding propargylic alcohols with moderate to good yields,[7] whereas alkynylations, using zinc reagents, are limited to aldehydes, but give good to excellent yields.[5, 6, 8] $CsOH{\cdot}H_2O$ as the base can be used to transform aliphatic aldehydes and ketones into the resulting ynols also with good to excellent yields.[4] While zinc derivatives in conjunction with chiral ligands affect enantioselective alkynylations, reactions with alkali or earth alkali bases generally cannot be conducted in a stereoselective fashion.

A possible way to overcome these limitations has been the use of a nonmetallic ammonium base (triton B) as catalyst by Saito and coworkers: a variety of aldehydes and ketones were transformed into propargylic alcohols with moderate to good yields; propargylic alcohols derived from aromatic aldehydes showed significant base-catalyzed rearrangement to the respective chalcones.[3] As the *in situ* preparation of ammonium bases should simplify this procedure by not having to use DMSO as the solvent (from which the dimsyl anion may be generated *in situ*) and by having a straightforward two-phase separation, we envisioned a phase-transfer catalytic (PTC) protocol for this reaction.

Results and Discussion

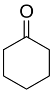
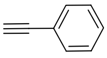
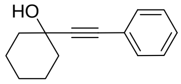
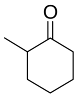
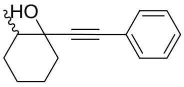
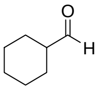
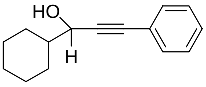
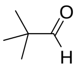
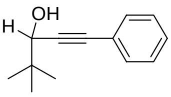
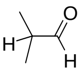
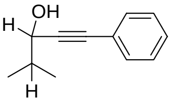
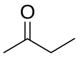
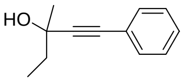
The use of strong alkaline bases for the title reaction is not new. The original report on this type of transformation – often referred to as the “Favorskii reaction”– utilizes KOH;[9, 10] This reaction does not involve an acid–base equilibrium involving a potassium acetylide; the reaction is assumed to proceed through the formation of a potassium hydroxide –acetylene complex.[10] Knochel et al. showed that the more soluble $CsOH{\cdot}H_2O$ can also be utilized.[4] Neither approach utilizes the PTC concept, and NaOH was deemed unsuitable as the base for this purpose.[10] Since we did not foresee any obvious problems with the use of NaOH as the inorganic base, in combination with a tetraalkyl ammonium salt as the PT catalyst, we put our proposal to test. Utilizing a two-phase system consisting of an aqueous sodium hydroxide layer, an organic layer with fluorobenzene and a quaternary ammonium salt as the PT catalyst, we developed a mild and efficient method for the organocatalytic alkynylation of a variety of aliphatic aldehydes and ketones (Scheme 1).

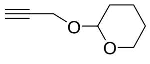
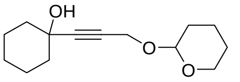
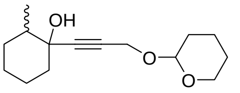
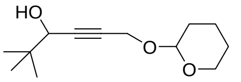
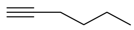
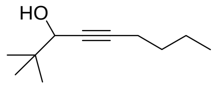
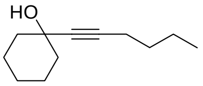
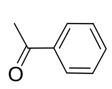
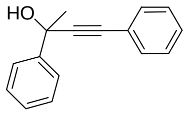
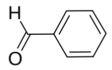
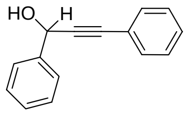
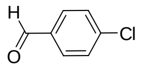
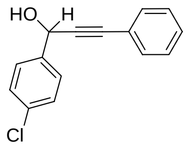


Scheme 1. General alkynylation conditions

The two-phase reaction conditions with relatively low base concentration in the organic layer reduce the formation of by-products resulting from aldol condensations or Cannizzaro reactions. Various aliphatic aldehydes as well as ketones (**1a–1f**) react cleanly with different alkynes (**2a–2c**) to give the corresponding propargylic alcohols (**3a–3k**, Table 1). Two slightly different methods A and B were employed; method A is typically used for aliphatic carbonyl compounds and acetophenones, whereas method B is more advantageous for aromatic aldehydes.

Table 1. PTC/organocatalytic alkynylation of selected aldehydes and ketones

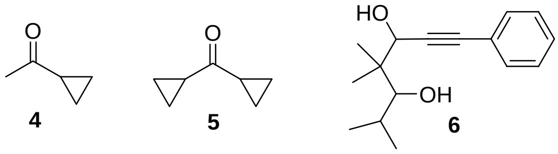
entry	carbonyl compound		alkyne		product		cond.[a] (time [h])	isol. yield [%]
1		**1a**		**2a**		**3a**	A (96)	88
2		**1b**		**2a**		**3b**	A (96)	87[b]
3		**1c**		**2a**		**3c**	B (72)	78
4		**1d**		**2a**		**3d**	A (48)	92
5		**1e**		**2a**		**3e**	A (48)	52
6		**1f**		**2a**		**3f**	A (96)	65

entry	carbonyl compound		alkyne		product		cond.[a] (time [h])	isol. yield [%]
7		**1a**		**2b**		**3g**	A (96)	51
8		**1b**		**2b**		**3h**	A (96)	50
9		**1d**		**2b**		**3i**[11]	A (72)	72
10		**1d**		**2c**		**3j**	A (72)	57
11		**1a**		**2c**		**3k**	A (96)	53
12		**1g**		**2a**		**3l**	A (48)	35
13		**1h**		**2a**		**3m**[12]	B (36)	30
14		**1i**		**2a**		**3n**[12]	B (36)	31

[a] Method A: 7 mmol alkyne, 8.4 mmol carbonyl compound, 1.4 mmol [20 mol%] TBABr; method B: 14 mmol alkyne compound, 7 mmol carbonyl compound, 1.4 mmol [20 mol%] TBABr. For details see experimental section. [b] 1:1 mixture of diastereomeric propargylic alcohols

Generally, the propargylic alcohols derived from aliphatic aldehydes and ketones with phenylacetylene were obtained in good yields; methods A and B gave similar results. As expected, aliphatic aldehydes react faster than aliphatic ketones; non-enolizable **1d** was converted fully after 24 h (at 100% catalyst loading). Even enolizable carbonyl compounds showed no significant aldol condensation, with *iso*-butyraldehyde being the only exception where we could isolate a by-product, identified as **6** (Scheme 2) in negligible amounts (~ 3%). Deactivated cyclopropyl ketones (**4** and **5**) showed little (20%) or no conversion, respectively.

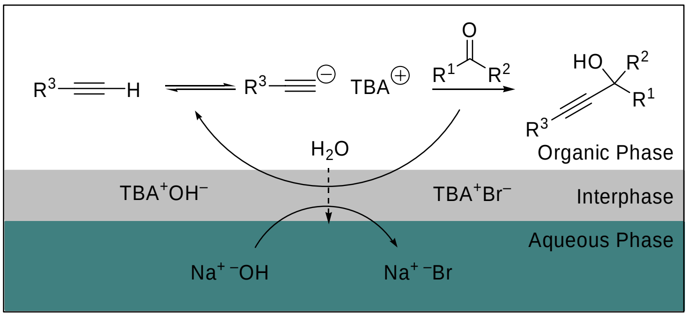
THP-protected propargylic alcohols as the alkyne component can also be utilized but give somewhat lower yields (entries 7–9). The resulting protected ynols with an additional functional group are also useful building blocks for organic synthesis. 1-Hexyne reacted slightly more effectively (entries 10 and 11).



Scheme 2

Aromatic ketones and aldehydes gave propargylic alcohols in moderate yields (entries 12–14), although this is not a problem of reactivity. Rather we found that under these conditions significant amounts of polymers and unidentified and inseparable by-products form.

Surprisingly little is known about phase-transfer catalytic mechanisms, probably owing to the fact that multicomponent mixtures are difficult to analyze.[13-16] As a working mechanistic hypothesis, we refer to Scheme 3 that shows the deprotonation of the alkyne, coordination to the PT-catalyst, and subsequent reaction with the carbonyl compound. With the available data we cannot distinguish between extraction and interphase mechanisms. The carbanion-ammonium ion pairs were also proposed in the reactions with triton B;[3] our present work lends further evidence to this mechanistic suggestion. We therefore addressed two key factors, namely the concentration dependence of the PTC-catalyst and base in these reactions.



Scheme 3. Proposed PTC alkynylation mechanism

The model reaction of cyclohexanone and phenylacetylene (entry 1) was optimized by varying parameters such as catalyst concentration (Figure 1a), concentration of sodium hydroxide (Figure 1b), reaction time, solvent, ratio of carbonyl compound and alkyne, and mode of addition. Using dichloromethane instead of fluorobenzene for entry 1 gave only 25% of **3a**. Fluorobenzene and toluene are suitable solvents for PTC reactions.[17] In our experience, the higher dipole moment of fluorobenzene facilitates the extraction of the ammonium compound into the organic phase; it also does not display many of the typical side reactions often observed in methylene chloride. Figure 1a demonstrates that the overall reaction *is* phase-transfer catalytic: while a minimum concentration of about 10 mol% is required for satisfactory yields within 24 h, it is noteworthy that the reactions do run to completion at any catalyst concentration (at the expense of longer reaction times). Apparently up to a catalyst concentration of ~10–15 mol% the rate limiting step is the transport of OH^- into the organic phase promoted by the PT catalyst. Higher catalyst concentrations result in a change of mechanism; the rate limiting step is now likely to be the nucleophilic addition of the acetylide anion to the carbonyl compound. From this point on an increase of catalyst concentration has only little effect.

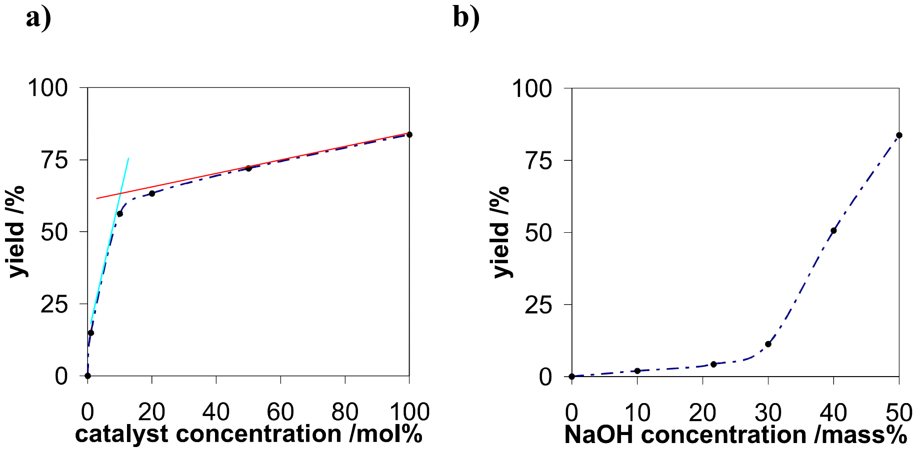


Figure 1. a) Yields of **3a** vs. concentration of phase-transfer catalyst TBABr [x mol%]; 50 mass% NaOH; reaction time 24 h. b) Yields of **3a** vs. NaOH concentration [y mass%]; 100 mol% catalyst; reaction time 24 h.

A practical protocol therefore utilizes 15–20 mol% PTC-catalyst and adjustable reaction times. As the *in situ* generation of the ammonium hydroxide takes place in form of equilibrium reactions at the phase boundary (Scheme 3),[18] its relative concentration in the organic phase depends on the absolute concentration of aqueous sodium hydroxide. This is evident from the yield dependence of **3a** on the NaOH concentration (Figure 1b) that must exceed 30 mass% for an efficient reaction to occur. For this purpose we determined the p*H* and thus the relative concentration of hydroxide anions in the organic phase with a simple experiment. We simulated the reaction conditions by stirring 10 mL of fluorobenzene, 10 mL 50% aqueous sodium hydroxide, and 3 mmol of TBABr for two hours to reach equilibrium. Then we separated the organic layer and extracted the dissolved salts with 10 mL of distilled water. Measuring the p*H* (12.51–13.05 ± 0.05) and the volume of the resulting aqueous phase (including the former interphase) and conversion to the volume of OH^- gave an average relative concentration of $c[OH^-] = 0.11$ mol/L. These experiments were repeated three times.

The hydroxide anion is much more basic in the organic phase than in water. Whereas an aqueous solution of NaOH (1 mol/L) deprotonates weak acids up to pKa ~14–15, the "naked" hydroxide ion is, owing to loss of its solvating water molecules, highly activated: extracted into the organic phase it is able to deprotonate reactants up to a pKa of about 35![17] Consequently alkynes with p*K*a of ~22–26 (phenylacetylene ~23.2–23.7[19]) are easily converted into their corresponding anions that can subsequently act as nucleophiles. This remarkably behaviour of OH^- is driven to extreme in PTC halogenation reactions of alkanes, where it functions even as electron donor, i.e., as a reduction agent.[17, 20-22]

Conclusions and Outlook

We present a mild and effective organocatalytic PTC protocol for the alkynylation of various aldehydes and ketones. Best results are obtained for aliphatic ketones and non-enolizable aldehydes; the alkyne component can be varied widely and can be aromatic or aliphatic. As the coordination between the PT-catalyst and the carbanion is implied in this and other PTC reactions, we also hope to develop stereoselective alkynylations.[23-25] Experiments in this direction are currently under way and will be reported in due course.

Experimental Section

All chemicals were purchased from Acros Organics, Aldrich, and Lancaster in highest purities available; liquid aldehydes were freshly distilled over a 10 cm Vigreux column prior use, solid aldehydes were used without further purification. Reactions were monitored with a HP 5890 GC spectrometer with a HP 5971 mass selective detector. ^{1}H-NMR and ^{13}C-NMR spectra were recorded with a Bruker AM 400 spectrometer using

TMS as internal standard; chemical shift values are given in ppm. IR spectra were measured with a Bruker IFS 25 spectrometer. Elemental analysis (CHN) was determined with a Carlo Erba EA 1106.

Method A: To an intensively stirred solution of 7 mmol alkyne compound, 8.4 mmol carbonyl compound and 1.4 mmol [20 mol%] TBABr in 5 mL of fluorobenzene, 5 mL of aqueous sodium hydroxide (50%) was added. After stirring for the corresponding reaction time mentioned in Table 1, 10 mL of water were added and the phases were separated. The organic layer was washed with water and brine and subsequently dried over anhydrous sodium sulphate. Filtration from the drying agent and removal of the solvent by distillation left in all cases a colored mixture of product, reactant and PT catalyst. The product was isolated by high-vacuum distillation or column chromatography (SiO_2/ EtOAc/hexane 1:3) to give the propargylic alcohols as colorless solids or colorless to slightly yellowish oils. All propargylic alcohols prepared are known in the literature.

Method B: To an intensively stirred mixture consisting of 14 mmol alkyne compound, 1.4 mmol [20 mol%] TBABr, 3 mL of fluorobenzene and 5 mL of aqueous sodium hydroxide (50%), a solution of 7 mmol carbonyl compound in 2 mL of fluorobenzene was added over a period of 2 hours via an addition funnel. Reaction time and workup are identical to method A.

Side product (new compound):

1-Phenyl-4,4,6-trimethyl-hept-1-yne-3,5-diol (6): Colorless solid, mp = 98.5 °C, R_f = 0.23 (ethyl acetate/hexane 1:3), 3% isolated product. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.44 (m, 2H, CH), 7.32 (m, 3H, CH), 4.55 (s, 1H, CH), 3.57 (d, J = 2.3 Hz, 1H, CH), 2.73 (s, br, 2H, OH), 2,03 (m, 1H, CH), 1.17 (s, 3H, CH_3), 1.05 (d, J = 6.8 Hz, 3H, CH_3), 1.03 (s, 3H, CH_3), 0.97 (d, J = 6.8 Hz, 3H, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 131.7, 128.4, 128.3, 122.6, 88.4, 86.2, 82.3, 73.3, 43.1, 29.5, 23.2, 21.7, 16.4, 16.2. IR (KBr): ν = 3236.3, 2964.3, 2360.9, 1597.0, 1490.8, 1332.8, 1045.8. Anal. calcd. for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00. Found: C, 77.86; H, 9.18.

Acknowledgment

This work was supported by the Fonds der chemischen Industrie.

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[1] K. Schulte, G. Rucker, *Progr. Drug. Res., Basel Stuttgart* **1970**, *14*, 387-563.

[2] L. Tan, C. Y. Chen, R. D. Tillyer, E. J. J. Grabowski, P. J. Reider, *Angew. Chem. Int. Ed.* **1999**, *38*, 711-713.

[3] T. Ishikawa, T. Mizuta, K. Hagiwara, T. Aikawa, T. Kudo, S. Saito, *J. Org. Chem.* **2003**, *68*, 3702-3705.

[4] D. Tzalis, P. Knochel, *Angew. Chem. Int. Ed.* **1999**, *38*, 1463-1465.

[5] N. K. Anand, E. M. Carreira, *J. Am. Chem. Soc.* **2001**, *123*, 9687-9688.

[6] D. Boyall, F. Lopez, H. Sasaki, D. Frantz, E. M. Carreira, *Org. Lett.* **2000**, *2*, 4233-4236.

[7] J. H. Babler, V. P. Liptak, N. Phan, *J. Org. Chem.* **1996**, *61*, 416-417.

[8] P. G. Cozzi, R. Hilgraf, N. Zimmermann, *Eur. J. Org. Chem.* **2004**, 4095-4105.

[9] A. E. Favorskii, *J. Russ. Phys. Chem. Soc.* **1905**, *37*, 643.

[10] R. J. Tedeschi, *J. Org. Chem.* **1965**, *30*, 3045-3049.

[11] M. Kimura, S. Tanaka, Y. Tamura, *Bull. Chem. Soc. Jpn.* **1995**, *68*, 1689-1705.

[12] Z. B. Li, L. Pu, *Org. Lett.* **2004**, *6*, 1065-1068.

[13] C. Starks, C. Liotta, M. Halpern, *Phase-Transfer Catalysis: Fundamentals, Applications and Industrial Perspectives*, Chapman & Hall, New York, **1994**.

[14] E. V. Dehmlow, S. S. Dehmlow, *Pase-Transfer Catalysis*, VCH, Weinheim, **1993**.

[15] W. P. Weber, G. G. W. Gokel, *Phase-Transfer Catalysis in Organic Synthesis,*, Springer, Berlin, **1977**.

[16] Y. Sasson, R. Neumann, *Handbook of Phase-Transfer Catalysis*, Blacky Academic & Professional, London, **1997**.

[17] P. R. Schreiner, O. Lauenstein, E. D. Butova, P. A. Gunchenko, I. V. Kolomitsin, A. Wittkopp, G. Feder, A. A. Fokin, *Chem. Eur. J.* **2001**, *7*, 4996-5003.

[18] M. Makosza, I. Krytowa, *Tetrahedron* **1999**, *55*, 6395-6402.

[19] O. A. Reutov, I. P. Beletskaya, K. P. Butin, *CH-Acids*, Moscow State University, USSR, **1978**.

[20] A. A. Fokin, P. R. Schreiner, *Adv. Synth. Cat.* **2003**, *345*, 1035-1052.

[21] P. R. Schreiner, O. Lauenstein, E. D. Butova, A. A. Fokin, *Angew. Chem. Int. Ed.* **1999**, *38*, 2786-2788.

[22] A. A. Fokin, P. R. Schreiner, *Chem. Rev.* **2002**, *102*, 1551-1593.

[23] T. Ooi, Y. Uematsu, K. Maruoka, *Tetrahedron Lett.* **2004**, *45*, 1675-1678.

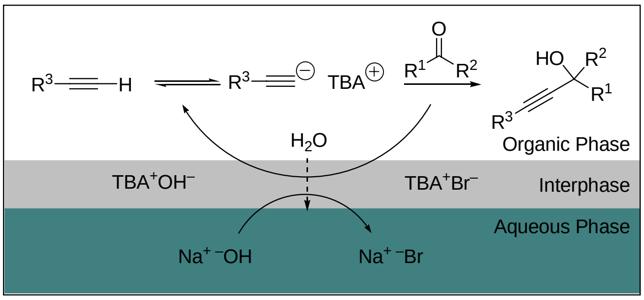
[24] T. Ooi, D. Sakai, M. Takeuchi, E. Tayama, K. A. C. I. E. Maruoka, 42, 5868-5870, *Angew. Chem. Int. Ed.* **2003**, *42*, 5868-5870.

[25] C. Lemaire, S. Gillet, S. Guillouet, A. Plenevaux, J. Aerts, A. Luxen, *Eur. J. Org. Chem.* **2004**, 2899-2904.

Graphical abstract for Table of Contents

T. Weil, P. R. Schreiner*

Organocatalytic Alkynylation of Aldehydes and Ketones under Phase-Transfer Conditions



Keywords: Alkynylation / Propargylic alcohols / C–C coupling / Organocatalysis / Phase- transfer catalysis

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[A]Torsten Weil and Peter R. Schreiner: Organocatalytic Alkynylation of Aldehydes and Ketones under Phase-Transfer Catalytic Conditions, *Eur. J. Org. Chem.* **2005**, 2213-2217. Copyright WILEY-VCH Verlag GmbH & Co. KGaA. Reproduced with permission.

4.2. Cooperative Brønsted Acid-Type Organocatalysis: Alcoholysis of Styrene Oxides

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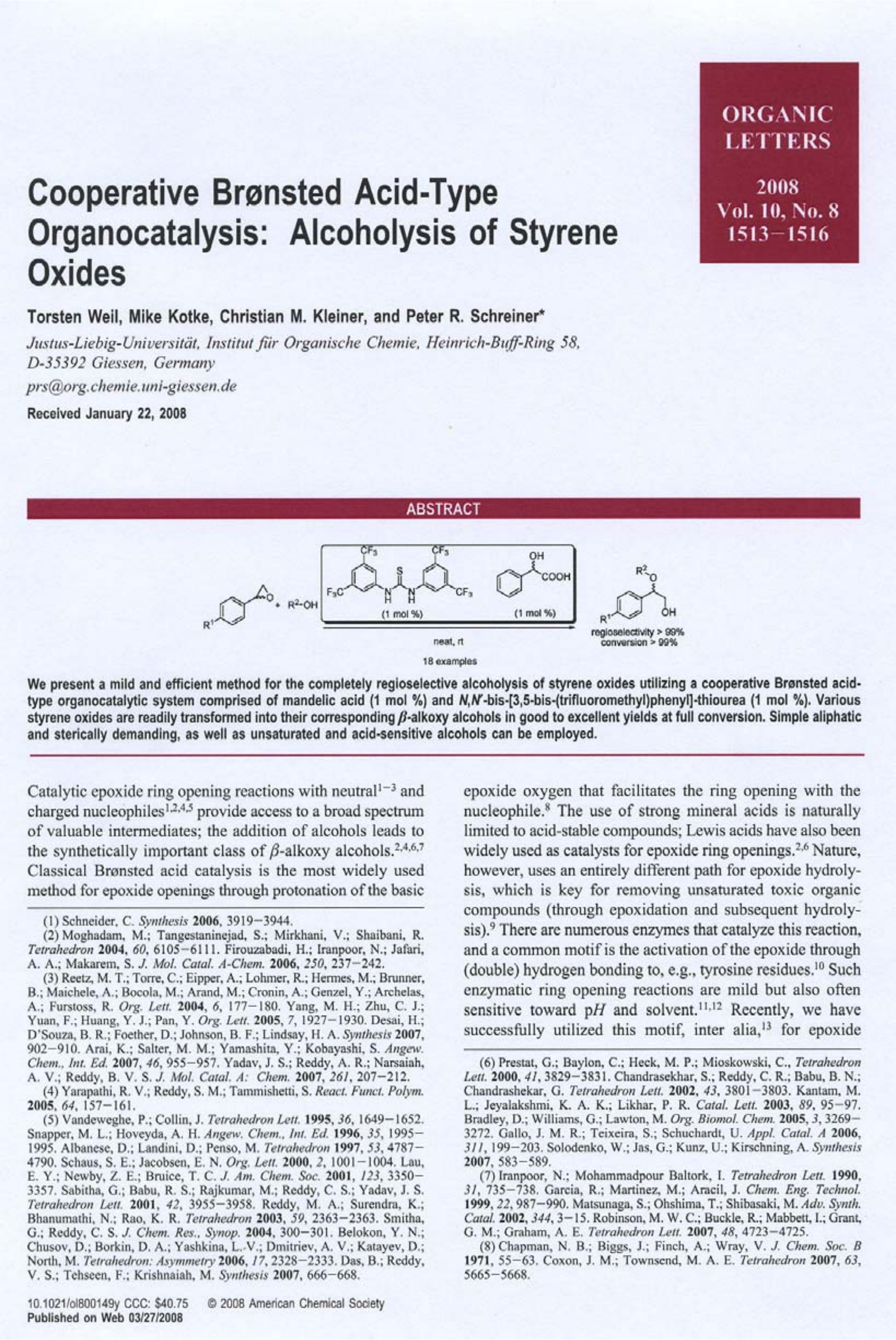

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Cooperative Brønsted Acid-Type Organocatalysis: Alcoholysis of Styrene Oxides

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Received January 22, 2008

ABSTRACT

We present a mild and efficient method for the completely regioselective alcoholysis of styrene oxides utilizing a cooperative Brønsted acid-type organocatalytic system comprised of mandelic acid (1 mol %) and *N,N'*-bis-[3,5-bis-(trifluoromethyl)phenyl]-thiourea (1 mol %). Various styrene oxides are readily transformed into their corresponding β-alkoxy alcohols in good to excellent yields at full conversion. Simple aliphatic and sterically demanding, as well as unsaturated and acid-sensitive alcohols can be employed.

Catalytic epoxide ring opening reactions with neutral[1−3] and charged nucleophiles[1,2,4,5] provide access to a broad spectrum of valuable intermediates; the addition of alcohols leads to the synthetically important class of β-alkoxy alcohols.[2,4,6,7] Classical Brønsted acid catalysis is the most widely used method for epoxide openings through protonation of the basic epoxide oxygen that facilitates the ring opening with the nucleophile.[8] The use of strong mineral acids is naturally limited to acid-stable compounds; Lewis acids have also been widely used as catalysts for epoxide ring openings.[2,6] Nature, however, uses an entirely different path for epoxide hydrolysis, which is key for removing unsaturated toxic organic compounds (through epoxidation and subsequent hydrolysis).[9] There are numerous enzymes that catalyze this reaction, and a common motif is the activation of the epoxide through (double) hydrogen bonding to, e.g., tyrosine residues.[10] Such enzymatic ring opening reactions are mild but also often sensitive toward p*H* and solvent.[11,12] Recently, we have successfully utilized this motif, inter alia,[13] for epoxide

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(1) Schneider, C. *Synthesis* **2006**, 3919−3944.

(2) Moghadam, M.; Tangestaninejad, S.; Mirkhani, V.; Shaibani, R. *Tetrahedron* **2004**, *60*, 6105−6111. Firouzabadi, H.; Iranpoor, N.; Jafari, A. A.; Makarem, S. *J. Mol. Catal. A-Chem.* **2006**, *250*, 237−242.

(3) Reetz, M. T.; Torre, C.; Eipper, A.; Lohmer, R.; Hermes, M.; Brunner, B.; Maichele, A.; Bocola, M.; Arand, M.; Cronin, A.; Genzel, Y.; Archelas, A.; Furstoss, R. *Org. Lett.* **2004**, *6*, 177−180. Yang, M. H.; Zhu, C. J.; Yuan, F.; Huang, Y. J.; Pan, Y. *Org. Lett.* **2005**, *7*, 1927−1930. Desai, H.; D'Souza, B. R.; Foether, D.; Johnson, B. F.; Lindsay, H. A. *Synthesis* **2007**, 902−910. Arai, K.; Salter, M. M.; Yamashita, Y.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2007**, *46*, 955−957. Yadav, J. S.; Reddy, A. R.; Narsaiah, A. V.; Reddy, B. V. S. *J. Mol. Catal. A: Chem.* **2007**, *261*, 207−212.

(4) Yarapathi, R. V.; Reddy, S. M.; Tammishetti, S. *React. Funct. Polym.* **2005**, *64*, 157−161.

(5) Vandeweghe, P.; Collin, J. *Tetrahedron Lett.* **1995**, *36*, 1649−1652. Snapper, M. L.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **1996**, *35*, 1995−1995. Albanese, D.; Landini, D.; Penso, M. *Tetrahedron* **1997**, *53*, 4787−4790. Schaus, S. E.; Jacobsen, E. N. *Org. Lett.* **2000**, *2*, 1001−1004. Lau, E. Y.; Newby, Z. E.; Bruice, T. C. *J. Am. Chem. Soc.* **2001**, *123*, 3350−3357. Sabitha, G.; Babu, R. S.; Rajkumar, M.; Reddy, C. S.; Yadav, J. S. *Tetrahedron Lett.* **2001**, *42*, 3955−3958. Reddy, M. A.; Surendra, K.; Bhanumathi, N.; Rao, K. R. *Tetrahedron* **2003**, *59*, 2363−2363. Smitha, G.; Reddy, C. S. *J. Chem. Res., Synop.* **2004**, 300−301. Belokon, Y. N.; Chusov, D.; Borkin, D. A.; Yashkina, L.-V.; Dmitriev, A. V.; Katayev, D.; North, M. *Tetrahedron: Asymmetry* **2006**, *17*, 2328−2333. Das, B.; Reddy, V. S.; Tehseen, F.; Krishnaiah, M. *Synthesis* **2007**, 666−668.

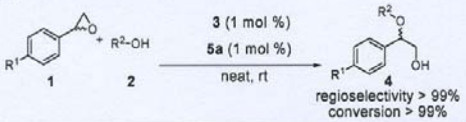
(6) Prestat, G.; Baylon, C.; Heck, M. P.; Mioskowski, C., *Tetrahedron Lett.* **2000**, *41*, 3829−3831. Chandrasekhar, S.; Reddy, C. R.; Babu, B. N.; Chandrashekar, G. *Tetrahedron Lett.* **2002**, *43*, 3801−3803. Kantam, M. L.; Jeyalakshmi, K. A. K.; Likhar, P. R. *Catal. Lett.* **2003**, *89*, 95−97. Bradley, D.; Williams, G.; Lawton, M. *Org. Biomol. Chem.* **2005**, *3*, 3269−3272. Gallo, J. M. R.; Teixeira, S.; Schuchardt, U. *Appl. Catal. A* **2006**, *311*, 199−203. Solodenko, W.; Jas, G.; Kunz, U.; Kirschning, A. *Synthesis* **2007**, 583−589.

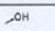
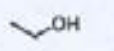
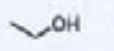
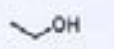
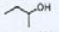
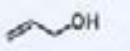
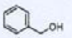
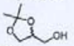
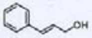
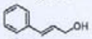
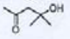
(7) Iranpoor, N.; Mohammadpour Baltork, I. *Tetrahedron Lett.* **1990**, *31*, 735−738. Garcia, R.; Martinez, M.; Aracil, J. *Chem. Eng. Technol.* **1999**, *22*, 987−990. Matsunaga, S.; Ohshima, T.; Shibasaki, M. *Adv. Synth. Catal.* **2002**, *344*, 3−15. Robinson, M. W. C.; Buckle, R.; Mabbett, I.; Grant, G. M.; Graham, A. E. *Tetrahedron Lett.* **2007**, *48*, 4723−4725.

(8) Chapman, N. B.; Biggs, J.; Finch, A.; Wray, V. *J. Chem. Soc. B* **1971**, 55−63. Coxon, J. M.; Townsend, M. A. E. *Tetrahedron* **2007**, *63*, 5665−5668.

10.1021/ol800149y CCC: $40.75

Table 1. Alcoholysis of Styrene Oxides with Mandelic Acid (**5a**)



no.[a]	R¹	**1**	alcohol (R²-OH)	**2**	prod.	*t* [h]	%[d]
1	H	**1a**		**2a**	**4a**	18	85
2	H	**1a**		**2b**	**4b**	22	86
3	F	**1b**		**2b**	**4c**	24	57
4	*t*Bu	**1c**		**2b**	**4d**	15	65
5	H	**1a**		**2c**	**4e**	21	73
6[b]	H	**1a**		**2d**	**4f**	15	74
7[b]	F	**1b**		**2d**	**4g**	18	57
8[b]	*t*Bu	**1c**		**2d**	**4h**	16	65
9	H	**1a**		**2e**	**4i**	21	94
10	H	**1a**		**2f**	**4j**	20	73
11	H	**1a**		**2g**	**4k**	23	89
12	H	**1a**		**2h**	**4l**	18	80
13	H	**1a**		**2i**	**4m**	23	78
14[c]	H	**1a**		**2j**	**4n**	32	41
15	H	**1a**		**2k**	**4o**	16	65
16	F	**1b**		**2k**	**4p**	17	63
17	*t*Bu	**1c**		**2k**	**4q**	39	70
18[b]	H	**1a**		**2l**	**4r**	18	58

[a] Reaction conditions: 1 equiv of **1**, 12 equiv of alcohol, and 1 mol % of **3** and **5a** respectively; rt. All catalyzed reactions were accompanied by parallel reference experiments without **3**, as well as experiments with **3** and without acid co-catalyst under identical reaction conditions. No polymers of styrene oxide were detected. All reference experiments showed no conversion at the presented reaction time if not otherwise noted. Reactions were monitored by GC/MS. Regiochemistry was determined by NMR experiments (^3J CH-coupling) and fragmentation in MS. [b] At 50 °C. [c] 3 mol % of **5a**; 2 equiv of alcohol; at 50 °C. [d] Yield of isolated product.

openings with strong nucleophiles. We demonstrated that the effects of hydrogen-bonding organocatalysis and water as the solvent are *cooperative* and termed this "hydrophobic amplification".[14] Apparently, the approximately neutral p*H* and the presence of water also are key factors in THP-templated epoxide openings in cascade reactions leading to structures akin to Brevetoxin A.[12] As water can effectively compete with weaker nucleophiles, we set out to develop an alternative approach that relies on using *two* cooperative hydrogen-bonding catalysts. With regards to the choice of mild acid (**5**) to be used with *N,N'*-bis-[3,5-bis-(trifluoromethyl)phenyl]-thiourea (**3**),[15] we were helped by the fact that we observed that undistilled styrene oxide (**1a**) readily reacted with various alcohols while freshly distilled **1a** did not. As the oxidation product of **1a** is mandelic acid (**5a**),[9,16] this acid was our first choice. The initial results were very promising and encouraged us to examine this remarkable reaction further.

While carboxylic acids are known to increase the reaction rates of some nucleophilic organocatalytic reactions[17] this is a rare example of a cooperative Brønsted acid-type organocatalytic system.[18] Optimization of the reaction conditions led to a protocol that utilizes 12 equiv of the alcohol as nucleophile and solvent; this effectively suppresses the formation of byproducts resulting from attack of the product on **1** (see Supporting Information for details).

Styrene oxides can readily be transformed into β-alkoxy alcohols in good to excellent yields; all catalyzed reactions are completely regioselective and show full conversion. Both simple aliphatic and sterically demanding (Table 1, entries 1−10), as well as unsaturated (entries 12, 13) and especially acid-labile alcohols (entries 14−18) can be utilized. In general, the reaction times depend more on the nature of the epoxide substrate (**1**) than on the alcohol (**2**). The more reactive **1c** leads nearly in all cases to faster conversions (Table 1, entries 4 and 8); the sole exception is the reaction of cinnamyl alcohol (**2k**) with **1c**. An electron-deficient styrene oxide (**1b**) leads to longer reaction times and lower yields. The reactions of styrene oxides with *tert*-butanol (**2d**, entries 6−8) were all carried out at 50 °C and afforded yields from 57% to 74% without byproduct formation. All reference experiments for these reactions (entries 6−8) showed no conversion; even after 17 days the reference experiment of entry 8 without **3** showed less than 5% conversion. No decomposition or polymerization reactions could be detected for the acid-labile substrates **2j**, **2k**, and **2l**.

Table 2. Solvent Effect on the Alcoholysis of Styrene Oxide with Ethanol[a]

solvent	time [h]	temp. [°C]	conv. of **1** [%]
ethanol	22	rt	>99
acetonitrile	48	rt	–
acetonitrile	20	50	~9
THF	48	rt	>99
toluene	20	rt	–
toluene	16	50	>99
n-hexane	48	rt	>99

[a] Reaction conditions: 1 equiv of **1**, 2 equiv of **2b**, 2 vol equiv of solvent, and 1 mol % of **3** and **5a**, respectively, rt.

We examined various solvents for the conversion of solid alcohols or epoxides (Table 2) with our test reaction and

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(9) Korn, M.; Wodarz, R.; Schoknecht, W.; Weichardt, H.; Bayer, E. *Arch. Toxicol.* **1984**, *55*, 59−63.

(10) Gallimore, A. R.; Stark, C. B. W.; Bhatt, A.; Harvey, B. M.; Demydchuk, Y.; Bolanos-Garcia, V.; Fowler, D. J.; Staunton, J.; Leadlay, P. F.; Spencer, J. B. *Chem. Biol.* **2006**, *13*, 453−460.

(11) Schreiner, P. R.; Wittkopp, A. *Org. Lett.* **2002**, *4*, 217−220. Schreiner, P. R., *Chem. Soc. Rev.* **2003**, *32*, 289−296. Wittkopp, A.; Schreiner, P. R., *Chem. Eur. J.* **2003**, *9*, 407−414.

(12) Vilotijevic, I.; Jamison, T. F. *Science* **2007**, *317*, 1189−1192.

(13) Kotke, M.; Schreiner, P. R. *Tetrahedron* **2006**, *62*, 434−439. Kotke, M.; Schreiner, P. R. *Synthesis* **2007**, 779−790. Zhang, Z.; Schreiner, P. R., *Synlett* **2007**, 1455−1457.

(14) Kleiner, C. M.; Schreiner, P. R. *Chem. Commun.* **2006**, 4315−4317.

(15) Pihko, P. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2062−2064. Takemoto, Y. *Org. Biomol. Chem.* **2005**, *3*, 4299−4306. Doyle, A. G.; Jacobsen, E. N., *Chem. Rev.* **2007**, *107*, 5713−5743.

(16) Ensign, S. A.; Allen, J. R. *Annu. Rev. Biochem.* **2003**, *72*, 55−76.

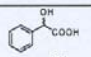
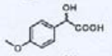
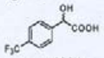
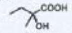
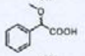
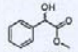
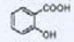
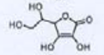
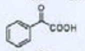
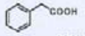
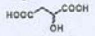
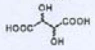
(17) Cao, C. L.; Ye, M. C.; Sun, X. L.; Tang, Y. *Org. Lett.* **2006**, *8*, 2901−2904.

(18) Yong-Ling Shi, M. S. *Adv. Synth. Catal.* **2007**, *349*, 2129−2135. Zuend, S. J.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2007**, *129*, 15872−15883.

found a remarkable solvent effect. Reactions in ethanol were more than two times faster than reactions in nonpolar or aprotic solvents.[19] To optimize our cooperative catalyst system, we also varied the ratio between **3** and **5a**[20] and utilized various mandelic acid derivatives.[21]

Further Brønsted acid screening (Table 3) revealed that only aromatic acids bearing a second coordination center in the α-position (hydroxy or carbonyl) led to appreciable conversions (entries 1−3, 9). The removal or blocking of the α-coordination center (**5j** and **5e**) or removal of the aromatic system dramatically reduces the conversion rates. Aqueous acidity (pK_a) appears not to be a good predictor for catalyst activity (entry 12).

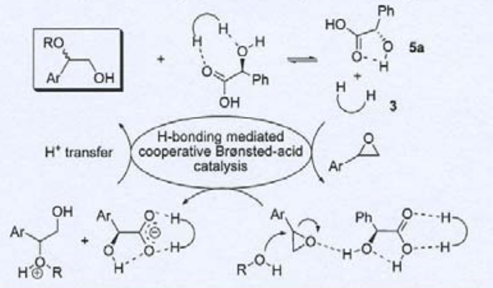
Table 3. Brønsted Acid Screening

no.[a]	acid additive		pK_a	t [h]	conv. [%][b]
1		**5a**	3.37	22	> 99
2		**5b**	3.43[e]	19	> 99
3[c]		**5c**	3.01[e]	16	> 99
4		**5d**	4.05[e]	24	~5
5		**5e**	3.10[e]	26	--
6		**5f**	--[f]	26	--
7		**5g**	3.00	26	~12
8		**5h**	4.10	26	--
9[d]		**5i**	2.10[e]	12	> 99
10		**5j**	4.28	26	--
11		**5k**	3.41	26	--
12		**5l**	2.93	26	--

[a] Reaction conditions: 1 equiv of **1**, 12 equiv of ethanol, and 1 mol % of **3** and **5a−l**, respectively, rt. All catalyzed reactions were accompanied by parallel reference experiments without **3**, as well as experiments with **3** and without acid co-catalyst under identical reaction conditions. Reference experiments showed no conversion. [b] Reactions were monitored by GC/MS. [c] Reference without **3** showed 12% conversion after 18 h. [d] Reference without **3** showed 80% conversion after 15 h; remarkably, the reaction does not run to completion even after 3 days. [e] Calculated data. [f] No experimental or calculated data available.

Our experimental findings suggest an H-bonding-mediated cooperative Brønsted-acid catalysis mechanism (Scheme 1).

Scheme 1. Proposed Catalytic Cycle for Epoxide Alcoholysis through H-Bonding-Mediated Cooperative Catalysis



It is likely that co-catalyst **3** coordinates to the acid **5a** through double H-bonding, stabilizes **5a** in the chelate-like *cis*-hydroxy conformation, and acidifies the α-OH proton via an additional intramolecular H-bond. The epoxide then is activated by a single-point hydrogen bond that facilitates regioselective nucleophilic attack of the alcohol at the benzylic position. Such monodentate binding was recently suggested for diol catalysts.[22] The incipient oxonium ion reprotonates the mandelate and affords the β-alkoxy alcohol product.

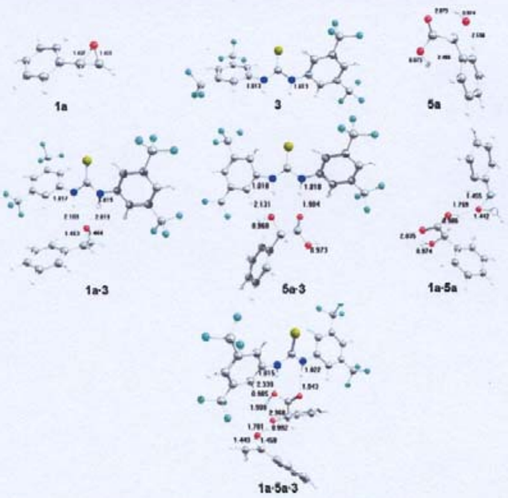


Figure 1. Minimum-energy structures of monomers **1a**, **3**, and **5a**, binary (**1a·3**, **5a·3**, and **1a·5a**) and ternary complexes (**1a·5a·3**) optimized at B3LYP/6-31+G(d,p).

---

[19] Park, K. S.; Kim, J.; Choo, H.; Chong, Y. *Synlett* **2007**, 395−398. Shirakawa, S.; Shimizu, S. *Synlett* **2007**, 3160−3164.

[20] Suprisingly, reaction times in all cases are nearly equal, although GC/MS analysis after 15 h showed more than two times faster conversion in case of 7 mol % of **3** than in case of our standard protocol (1 mol % of **3**). The results are available in the Supporting Information.

[21] We observed a nonlinear catalytic effect for the ethanolysis of **1** with a notable rate enhancement in the second half of the reaction period. This is apparently not a case of autocatalysis through product **4b** because addition of 20 mol% of **4b** to our standard test reaction showed no variation relative to our standard protocol. Further mechanistic investigations are currently underway.

[22] McGilvra, J. D.; Unni, A. K.; Modi, K.; Rawal, V. H. *Angew. Chem., Int. Ed.* **2006**, *45*, 6130−6133.

[23] Frisch; et al. *Gaussian 03* (for full reference see Supporting Information).

[24] Becke, A. D. *Phys. Rev. A* **1988**, *38*, 3098−3100. Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785−789.

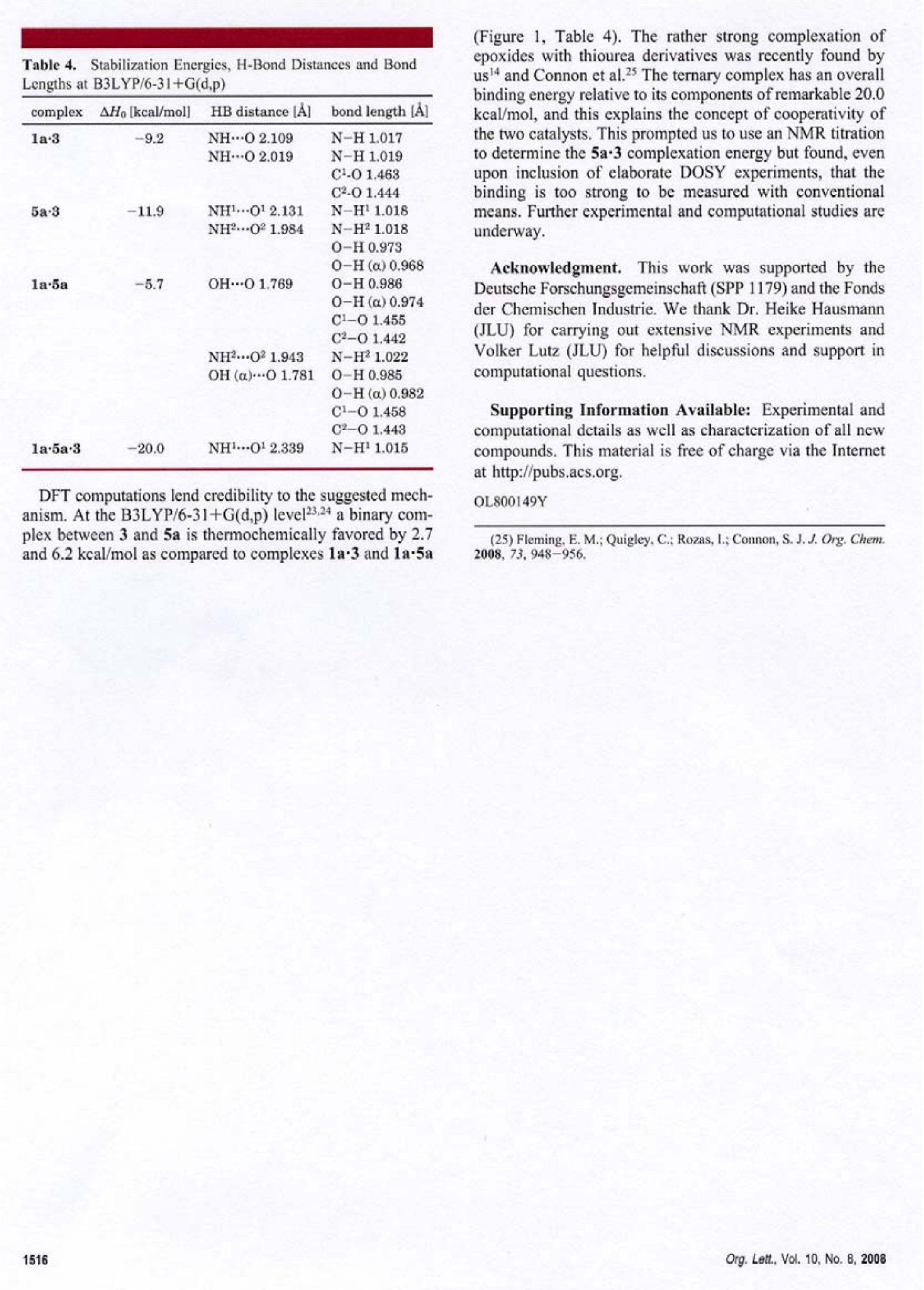


Table 4. Stabilization Energies, H-Bond Distances and Bond Lengths at B3LYP/6-31+G(d,p)

complex	ΔH_0 [kcal/mol]	HB distance [Å]	bond length [Å]
1a·3	−9.2	NH···O 2.109	N−H 1.017
		NH···O 2.019	N−H 1.019
			C^1-O 1.463
			C^2-O 1.444
5a·3	−11.9	NH^1···O^1 2.131	N−H^1 1.018
		NH^2···O^2 1.984	N−H^2 1.018
			O−H 0.973
			O−H (α) 0.968
1a·5a	−5.7	OH···O 1.769	O−H 0.986
			O−H (α) 0.974
			C^1−O 1.455
			C^2−O 1.442
		NH^2···O^2 1.943	N−H^2 1.022
		OH (α)···O 1.781	O−H 0.985
			O−H (α) 0.982
			C^1−O 1.458
			C^2−O 1.443
1a·5a·3	−20.0	NH^1···O^1 2.339	N−H^1 1.015

DFT computations lend credibility to the suggested mechanism. At the B3LYP/6-31+G(d,p) level[23,24] a binary complex between **3** and **5a** is thermochemically favored by 2.7 and 6.2 kcal/mol as compared to complexes **1a·3** and **1a·5a** (Figure 1, Table 4). The rather strong complexation of epoxides with thiourea derivatives was recently found by us[14] and Connon et al.[25] The ternary complex has an overall binding energy relative to its components of remarkable 20.0 kcal/mol, and this explains the concept of cooperativity of the two catalysts. This prompted us to use an NMR titration to determine the **5a·3** complexation energy but found, even upon inclusion of elaborate DOSY experiments, that the binding is too strong to be measured with conventional means. Further experimental and computational studies are underway.

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Supporting Information Available: Experimental and computational details as well as characterization of all new compounds. This material is free of charge via the Internet at http://pubs.acs.org.

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[25] Fleming, E. M.; Quigley, C.; Rozas, I.; Connon, S. J. *J. Org. Chem.* **2008**, *73*, 948−956.

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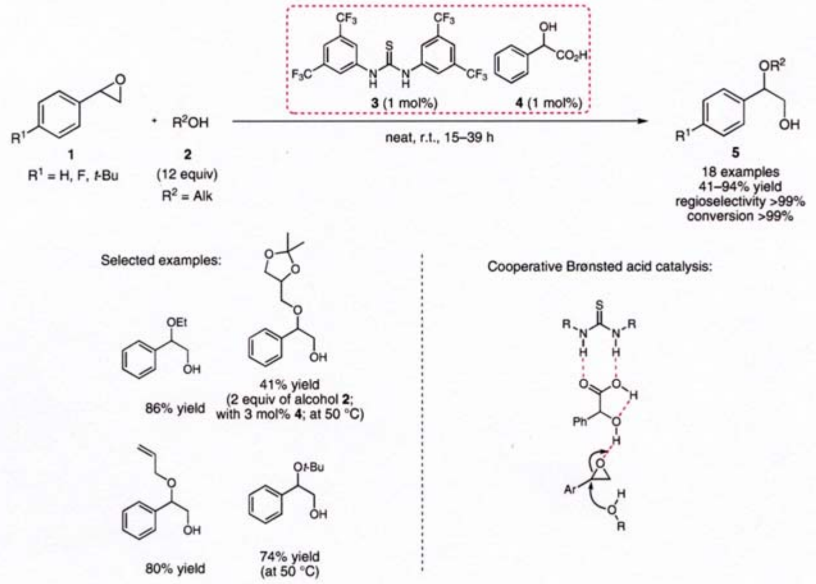
Cooperative Brønsted Acid-Type Organocatalysis: Alcoholysis of Styrene Oxides

Org. Lett. **2008**, *10*, 1513-1516.

Cooperative Brønsted Acid Catalysis



Significance: A completely regioselective alcoholysis of styrene oxides **1** has been accomplished utilizing a catalyst system comprised of *N,N'*-bis[3,5-bis(trifluoromethyl)phenyl]-thiourea (**3**, 1 mol%) and mandelic acid (**4**, 1 mol%). Both simple aliphatic and sterically demanding as well as unsaturated or acid-labile alcohols **2** can be used furnishing the corresponding β-alkoxy alcohols **5** in moderate to high yields. Thiourea **3** or mandelic acid (**4**) alone were both uneffective. The authors invoke an H-bonding-mediated cooperative Brønsted acid catalysis mechanism to rationalize their experimental findings (see scheme). Support is also provided by DFT computations.

Comment: Epoxide hydrolysis in nature is commonly facilitated by the activation of the epoxide through (double) hydrogen bonding involving the phenolic protons of two tyrosine residues of epoxide hydrolases. By means of this motif, the Schreiner group has earlier developed epoxide openings with strong nucleophiles catalyzed by the Schreiner thiourea **3** (*Chem. Commun.* **2006**, 4315). Herein, they present an alternative approach which allows for the use of weaker nucleophiles. Further applications of the intriguing concept of cooperative Brønsted acid catalysis are highly desirable, especially in asymmetric catalysis.

SYNFACTS Contributors: Benjamin List, Corinna Reisinger
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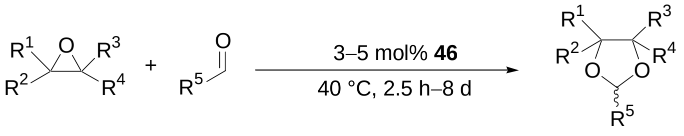
4.3 Organocatalytic Formation of 1,3-Dioxolanes (Manuscript in preparation)

1,3-dioxolanes are commonly synthesized by treatment of epoxides or 1,2-diols and aldehydes or ketones with Lewis acids. Since many of the utilized Lewis acids do not tolerate acid sensitive functionalities, new approaches have been investigated to solve this problem. Recent developments in the field of organocatalysis, notably in transformation reactions of epoxides, offered new alternatives to overcome the mentioned limitations.[150, 151, 193, 194]

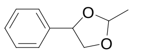
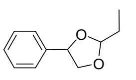
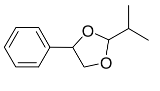
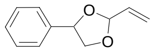
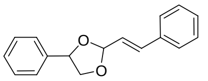
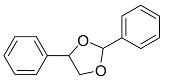
Continuous work based on these developments afforded a mild and efficient methodology utilizing *N,N′*-bis-[3,5-bis-(trifluoromethyl)phenyl]-thiourea (**46**) as hydrogen-bonding catalyst for the conversion of epoxides to the corresponding 1,3-dioxolanes (Scheme 29).

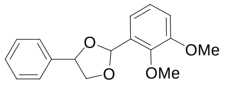
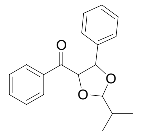


Scheme 29. Organocatalytic formation of 1,3-dioxolanes mediated by *N,N′*-bis-[3,5-bis-(trifluoromethyl)phenyl]-thiourea (**46**)

First results seemed promising and various aldehydes reacted cleanly with **25** to the desired products in appropriate reaction times and good to excellent product yields at full conversion (Table 1, entries 1-7). Acid labile substrates such as cinnamaldehyde or acrolein could be transformed without significant formation of by-products (Table 1, entries 4, 5).

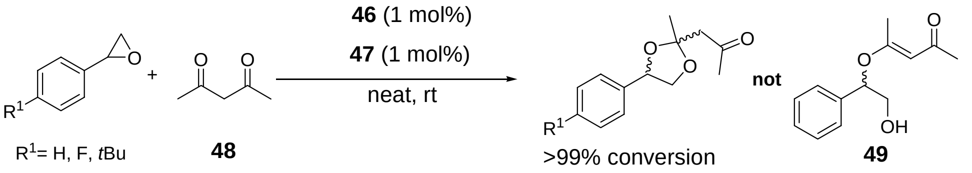
Table 1. Formation of 1,3-dioxolanes mediated by *N,N′*-bis-[3,5-bis- (trifluoromethyl)phenyl]-thiourea (**46**)

#	mol% cat.	t	product	conv. [%][a]	isol. prod. [%][b]	*dr*[a]
1	5	3.5 h		> 99	84	2.3:1
2	5	3 d (rt)		> 99	87	1.4:1
3	3	2.5 h		> 99	92	3:1
4	5	36 h		> 99	86	3:1
5	5	3.5 d		> 99	85	1.2:1
6	5	4 h		> 99	88	2.6:1

#	mol% cat.	t	product	conv. [%][a]	isol. prod. [%][b]	*dr*[a]
7	5	5 d		> 99	76	1.4:1
8	5	8 d		> 99	80	1.8:1

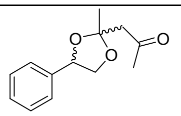
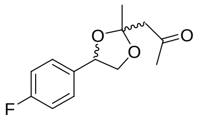
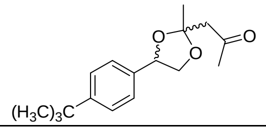
Reaction conditions: 1 mmol epoxide, 3 mmol of aldehyde. Epoxide and **46** were stirred for approximately 0.5 h at rt, then aldehyde was added (10 min) Solution was warmed to 40 °C. After reaction control by GC/MS, the solution was evaporated and purified by flash-chromatography (*n*-hexane/TBME). [a] GC/MS, [b] isolated product yield.

Unfortunately ketones could not be converted to the corresponding 1,3-dioxolanes under the elaborated reaction conditions. In this context we were helped by the fact that we already examined the alcoholysis reaction of enolizable acetylacetone[195-198] (**48**) with various styrene oxides under our established cooperative Brønsted acid conditions.[151] Suprisingly we could not isolate the expected enol ether (**49**) but instead the corresponding 1,3-dioxolane (Scheme 30, Table 2).



Scheme 30. Formation of 1,3-dioxolanes mediated by cooperative Brønsted acid catalysis

Table 2. Formation of 1,3-dioxolanes derived from acetylacetone mediated by **46** and mandelic acid (**47**)

#[a]	product	t [h]	isol. prod. [%][b]	*dr*[c]
1		62	62	1.3:1
2		68	62	1.4:1
3[d]		18	54	1.4:1

[a] Reaction conditions: 1 equiv of styrene oxide, 12 equiv of alcohol, and 1 mol% of **46** and **47** respectively; rt. All catalyzed reactions were accompanied by parallel reference experiments without **3** as well as experiments with **1** and without acid co-catalyst under identical reaction conditions. All reference experiments showed no conversion at all at the presented reaction time if not otherwise noted. [b] Products were seperated by HPLC. [c] Detected by GC/MS. [d] Reaction carried out at 50 °C.

Further investigations are currently under way to make this methodology universally applicable for conversions of, e.g. aliphatic or deactivated epoxides (Table 1, entry 8) as well as various ketones. Furthermore diastereomeric control is desirable and should be possible by chiral induction utilizing suited catalysts. Mechanistic studies are necessary as well to get insights to significant steps of this ring expansion reaction. The fact that electron rich aldehydes react faster with **25** than electron deficient compounds seems to affirm the proposed mechanism mentioned in chapter 3 (**3.1**).

5. Experimental Section

5.1 Organocatalytic Alkynylation of Aldehydes and Ketones under Phase-Transfer Catalytic Conditions

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5.1.2 General Data. All chemicals were purchased from Acros Organics, Aldrich, and Lancaster in highest purities available; liquid aldehydes as well as the alkynes were freshly distilled over a 10 cm Vigreux column prior use, solid aldehydes were used without further purification. Reactions were monitored with a HP 5890 GC spectrometer with a HP 5971 mass selective detector. ^{1}H NMR and ^{13}C NMR spectra were recorded with a Bruker AM 400 spectrometer using TMS as internal standard; chemical shift values are given in ppm. IR spectra were measured with a Bruker IFS 25 spectrometer. p*H* was determined with a HANNA HI 8314 p*H* meter. Elemental analysis (CHN) was determined with a Carlo Erba EA 1106.

Method A: To an intensively stirred solution of 7 mmol alkyne compound, 8.4 mmol carbonyl compound and 1.4 mmol [20 mol%] TBABr in 5 mL of fluorobenzene, 5 mL of aqueous sodium hydroxide (50%) was added. After stirring for the corresponding reaction time mentioned in Table 1, 10 mL of water were added and the phases were separated. The organic layer was washed with water and brine and subsequently dried over anhydrous sodium sulphate. Filtration from the drying agent and removal of the solvent by distillation left in all cases a colored mixture of product, reactant and PT catalyst. The product was isolated by high-vacuum distillation or column chromatography (SiO_2/ethyl acetate/hexane 1:3) to give the propargylic alcohols as colorless solids or colorless to slightly yellowish oils. All propargylic alcohols prepared are known in the literature.[42, 76, 83]

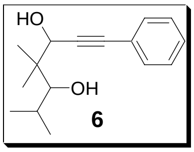
Method B: To an intensively stirred mixture consisting of 14 mmol alkyne compound, 1.4 mmol TBABr, 3 mL of fluorobenzene and 5 mL of aqeous sodium hydroxide (50%), a solution of 7 mmol carbonyl compound in 2 mL of fluorobenzene was added over a period of 2 hours via an addition funnel. Reaction time and workup are identical to method A.

p*H* determination. We determined the p*H* and thus the relative concentration of hydroxide anions in the organic phase with a simple experiment. We simulated the reaction conditions by stirring 10 mL of fluorobenzene, 10 mL 50% aqueous sodium hydroxide, and 3 mmol of TBABr for two hours to reach equilibrium. Then we separated the organic layer and exctracted the dissolved salts with 10 mL of distilled water. Measuring the pH (12.51–13.05 ± 0.05) and the volume of the resulting aqueous phase (including the former interphase) and conversion to the volume of OH^- gave an average relative concentration of $c[OH^-] =$ 0.11 mol/L. The experiment was repeated three times.

5.1.3. Compound Characterization

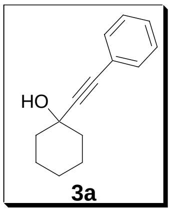
Side product (new compound):

1-Phenyl-4,4,6-trimethyl-hept-1-yne-3,5-diol (6): Colorless solid, mp = 98.5 °C, R_f = 0.23 (ethyl acetate/hexane 1:3), 3% isolated yield. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44 (m, 2H), 7.32 (m, 3H), 4.55 (s, 1H), 3.57 (d, 1H, J = 2.3 Hz), 2.73 (s, br, 2H), 2,03 (m, 1H), 1.17 (s, 3H), 1.05 (d, 3H, J = 6.8 Hz), 1.03 (s, 3H), 0.97 (d, 3H, J = 6.8 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 131.7, 128.4, 128.3, 122.6, 88.4, 86.2, 82.3, 73.3, 43.1, 29.5, 23.2, 21.7, 16.4, 16.2. IR (KBr): ν = 3236.3, 2964.3, 2360.9, 1597.0, 1490.8, 1332.8, 1045.8. Anal. calcd. for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00. Found: C, 77.86; H, 9.18.



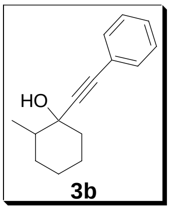
6

1-(Phenylethynyl)-cyclohexanol (3a): Colorless solid, 88% isolated product yield. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.54-7.39 (m, 2H), 7.38-7.28 (m, 3H), 2.12-1.96 (m, 7H), 1.36-1.22 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 131.7, 128.2, 128.1, 122.9, 92.9, 84.4, 69.1, 40.1, 25.2, 23.4.



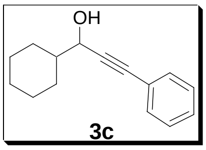
3a

2-Methyl-1-(phenylethynyl)-cyclohexane-1-ol (3b): Colorless solid, 87% isolated product yield. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.50-7.40 (m, 2H), 7.36-7.25 (m, 3H), 2.19 (s, 1H, OH), 2.18-2.08 (m, 1H), 1.82-1.48 (m, 6H), 1.42-1.19 (m, 2H), 1.12 (d, 3H, *J*=6.39). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 131.7, 128.2, 128.1, 122.9, 90.1, 86.4, 73.7, 42.9, 40.9, 32.4, 25.6, 24.4, 16.2.



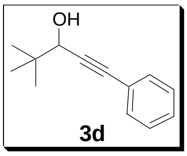
3b

1-Cyclohexyl-3-phenyl-prop-2-yn-1-ol (3c): Colorless oil, 78% isolated product yield. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.46-7.39 (m, 2H), 7.32-7.26 (m, 3 H), 4.37 (d, 1H, *J*=5.91), 2.18 (s, br, 1H, OH), 1.97-1.88 (m, 2H), 1.84-1.74 (m, 2H), 1.73-1.59 (m, 2H), 1.37-1.18 (m, 5H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 131.7, 128.2, 128.1, 122.8, 89.3, 85.6, 67.6, 44.3, 28.6 (diastereotopic), 28.2 (disastereotopic), 26.4, 25.9 (diastereotopic), 25.8 (diastereotopic).



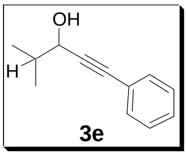
3c

4,4-Dimethyl-1-phenyl-1- pentyn-3-ol (3d): Colorless oil, 92% isolated product yield. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.46-7.41 (m, 2H), 7.33-7.28 (m, 3H), 4.24 (s, 1H), 1.91 (s, br, 1H, OH), 1.06 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 131.7, 128.3, 128.2, 122.8, 88.9, 85.7, 71.8, 36.1, 25.6, 25.3.



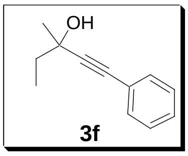
3d

4-Methyl-1-phenyl-1-pentyn-3-ol (3e): Colorless oil, 52% isolated product yield. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.46-7.41 (m, 2H), 7.32-7.28 (m, 3H), 4.41 (d, 1H, J=5.57), 2.10 (s, br, 1H, OH),2.05-1.90 (m, 1H), 1.08 (d, 3H, *J*=6.82Hz), 1.05 (d, 3H, *J*=6.82Hz). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 131.7, 128.3, 128.2, 122.7, 88.9, 85.5, 68.3, 34.7, 18.1, 17.5.



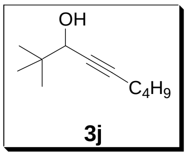
3e

3-Methyl-1-phenyl-1-pentyn-3-ol (3f): Slightly yellowish oil, 65% isolated product yield. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44-7.37 (m, 2H), 7.30-7.26 (m, 3H), 2.28 (s, br, 1H, OH), 1.84-1.73 (m, 2H), 1.56 (s, 3H), 1.10 (t, 3H, *J*=7.38, 15.26). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 131.6, 128.2, 128.1, 122.8, 92.7, 83.3, 69.1, 36.6, 29.2, 9.0.



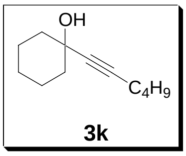
3f

2,2-Dimethyl-4-nonyn-3-ol (3j): Colorless to slightly yellowish oil, 57% isolated product yield. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.95 (s, 1H), 2.18 (t, 2H, *J*=6.54 Hz), 1.51-1.45 (m, 2H), 1.42-1.38 (m, 2H), 0.95 (s, 9H),



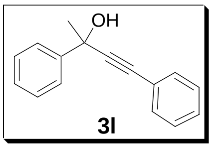
3j

0.90 (t, 3H, *J*=7.03Hz); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 86.2, 80.2, 71.8, 36.1, 31.0 25.3, 22.1, 18.5, 13.7.



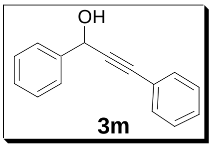
3k

1-(1-Hexynyl)cyclohexanol (3k): Colorless oil, 53% isolated product yield. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.21 (t, 2H, J=7.02Hz), 1.88-1.84 (m, 2H), 1.68-1.64 (m, 2H), 1.57-1.46 (m, 8H), 1.43-1.39 (m, 2H), 0.91 (t, 3H, J=7.02 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 146.7, 131.1, 43.6, 31.9, 30.9, 30.1, 28.9, 28.5, 26.8, 25.8.



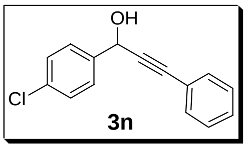
3l

2,4-Diphenyl-3-butyn-2-ol (3l): Colorless to slightly yellowish oil, 35% isolated product yield. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.77-7.71 (m, 2H), 7.45-7.50 (m, 2H), 7.41-7.27 (m, 6H), 1.86 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 145.8, 131.7, 128.4, 128.3, 128.2, 127.6, 124.9, 122.6, 92.6, 84.8, 70.2, 33.3.



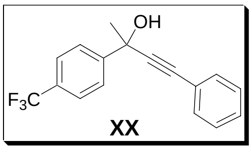
3m

1,3-Diphenyl-2-propyn-1-ol (3m): Colorless oil, 30% isolated product yield. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.65-7.30 (m, 10H), 5.70 (d, 1H, *J*=5.93Hz), 2.29 (d, 1H, *J*=5.93 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 140.8, 131.8, 128.9, 128.8, 128.7, 128.5, 127.1, 122.5, 88.9, 87.0, 65.4.



3n

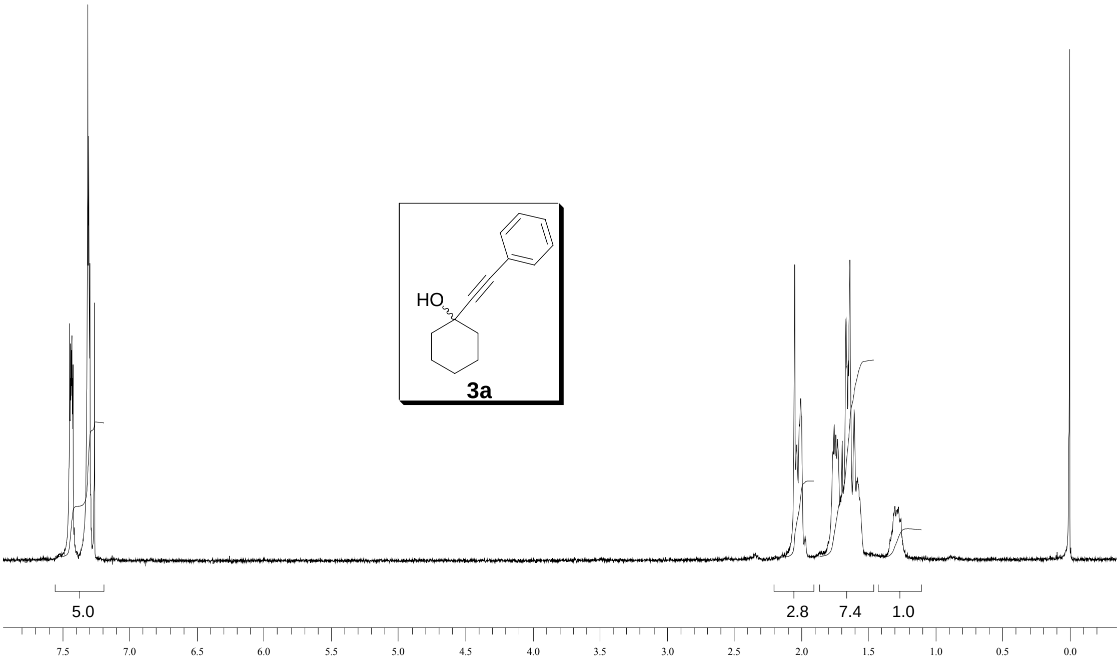
1-(4-Chlorophenyl)-3-phenyl-2-propyn-1-ol (3n): Yellowish oil, 31% isolated product yield. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.51 (dd, 2H, *J*=7.22Hz, *J*=1.61Hz), 7.44-7.41 (m, 2H), 7.34-7.25 (m, 5H), 5.64 (s, 1H), 2.64 (s, br, 1H, OH). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 139.1, 134.4, 132.1, 129.0, 128.9, 128.6, 128.3, 122.3, 88.3, 87.3, 64.7.

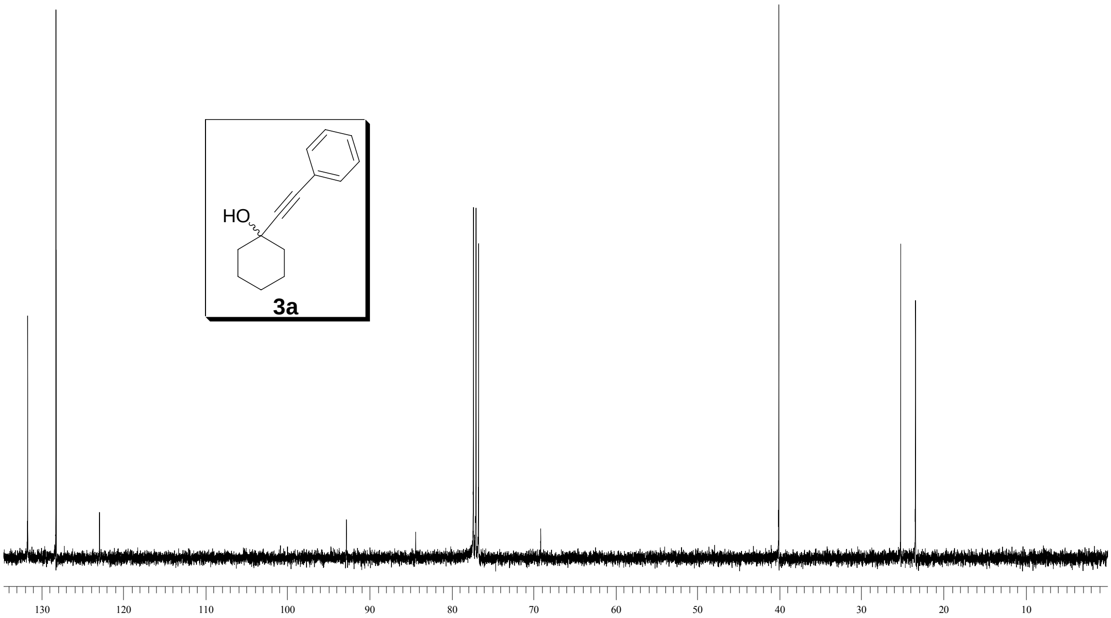


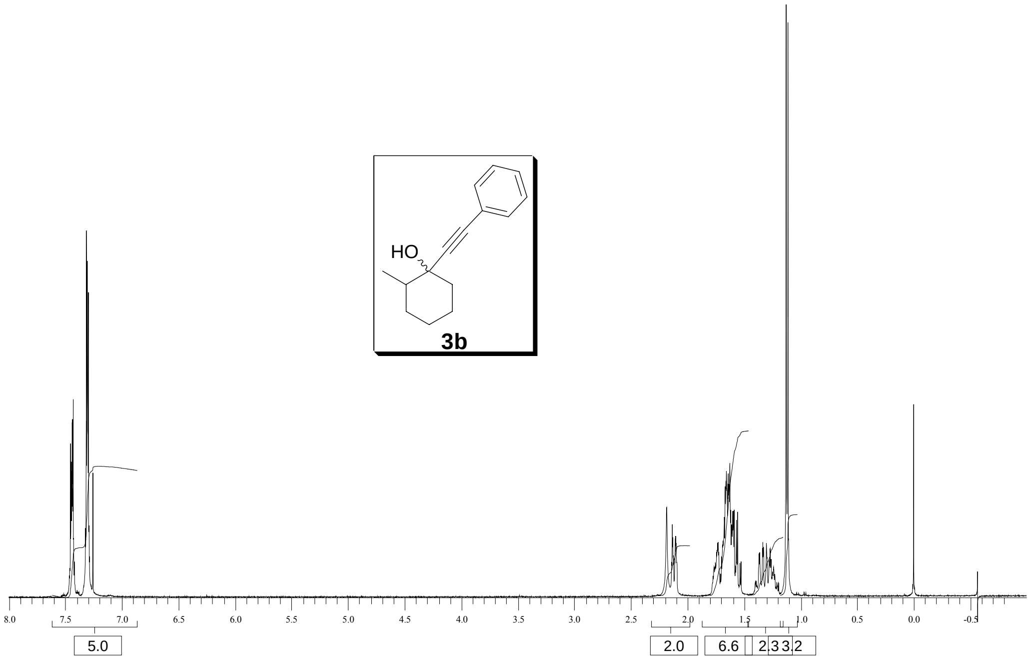
XX

2-(4-(Trifluormethyl)phenyl)-4-phenyl-3-butyn-2-ol (XX, new compound, not published): Yellowish solid, 46% isolated product yield. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.87-7.81 (d, 2H, *J*=8.37 Hz), 7.67-7.60 (d, 2H, *J*=8.37 Hz), 7.50-7.43 (m, 2H), 7.37-7.28 (m, 3H), 2.76 (s, br, 1H, OH), 1.85 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 149.6 (d, *J*=1.53 Hz), 131.7, 131.6, 128.7, 128.4, 128.3, 125.5, 125.3 (q, *J*=3.82Hz, *J*=7.63 Hz), 122.2, 91.7, 85.4, 70.1, 33.4.

5.1.4 ^{1}H and ^{13}C NMR spectra






HO
3b
8.0
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7.0
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6.0
5.5
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4.5
4.0
3.5
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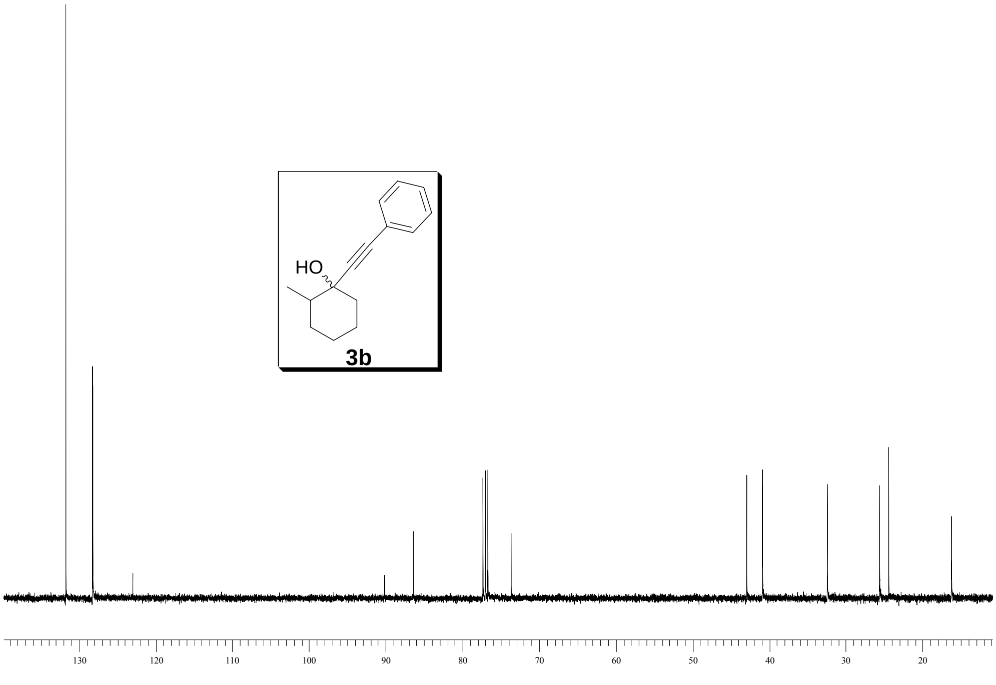
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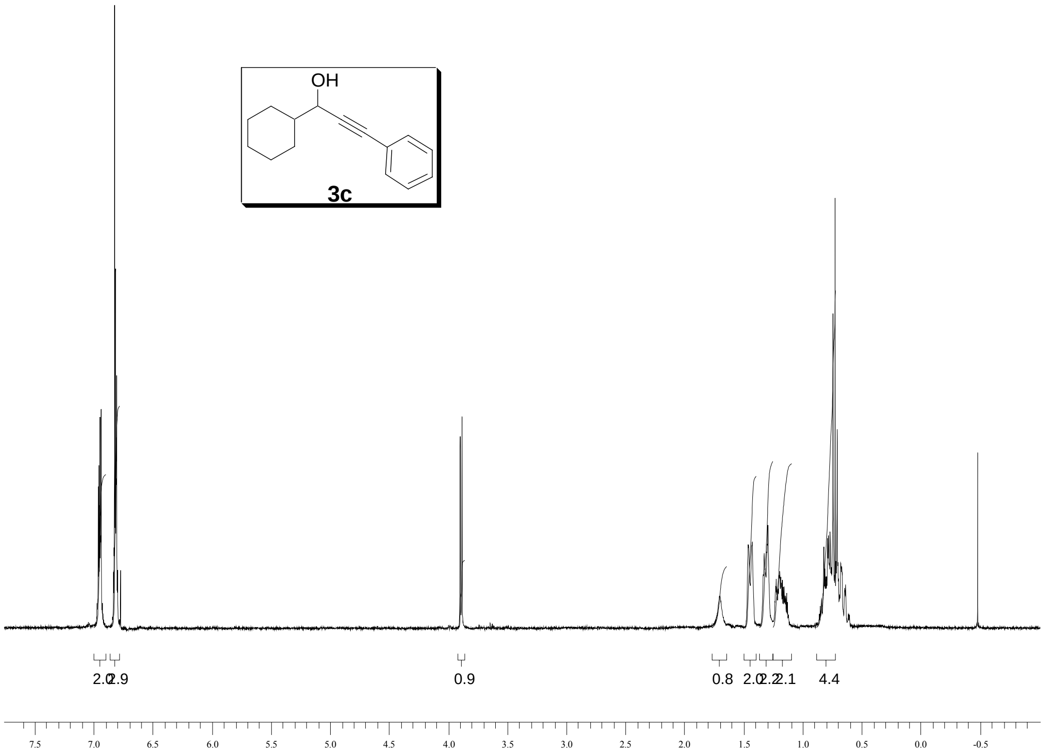
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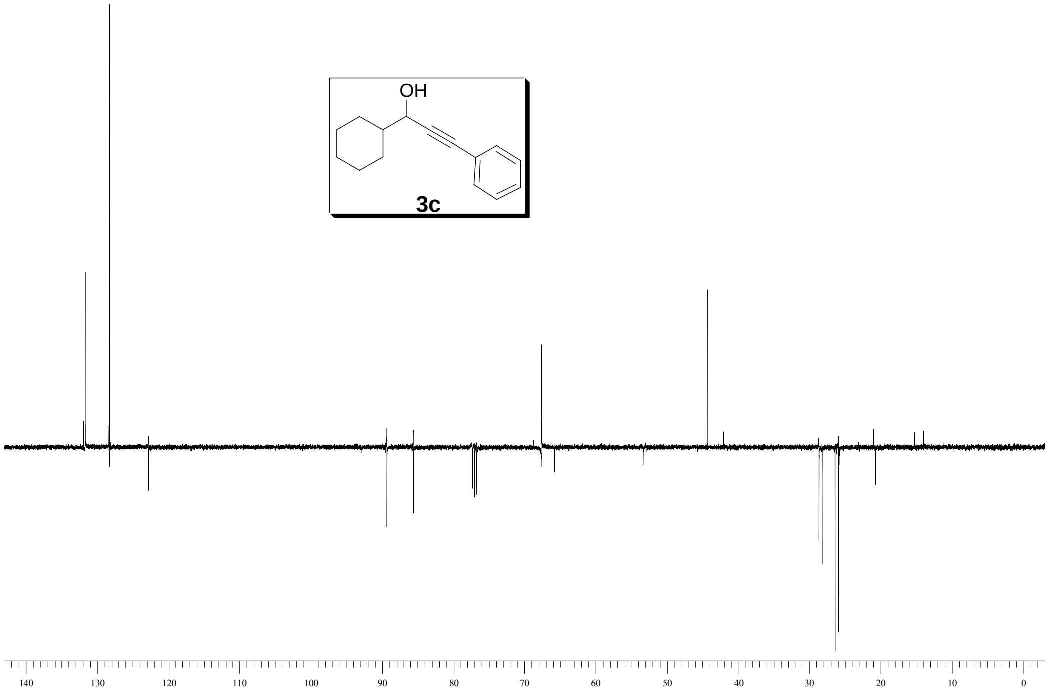
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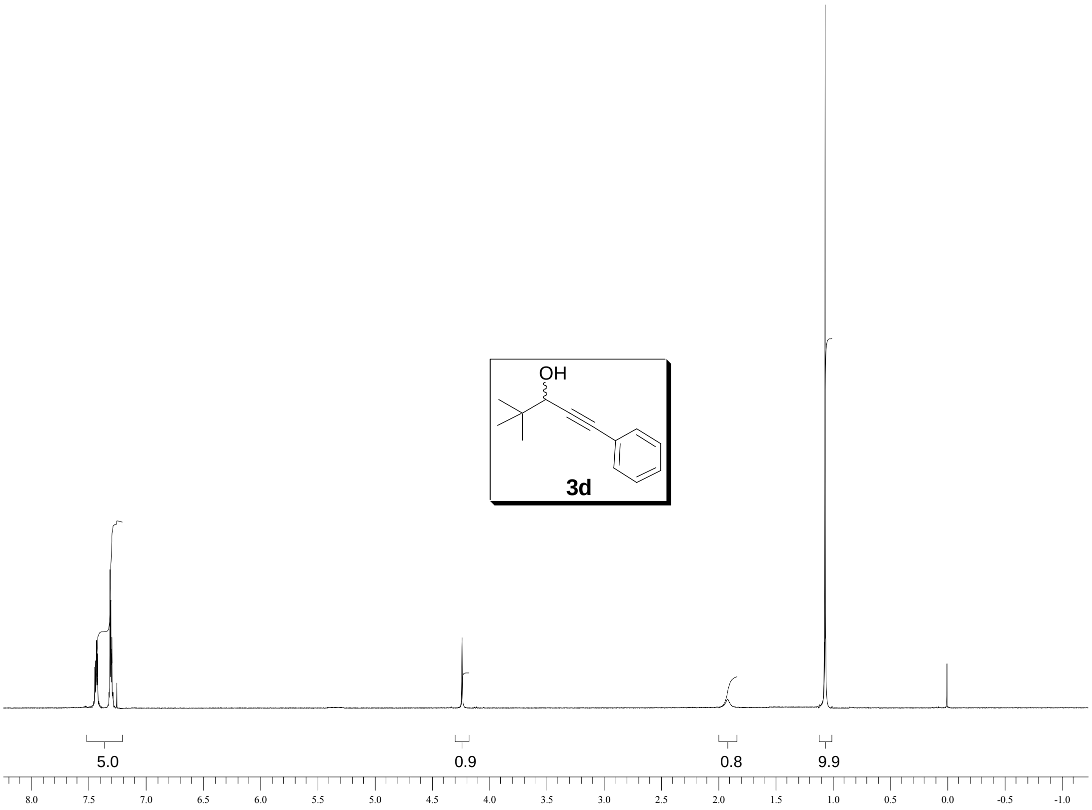
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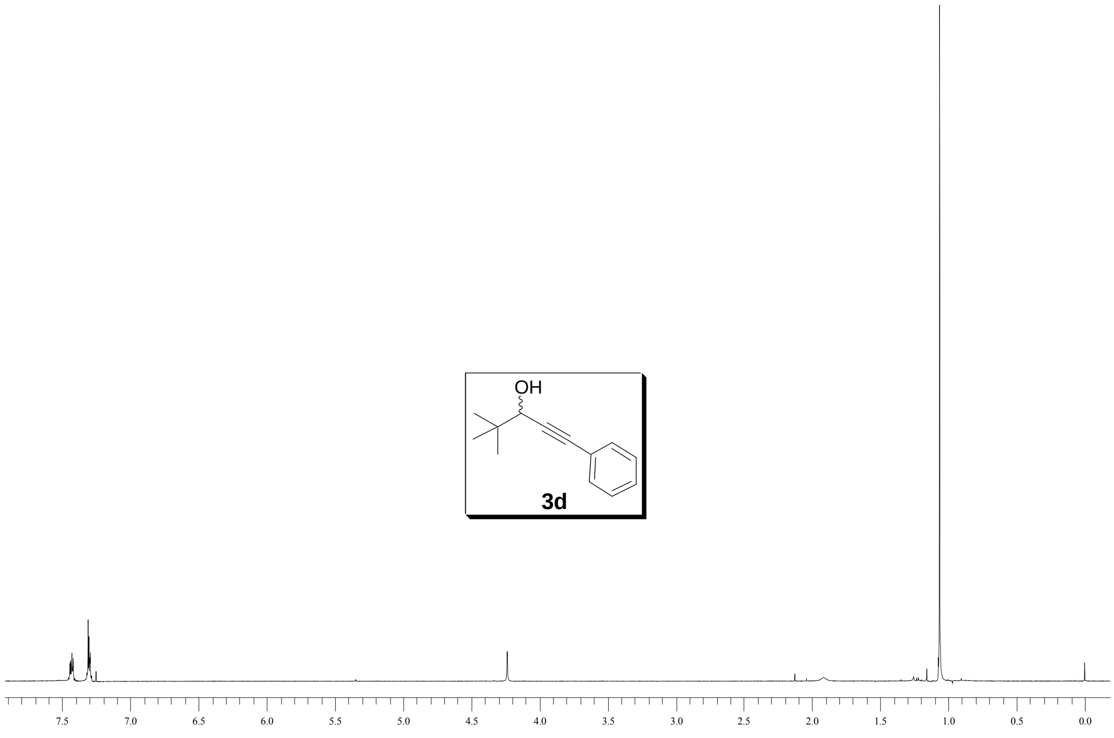
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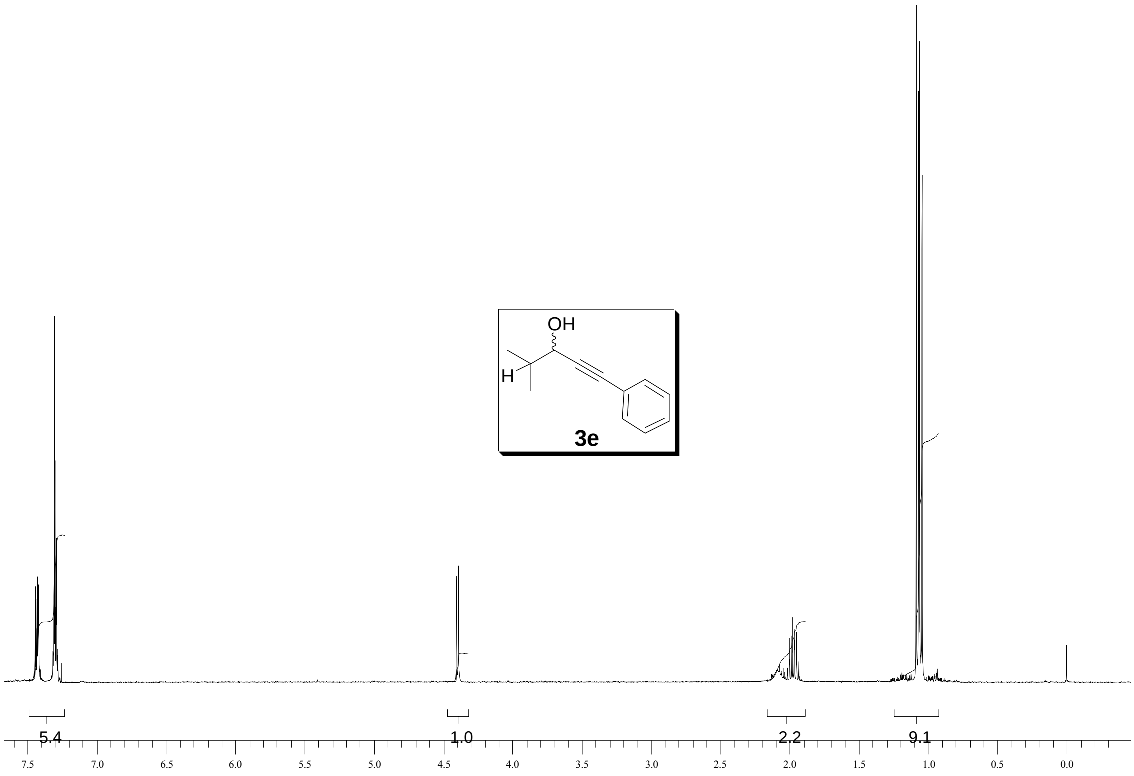
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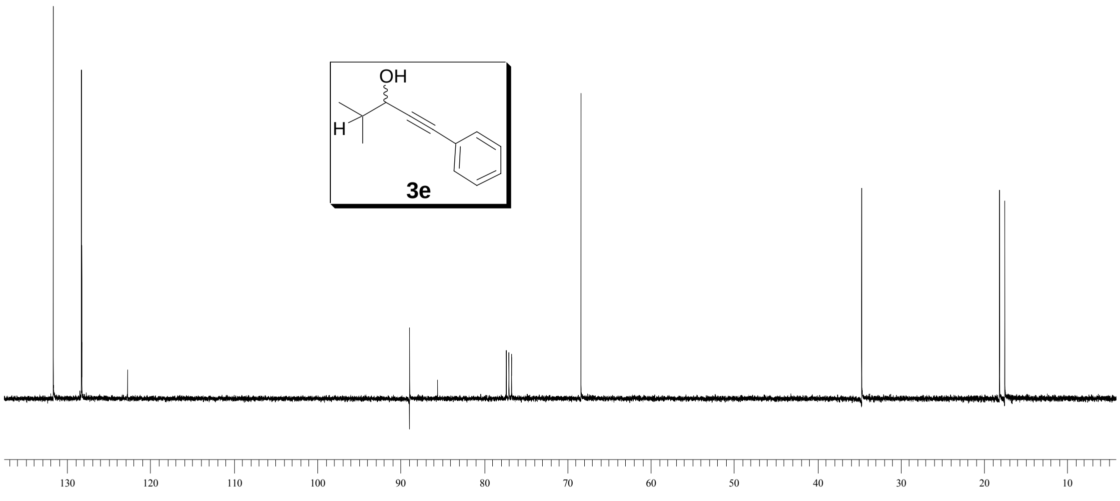
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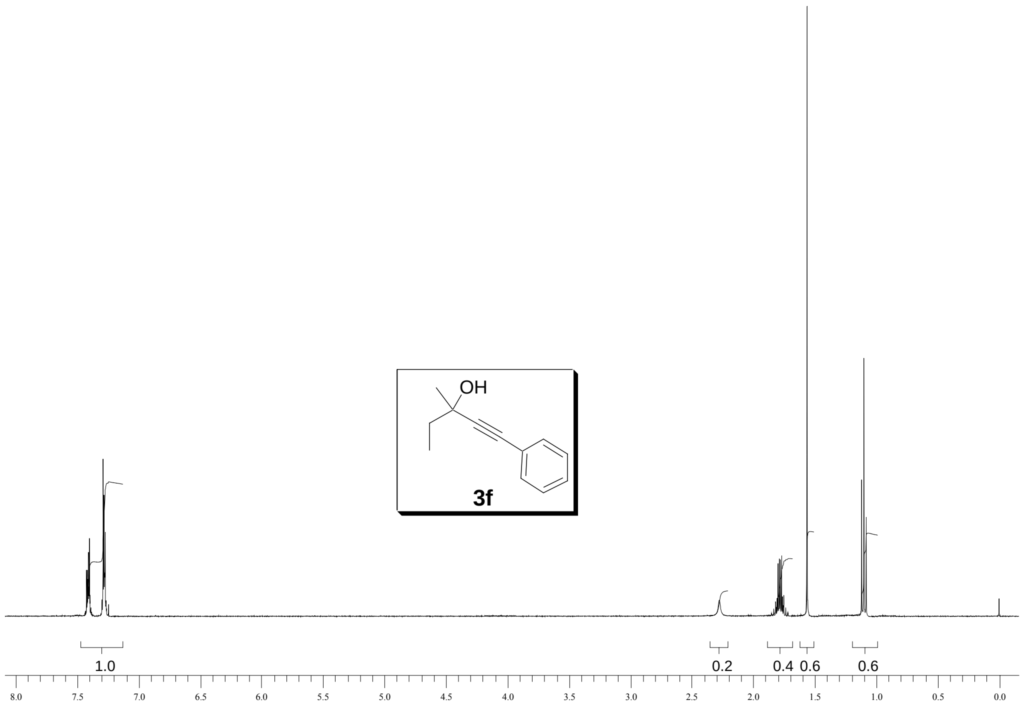
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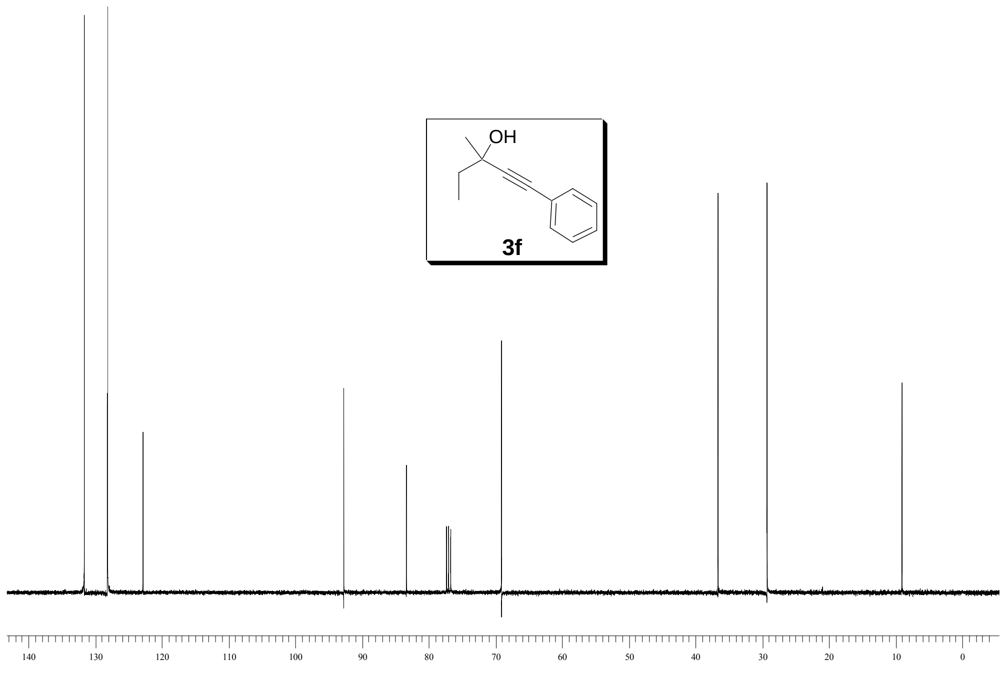
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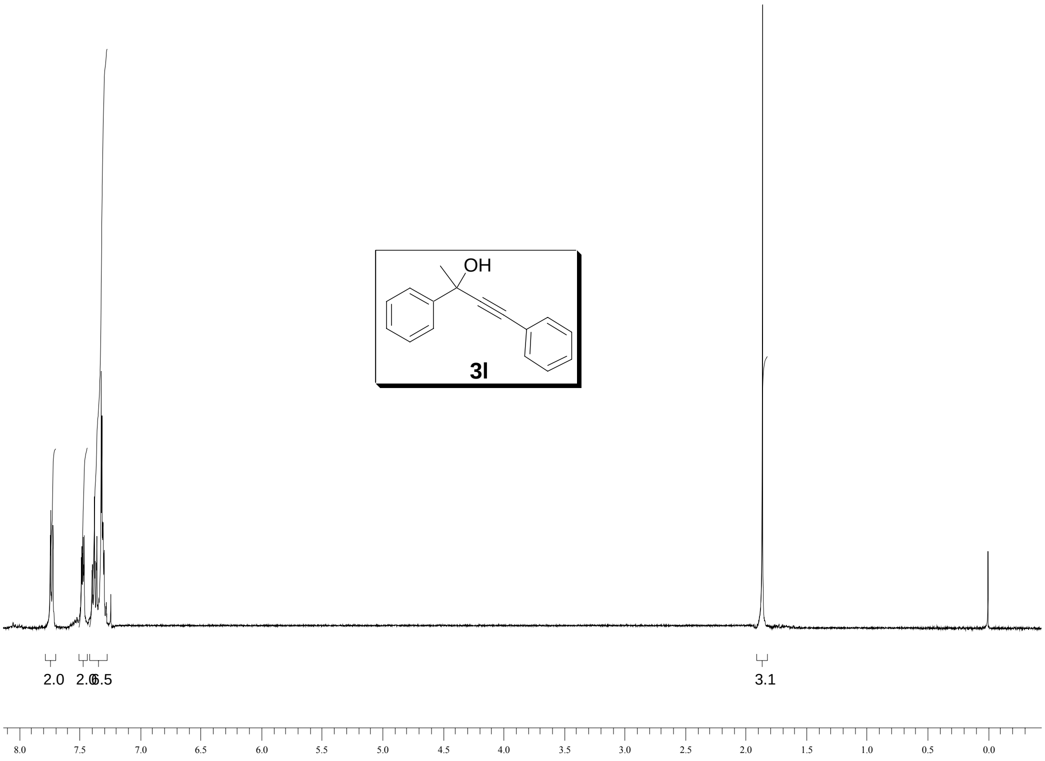
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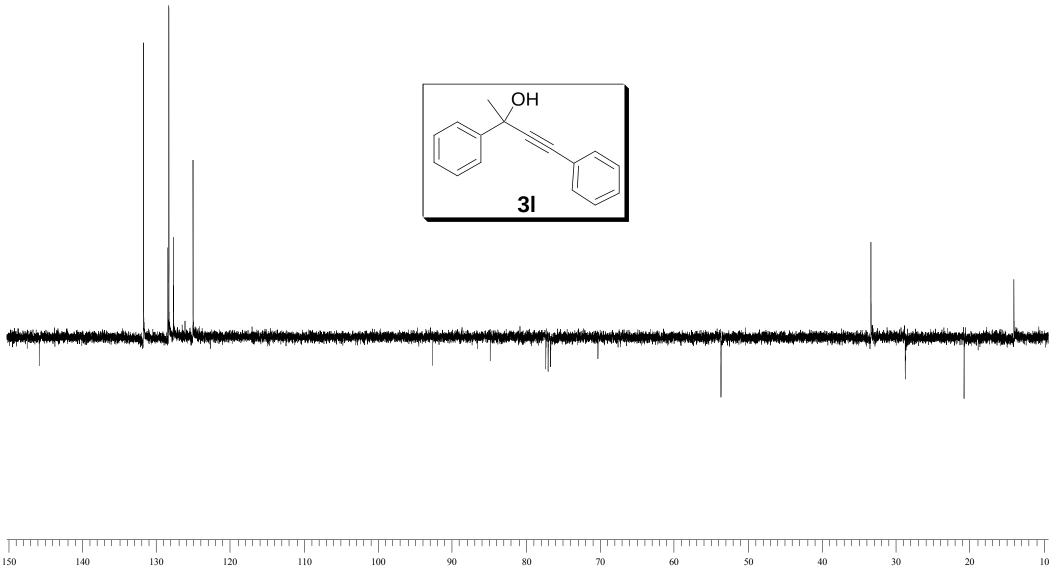
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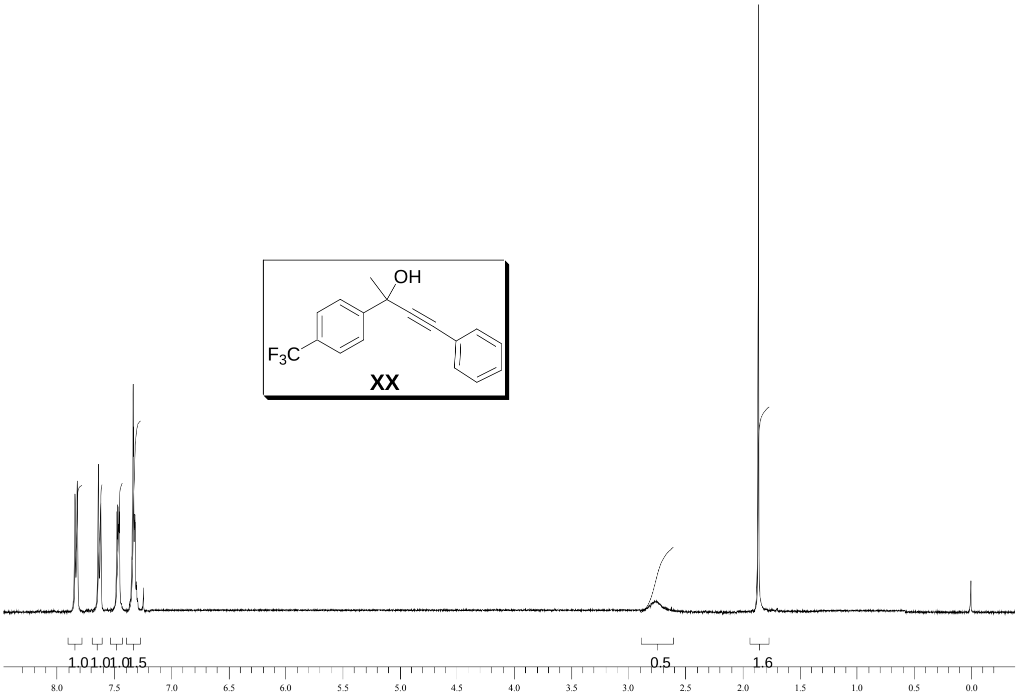
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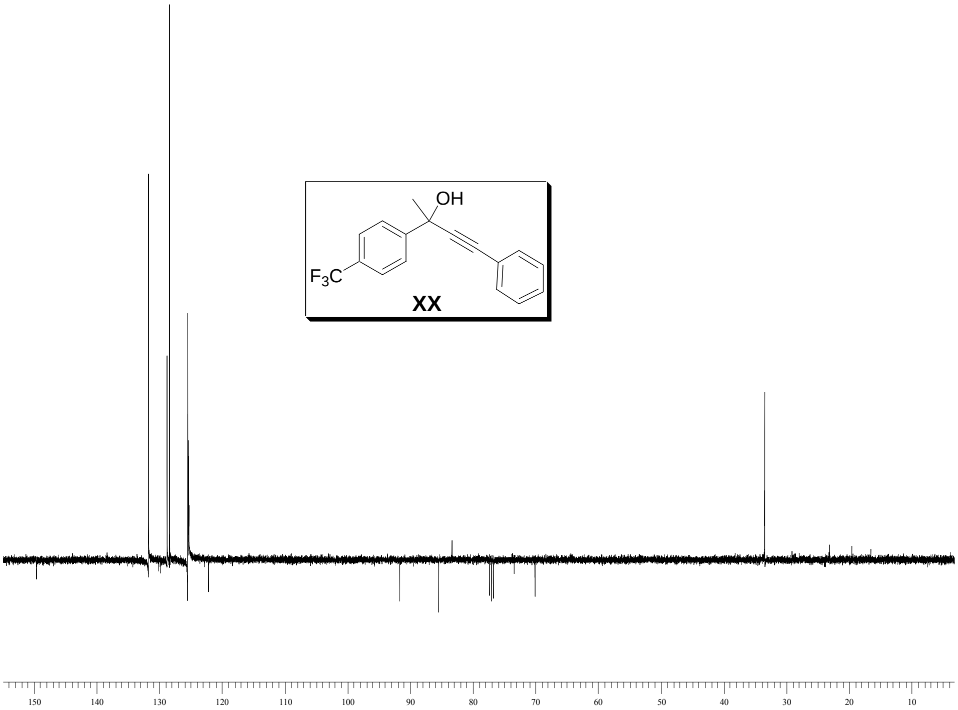
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20
10

5.2. Cooperative Brønsted Acid Type Organocatalysis: Alcoholysis of Styrene Oxides

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5.2.1. General Experimental Details

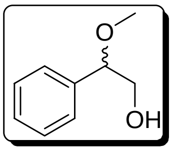
All chemicals were purchased from Aldrich, Acros Organics, Alfa Aesar, Merck, and Lancaster in the highest purity available and were used without further purification unless otherwise noted. Liquid epoxides were distilled once over a 10 cm Vigreux-column and stored until use in Schlenk-tubes under an argon atmosphere at 8 °C in a fridge. All carboxylic acids were used as purchased without further purification. All solvents used for extractions or filtrations were distilled once with a rotary evaporator. Drying followed established literature procedures: THF, *n*-hexane, and toluene were freshly distilled from Na/benzophenone ketyl; EtOH (Na/diethyl phthalate, reflux); PrOH, *i*-PrOH, BuOH (distilled once, 20 cm Vigreux column), and acetonitrile (5 h refluxed over P_2O_5 and distilled once over 30 cm column filled with Raschig rings). All dry chemicals were stored under an argon atmosphere and over activated 3 Å molecular sieve (MS) (alcohols and acetonitrile) and Na wire (THF, *n*-hexane, toluene), respectively: *t*-BuOH, allyl alcohol and BnOH were stored over MS 3 Å without prior distillation; $CDCl_3$ (99.8%, purchased from Deutero GmbH) was stored over MS 4 Å. TLC was carried out on pre-coated Macherey-Nagel plastic sheets Polygram SiO_2 N/UV254 (40–80 mm) using UV light for visualization. The progress of reactions was monitored by GC-MS analyses with a Quadrupol-MS HP MSD 5971(EI) and HP 5890A GC equipped with a J & W Scientific fused silica GC column (30 m × 0.250 mm, 0.25 micron DB–5MS stationary phase: 5% phenyl and 95% methyl silicone) using He (4.6 grade) as carrier gas; T-program standard 60–250 °C (15 °C/min heating rate), injector and transfer line 250 °C. ^1H and ^{13}C NMR spectra were recorded with Bruker spectrometer Avance II 200 Hz (AV 200) and Avance II 400 MHz (AV 400) using as the internal standard: TMS δ (^1H) = 0.00, δ (^{13}C) = 0.0; $CHCl_3$ [δ (^1H) = 7.26], $CHCl_3$ [δ (^{13}C) = 77.0]; ^{13}C signals were assigned with DEPT or APT (attached proton test) experiments. IR spectra were measured with Bruker IFS25 and IFS48 spectrophotometers. HRMS were recorded with a Sectorfield-MS: Finnigan MAT 95, CHN analyses were obtained with a Carlo Erba 1106 (balance: Mettler Toledo UMX-2) analyzer. To keep reaction temperature constant a standard mercury contact thermometer controlled by an IKAMAG RET-GS hot plate-stirrer was used. All analytical reaction mixtures were prepared in clean oven-dried one-necked 10 mL (5 mmol scale experiments) standard glass flasks (Schott DURAN) tightly sealed with a plastic plug. For experiments at 50 °C, reaction flasks were sealed with a clamped glass plug and were placed in a tempered oil bath (50 °C). For each test reaction thiourea derivative **3** and carboxylic acid **5a** or **5b-l**, respectively, were directly weighed out into the reaction flasks; liquid epoxides (5 mmol) were added via syringe (1 mL) and were dissolved in excess of alcohol (60 mmol). The quantity of additives (thiourea derivative **3** and carboxylic acid **5a-l**.) refers to the epoxide quantity that determines the scale of the experiment. If not otherwise noted all experiments were run in homogeneous solutions. For stirring, standard Teflon-coated magnetic stirring bars (1 to 1.5 cm) were used. Reaction temperature (25 or 50 °C) is given in Table 1. To determine the catalytic efficiency, all experiments were accompanied by parallel reference experiments under identical conditions, but without **3** or **5a-l** respectively. Sample volumes (~0.2 μL) were taken directly from the stirred reaction mixture via 10 μL Hamilton syringe and were injected immediately to record the GC-MS chromatogram. The course of each epoxide opening reaction was monitored by integrating the starting material and product signal; time-dependent conversion as a percentage was determined from the integral ratio of starting material and product signal. After completion of the reaction as confirmed by GC-MS, work-up followed according to the procedures described below.

All *ß*-hydroxyalkoxy alcohols **4a-r** (see Table 1) were isolated, purified, and characterized by ^{1}H and ^{13}C NMR, IR, and MS spectroscopy. New compounds are fully characterized and their data are listed below:

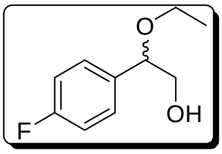
5.2.2 Representative protocol for alcoholysis of styrene oxides (1a-c):

Mandelic acid **5a** (7.6 mg, 0.05 mmol, 1 mol% loading) and thiourea derivative **3** (25 mg, 0.05 mmol, 1 mol% loading) were weighed into an oven-dried, one-necked, 10 mL flask. After addtition of styrene oxide **1a** (0.57 mL, 5 mmol) and dry ethanol (3.52 mL, 60 mmol) via a syringe the reaction flask was sealed with a plastic plug and the reaction solution was vigorously stirred with a magnetic stirring bar (1.5 cm) at room temperature. After full conversion (22 h, GC/MS analysis, see table 1) excess of ethanol was evaporated in vacuo and the crude product (yellow oil) was subjected to fractionated vacuum distillation over a 5 cm Vigreux column to afford analytically pure *ß*-hydroxyalkoxy alcohol (*ß*-ethoxy phenyl ethanol) **4b** (715 mg, 4.3 mmol, 86%, Sdp. 52−54 °C/~0.1 torr); physical data were consistent with those reported in literature.

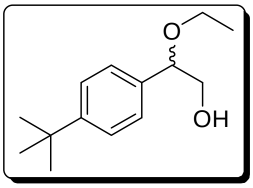
5.2.3. Representative and new compounds:



***rac*-2-Methoxy-2-phenyl-ethanol (4a)[130]:** High vacuum distillation of the crude residue afforded 646 mg of **4a** (4.25 mmol, 85 %) as colorless liquid, bp.: 48−49 °C/~0.1 torr. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.41−7.30 (5H, m), 4.39−4.32 (1H, dd, *J* = 12.1, 8.0), 3.80−3.58 (2H, m), 3.34 (3H, s), 3.15−3.09 (1H, dd, *J* = 12.6 Hz, 8.3 Hz). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 138.4, 128.5, 128.1, 126.9, 84.9, 67.3, 56.9. **IR** (cm^{-1}): 3415 (br), 2930 (m), 2871 (m), 2824 (m), 1452 (m), 1109 (s), 1061 (s), 1025 (s), 756 (s), 700 (vs), 636 (m). **LRMS** {EI, 70 eV, m/z (%)}: 152 (1), 122 (15), 121 (100), 105 (9), 91 (29), 77 (34), 65 (3), 51 (5). **HRMS** (M^+, $C_9H_{12}O_2$): cal.: 152.0837, found: 152.0834.

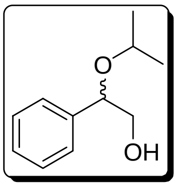


***rac*-2-Ethoxy-2-(4-fluorophenyl)-ethanol (4c, new compound):** High vacuum distillation of the crude residue furnished 526 mg of **4c** (2.85 mmol, 57 %) as slightly yellowish oil, bp.: 53−57 °C/~0,1 torr. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.32−7.25 (2H, m), 7.08−7.00 (2H, m), 4.39 (1H, dd, *J*=8.29 Hz, 3.99 Hz), 3.67−3.53 (2H, m), 3.52−3.35 (2H, m), 2.46 (1H, s, br, OH), 1.21 (3H, t, *J*=14.07 Hz, 7.02 Hz). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 162.5 (d, *J*=-245.9 Hz), 134.8 (d, *J*=3.0 Hz), 128.4 (d, *J*=8.07 Hz), 115.4 (d, *J*=21.8 Hz), 82.0, 67.3, 64.5, 15.3. **IR** (cm^{-1}): 3437.2 (br), 3070.5 (w), 2976.4 (s), 2930.3 (m), 2873.5 (s), 1896.1 (w), 1725.3 (w), 1685.0 (w), 1652.8 (w), 1604.7 (s), 1510.3 (vs), 1484.1 (m), 1445.3 (m), 1399.5 (s), 1370.5 (m), 1339.7 (m), 1296.2 (m), 1278.5 (m), 1225.3 (vs), 1190.3 (m), 1157.0 (s), 1106.3 (vs), 1071.1 (vs), 1047.7 (s), 1014.7 (m), 931.9 (m), 867.6 (s), 835.7 (vs). **HRMS:** cal.: 184.0899, found: 184.0898.

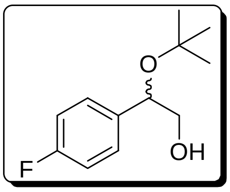


***rac*-2-Ethoxy-2-(4-*tert*-butylphenyl)-ethanol (4d, new compound):** High vacuum distillation of the crude residue afforded 722 mg of **4d** (3.25 mmol, 65 %) as colorless liquid, bp.: 78−82 °C/~0.1 torr. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.29 (2H, d, *J*=8.40 Hz), 7.16 (2H, d, *J*=8.40 Hz), 4.32 (1H, dd, *J*=8.45 Hz, 4.01 Hz), 3.63−3.48 (2H, m), 3.47−3.38 (1H, m), 3.36−3.26 (1H, m), 2.62 (1H, s, br, OH), 1.24 (9H, s), 1.14 (3H, t, *J*=14.02 Hz, 7.02 Hz). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 150.9, 135.9, 126.5, 125.4, 82.5, 67.4, 64.4, 34.6, 31.4, 15.3. **IR** (cm^{-1}): 3441.1 (br), 3055.6 (w), 3027.2 (w), 2965.3

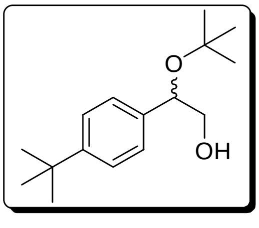
(vs), 2903.7 (s), 2869.3 (vs), 1910.1 (w), 1614.7 (w), 1509.9 (m), 1463.6 (m), 1397.2 (s), 1363.5 (m), 1340.8 (m), 1308.9 (m), 1270.0 (m), 1226.3 (m), 1202.9 (m), 1158.4 (m), 1119.7 (s), 1097.9 (vs), 1071.4 (s), 1047.8 (s), 933.1 (m), 867.3 (m), 831.2 (s). **HRMS:** cal.: 222.1619, found: 222.1587.



***rac*-2-Isopropoxy-2-phenyl-ethanol (4e):**[199] High vacuum distillation of the crude residue yielded 658 mg of **4e** (3.65 mmol, 73 %) as colorless liquid, bp.: 48 °C/~0.1 torr. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.25−7.14 (5H, m), 4.44−4.41 (1H, dd, J = 12.4 Hz, 8.4 Hz), 3.55−3.42 (3H, m), 2.76 (1H, s, br, OH), 1.10−1.08 (3H, d, J = 6 Hz), 1.03−1.01 (3H, d, J = 6.2 Hz). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 139.8, 128.4, 127.9, 126.9, 80.1, 69.5, 67.5, 23.5, 21.3. **IR** (cm^{-1}): 3426 (br), 2969 (m), 1452 (m), 1378 (m), 1123 (m), 1090 (s), 1055 (s), 969 (m), 756 (s), 700 (vs). **LRMS** {EI, 70 eV, m/z (%)}: 181 (1), 180 (5), 162 (4), 149 (49), 121 (8), 107 (100), 91 (12), 79 (49), 77 (17), 51 (5). **HRMS** ($M-CH_2=OH^+$, $C_{10}H_{13}O$): cal.: 149.0961, found: 149.0970.

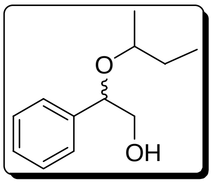


***ra*c-2-*tert*-Butoxy-2-(4-fluorophenyl)-ethanol (4g, new compound):** High vacuum distillation of the crude residue afforded 610 mg of **4g** (2.85 mmol, 57 %) as colorless liquid, bp.: 55 °C/~0.1 torr. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.34−7.28 (2H, m), 7.04-6.97 (2H, m), 4.59 (1H, dd, J=8.45 Hz, 4.27 Hz), 3.54−3.40 (2H, m), 2.10 (1H, s, br, OH), 1.16 (9H, s). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 162.3 (d, J=-245.18 Hz), 138.0 (d, J=2.95 Hz), 127.9, 127.8, 115.2, 115.0, 75.0, 74.5, 67.9 (diastereotopic), 67.8 (diastereotopic), 28.8. **IR** (cm^{-1}): 3439.5 (br), 3070.4 (w), 2975.8 (vs), 2903.7 (s), 2871.6 (m), 1892.7 (w), 1766.7 (w), 1726.8 (w), 1650.3 (w), 1605.7 (s), 1509.2 (vs), 1472.4 (m), 1462.4 (m), 1461.1 (m), 1391.6 (s), 1367.2 (s), 1295.8 (w), 1254.9 (m), 1223.0 (vs), 1192.8 (vs), 1155.3 (s), 1084.6 (vs), 1069.8 (vs), 953.9 (s), 864.1 (s), 834.3 (vs). **HRMS** ($C_{12}H_{17}FO_2$): cal.: 212.1212, found: 212.1200.

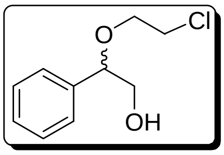


***ra*c-2-*tert*-Butoxy-2-(4-*tert*-butylphenyl)-ethanol (4h, new compound):** High vacuum distillation of the crude residue afforded 810 mg of **4h** (3.25 mmol, 65 %) as colorless solid, bp.: 62−67 °C/~0.1 torr. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.25 (2H, d, J=8.33 Hz), 7.18 (2H, d, J=8.33 Hz), 4.52 (1H, dd, J=8.40 Hz, 4.52 Hz), 3.48−3.36 (2H, m), 2.18 (1H, s, br, OH), 1.24 (9H, s), 1.10 (9H, s). **^{13}C NMR**

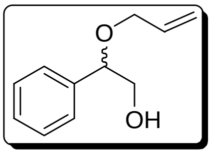
(100.6 MHz, $CDCl_3$): δ 150.2, 139.0, 126.0, 125.1, 74.9, 74.8, 67.9, 34.5, 31.4, 28.8. **IR** (cm^{-1}): 3393.6 (br), 3087.5 (w), 3056.8 (w), 2966.0 (s), 2921.7 (s), 2869.0 (m), 2797.2 (w), 2740.7 (w), 1913.4 (w), 1726.7 (w), 1508.1 (m), 1470.3 (m), 1407.5 (m), 1389.7 (m), 1377.9 (m), 1365.9 (s), 1342.2 (m), 1314.5 (w), 1259.9 (m), 1236.3 (m), 1192.9 (m), 1185.8 (m), 1106.6 (m), 1083.5 (vs), 1072.3 (vs), 1051.4 (s), 1016.6 (m), 957.4 (m), 862.6 (m), 828.1 (s). **HRMS** ($C_{16}H_{26}O_2$): cal.: 250.1933, found: 250.1930.



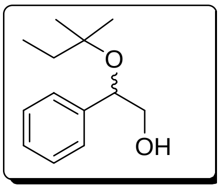
***rac*-2-sec-Butoxy-2-phenyl-ethanol (4i, new compound):** High vacuum distillation of the crude residue gave 931 mg of **4i** (4.70 mmol, 94 %) as colorless liquid, bp.: 64 °C/~0.1 torr. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.37–7.27 (5H, m), 4.57-4.51 (1H, m), 3.68–3.56 (2H, m), 3.46–3.41 (1H, m), 3.37–3.32 (1H, m), 2.66 (1H, s, br, OH), 1.70–1.38 (2H, m), 1.18–1.17 (1.5H, d, J = 6 Hz), 1.07-1.05 (1.5H, d, J = 6 Hz), 0.95–0.90 (1.5H, t, J = 15 Hz, 7.5 Hz), 0.87-0.83 (1.5H, t, J = 15 Hz, 7.5 Hz). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 140.0, 128.4, 127.2, 126.9, 80.7, 79.6, 75.1, 73.9, 67.6, 67.4, 30.3, 28.3, 20.4, 18.7, 10.1, 9.4. **IR** (cm^{-1}): 3442 (br), 2967 (vs), 2931 (s), 2877 (s), 1492 (m), 1453 (s), 1379 (m), 1092 (vs), 1059 (vs), 757 (s), 701 (vs). **LRMS** {EI, 70 eV, m/z (%)}: 194 (0.04), 163 (30), 121 (17), 107 (100), 91 (9), 79 (24), 77 (10), 65 (2), 57 (5), 51 (3). **HRMS** (M-CH_2=OH^+, $C_{11}H_{15}O$): cal.: 163.1127, found: 163.1128.



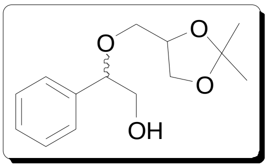
***rac*-2-(2-Chloro-ethoxy)-2-phenyl-ethanol (4j, new compound):** High vacuum distillation of the crude residue afforded 892 mg of **4j** (4.45 mmol, 89 %) as colorless liquid, bp.: 82 °C/~0.1 torr. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.39–7.29 (5H, m), 4.49–4.46 (1H, dd, J = 12.3 Hz, 8.7 Hz), 3.75–3.59 (6H, m), 2.59 (1H, s, br, OH). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 138.0, 128.7, 128.4, 126.8, 83.6, 69.1, 67.4, 43.2. **IR** (cm^{-1}): 3439 (br), 2872 (m), 1493 (m), 1453 (m), 1116 (vs), 1046 (s), 759 (s), 702 (vs). **LRMS** {EI, 70 eV, m/z (%)}: 200 (0.2), 171 (35), 169 (100), 121 (6), 107 (29), 105 (18), 91 (8), 84 (16), 79 (21), 77 (14), 65 (9), 63 (29), 51 (4). **HRMS** (M-CH_2=OH^+, $C_9H_{10}ClO$): cal.: 169.0424, found: 169.0434



***rac*-2-Allyloxy-2-phenyl-ethanol (4k)[199]:** High vacuum distillation of the crude residue afforded 712 mg of **4k** (4.0 mmol, 80 %) as colorless liquid, bp.: 56–57 °C/~0.1 torr. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.44–7.29 (5H, m), 6.01–5.91 (1H, m), 5.32–5.31 (0.5H, q, J = 4.9 Hz, 3.3 Hz), 5.28–5.27 (0.5H, q, J = 4.9 Hz, 3.3 Hz), 5.22–5.21 (0.5H, q, J = 4.2 Hz, 2.9 Hz), 5.18−5.17 (0.5H, q, *J* = 4.2 Hz, 2.8 Hz), 4.54−4.51 (1H, dd, *J* = 8.4 Hz, 3.8 Hz), 4.07−4.06 (0.25H, t, *J* =12.8 Hz, 6.2 Hz, 5.2 Hz, 1.5 Hz), 4.06−4.05 (0.25H, t, *J* = 12.8 Hz, 6.2 Hz, 5.2 Hz, 1.5 Hz), 4.04−4.03 (0.25H, t, *J* = 12.8 Hz, 6.2 Hz, 5.2 Hz, 1.5 Hz), 4.03−4.02 (0.25H, t, *J* = 12.8 Hz, 6.2 Hz, 5.2 Hz, 1.5 Hz), 3.92−3.91 (0.25H, t, *J* = 12.8 Hz, 6.2 Hz, 5.2 Hz, 1.3 Hz), 3.90−3.89 (0.25H, t, *J* = 12.8 Hz, 6.2 Hz, 5.2 Hz, 1.3 Hz), 3.89−3.88 (0.25H, t, *J* = 12.8 Hz, 6.2 Hz, 5.2 Hz, 1.3 Hz), 3.87−3.86 (0.25H, t, *J* = 12.8 Hz, 6.2 Hz, 5.2 Hz, 1.3 Hz), 3.78−3.73 (1H, dd, *J* = 11.8 Hz, 8.4 Hz), 3.67−3.62 (1H, dd, *J* = 11.8 Hz, 3.8 Hz), 3.02 (1H, s, br, OH). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 138.7, 134.6, 128.5, 128.1, 126.9, 117.2, 82.3, 69.8, 67.3. **IR** (cm^{-1}): 3405 (br), 2863 (m), 1492 (m), 1451 (m), 1343 (m), 1097 (s), 1040 (vs), 1027 (vs), 922 (s), 756 (s), 699 (vs). **LRMS** {EI, 70 eV, m/z (%)}: 178 (0.4), 148 (9), 147 (100), 121 (8), 105 (72), 91 (55), 79 (10), 77 (27), 65 (5), 51 (8), 41 (80). **HRMS:** ($M-CH_2=OH^+$, $C_{10}H_{11}O$): cal.: 147.0810, found: 147.0803.

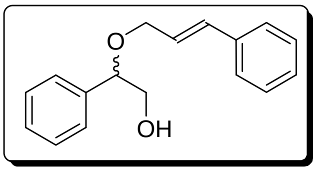


***rac*-2-(1,1-Dimethyl-propoxy)-2-phenyl-ethanol (4m, new compound):** High vacuum distillation of the reaction mixture furnished 760 mg of **4m** (3.65 mmol, 73 %) as colorless liquid, which becomes a white solid at ambient pressure; bp.: 101 °C/~0.1 torr. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.27−7.13 (5H, m), 4.49 (1H, t, *J*=12.54 Hz, 6.27 Hz), 3.39 (2H, d, *J*=6.27 Hz), 2.89 (1H, br, s), 1.41 (2H, m), 1.02 (3H, s), 0.89 (3H, s), 0.77 (3H, t, *J*=15.01 Hz, 7.51 Hz). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 142.6, 128.2, 127.4, 126.6, 77.2, 74.9, 67.9, 34.9, 29.3, 25.8, 8.7. **IR** (cm^{-1}): 3311.5 (br), 3061.6 (s), 3030.0 (s), 2965.6 (s), 2931.2 (s), 2879.3 (s), 2363.7 (w), 2337.7 (w), 1958.9 (w), 1895.1 (w), 1878.6 (w), 1808.8 (w), 1603.5 (m), 1504.4 (w), 1494.5 (s), 1451.1 (vs), 1386.6 (m), 1366.5 (m), 1350.5 (m), 1313.3 (m), 1228.2 (m), 1195.2 (m), 1177.1 (m), 1134.4 (m), 1088.4 (s), 1056.8 (s), 1026.7 (s), 1000.7 /m), 914.0 (m), 896.5 (m), 833.5 (m), 758.8 (s), 700.4 (s). **HRMS:** cal.: 208.1463, found 208.1465.

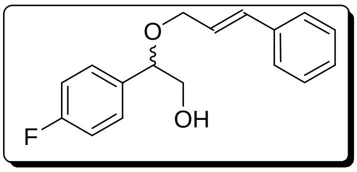


***rac*-2-(2,2-Dimethyl-[1,3]dioxolan-4-ylmethoxy)-2-phenyl-ethanol (4n [1:1 mixture of diastereomers], new compound)**: High vacuum distillation of the crude residue afforded 521 mg of **4n** (2.05 mmol, 41 %) as colorless oil, bp.: 115−118 °C/~0.5 torr. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.41−7.27 (5H, m), 4.47 (1H, m), 4.37−4.26 (1H, m), 4.08−4.01 (1H, m), 3.83−3.39 (5H, m), 2.42 (1H, s, br, OH), 1.41 (3H, s), 1.36 (3H, s).

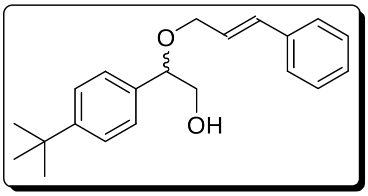
^{13}C NMR (100.6 MHz, $CDCl_3$): δ 138.3, 138.2, 128.6, 128.5, 128.3, 128.2, 126.8, 109.6, 109.5, 84.1, 83.8, 74.9, 74.7, 70.9, 69.9, 67.4, 66.7, 66.4, 26.7, 26.6, 25.3, 25.2. **IR** (cm^{-1}): 3454.3 (br), 3029.5 (w), 2985.7 (s), 2933.3 (s), 2872.6 (m), 1493.1 (m), 1453.1 (m), 1380.8 (s), 1371.0 (s), 1277.7 (m), 1256.0 (m), 1214.2 (s), 1157.1 (m), 1112.5 (s), 1053.6 (vs), 843.3, (m), 758.5 (m), 702.0 (m). **HRMS** (M-CH_2=OH^+, $C_{13}H_{17}O_3$): cal.: 221.1172, found: 221.1176.



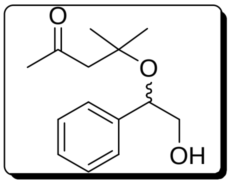
***rac*-2-Phenyl-2-(3-phenyl-allyloxy)-ethanol (4o, new compound):** High vacuum distillation of the crude residue yielded 833 mg of **4o** (3.27 mmol, 65 %) as colorless oil, bp.: 155 °C/~0.3 torr. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.36−7.15 (10H, m), 6.50 (1H, d, *J*=15.67 Hz), 6.21 (1H, m), 4.48 (1H, dd, *J*=8.64 Hz, 3.79 Hz), 4.11 (1H, dd, *J*=12.55 Hz, 5.59 Hz), 3.96 (1H, dd, *J*=12.61 Hz, 6.67 Hz), 3.67 (1H, dd, *J*=11.85 Hz, 8.54 Hz), 3.58 (1H, dd, *J*=11.85 Hz, 3.77 Hz), 2.24 (1H, br, s, OH). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 138.5, 136.6, 132.7, 131.2, 128.6, 128.2, 127.7, 126.9, 126.5, 125.7, 82.2, 69.5, 63.8. **IR** (cm^{-1}): 3385.4 (br), 3083.6 (m), 3061.8 (m), 3029.0 (m), 2924.9 (m), 2872.3 (m), 1953.7 (w), 1883.6, (w), 1811.3 (w), 1719.0 (m), 1675.8 (m), 1625.3 (w), 1601.8 (w), 1577.3 (w), 1559.5 (w), 1540.5 (w), 1494.7 (s), 1452.2 (s), 1395.7 (m), 1347.0 (m), 1308.6 (m), 1278.2 (m), 1197.7 (m), 1132.5 (m), 1093.3 (s), 1069.3 (s), 1027.3 (s), 968.5 (m), 914.8 (w), 889.5 (w), 835.1 (w), 751.2 (s), 700.4 (vs). **HRMS:** calc.: 254.1307, found: 254.1317.



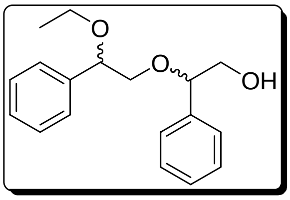
***rac*-2-(4-Fluor-phenyl)-2-(3-phenyl-allyloxy)-ethanol (4p, new compound).** High vacuum distillation of the crude residue yielded 858 mg of **4p** (3.15 mmol, 63 %) as colorless oil, bp.: ~152 °C/~0.3torr. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.32−7.14 (7H, m), 6.92−7.02 (2H, m), 6.47 1H, d, *J*=15.81 Hz), 6.19 (1H, m), 4.44 (1H, dd, *J*=8.34 Hz, 3.73 Hz), 4.07 (1H, dd, *J*=12.55, 5.69 Hz), 3.93 (1H, dd, *J*=12.55 Hz, 6.62 Hz), 3.63 (1H, dd, *J*=11.84 Hz, 8.39 Hz), 3.54 (1H, dd, *J*=12.02Hz, 3.46 Hz), 2.35 (1H, s, br, OH). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 162.6 (d, *J*=-246.3 Hz), 136.5, 134.3 (d, *J*=2.97 Hz), 132.8, 128.6, 127.9, 126.5, 125.6, 115.7, 115.5, 81.5, 69.5, 67.3. **IR** (cm^{-1}): 3431.9 (br), 3060.9 (m), 3028.3 (m), 2920.7 (m), 2867.6 (m), 1895.4 (w), 1703.2 (w), 1657.1 (w), 1604.9 (s), 1577.9 (w), 1508.7 (vs), 1449.7 (m), 1393.5 (m), 1343.0 (m), 1296.6 (m), 1224.0 (vs), 1156.9 (m), 1101.5 (s), 1049.1 (s), 968.3 (m), 835.4 (s), 736.0 (s), 693.2 (s). **HRMS:** calc.: 272.1220, found: 272.1222



***rac*-2-(4-*tert*-Butyl-phenyl)-2-(3-phenyl-allyloxy)-ethanol (4q, new compound).** High vacuum distillation of the crude residue yielded 1080 mg of **4q** (3.47 mmol, 70 %) as colorless oil, bp.: 168−173 °C/~0.3 torr. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.37−7.13 (9H, m), 6.51 (1H, d, *J*=15.72 Hz), 6.21 (1H, m), 4.44 (1H, dd, *J*=8.44 Hz, 3.39 Hz), 4.11 (1H, dd, *J*=12.63 Hz, 6.39 Hz), 3.95 (1H, dd, *J*=12.63 Hz, 6.39 Hz), 3.66 (1H, m), 3.55 (1H, m), 2.25 (1H, br, s, OH), 1.25 (9H, s). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 151.2, 136.6, 135.4, 132.5, 128.6, 127.7, 126.7, 126.5, 125.9, 125.5, 82.0, 69.5, 67.4, 34.6, 31.4. **IR** (cm^{-1}): 3422.5, (br), 3082.6 (m), 3058.7 (m), 3027.0 (m), 2962.3 (vs), 2904.7 (m), 2867,7 (m), 1910.3 (w), 1717.9 (w), 1653.7 (w), 1612.5 (w), 1599.3 (w), 1577.0 (w), 1508.7 (m), 1495.9 (m), 1462.2 (m), 1449.5 (m), 1393.4 (m), 1363.2 (m), 1343.2 (m), 1309.1 (m), 1269.7 (m), 1203.4 (m), 1185.5 (m), 1101.6 (s), 1043.7 (s), 967.1 (m), 875.8 (w), 831.8 (m), 744.8 (m), 693.2 (m). **HRMS:** calc.: 310.1933, found: 310.1973.

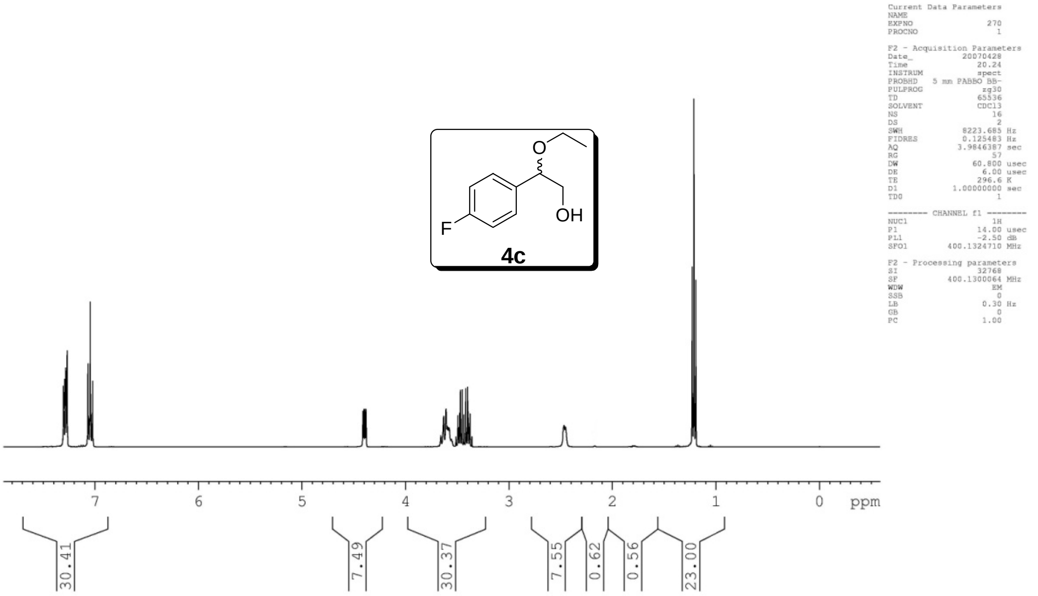


***rac*-4-(2-Hydroxy-1-phenyl-ethoxy)-4-methyl-pentan-2-one (4r, new compound)**: Separation of the crude residue by HPLC (diol phase, 20% TBME/ 80% *n*-Hexane) afforded 685 mg of **4r** (2.90 mmol, 58 %) as colorless oil, bp.: 91−96 °C/~0.1 torr. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.34−7.22 (5H, m), 4.65 (1H, t, *J*=10.62 Hz, 3.50 Hz), 3.53 (1H, s, br, OH,), 3.52 (2H, d, *J*=3.50 Hz), 2.67 (2H, d, *J*=2.06), 2.21 (3H, s),1.24 (3H, s), 1.16 (3H, s). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 208.4, 141.7, 128.3, 127.5, 126.3, 75.9, 75.8, 68.2, 53.4, 32.8, 27.9, 26.0. **IR** (cm^{-1}): 3429.5 (br), 2974.1 (s), 2933.7 (s), 2868.4 (m), 1704.4 (vs), 1492.9 (m), 1452.6 (s), 1386.1 (s), 1367.3 (s), 1312.5 (m), 1218.4 (m), 1146.5 (m), 1085.4 (vs), 1060.5 (vs), 963.3 (m), 758.0 (m), 702.6 (vs). **LRMS** {EI, 70 eV, m/z (%)}: 221 (8), 205 (5), 163 (58), 121 (15), 107 (40), 91 (17), 77 (14), 65 (4), 51 (6), 43 (100). **HRMS:** $(M\text{-}CH_2{=}OH^+, C_{13}H_{17}O_2)$: cal.: 205.1232, found: 205.1213.



***rac*-2-(2-Ethoxy-2-phenyl-ethoxy)-2-phenyl-ethanol (4s, by-product formed at non-optimized reaction conditions [1:1 mixture of diastereomers], new compound)**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.29 (10H, m), 4.53 (1H, m), 4.46 (1H, dd, *J*=8.79, 3.75 Hz), 3.80-3.35 (6H, m), 2.89 (1H, br, s, OH), 1.23 (1.5H, t, *J*=14.03 Hz, 7.01 Hz), 1.20 (1.5H, t, *J*=14.03 Hz, 7.01 Hz). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 139.6, 139.1, 138.9, 138.4, 128.4, 128.0, 126.9, 126.8, 126.7, 126.6, 84.7, 83.1, 81.9, 80.4, 74.9, 73.2, 67.7, 67.3, 64.6, 64.5, 15.3, 15.2. **IR** (cm^{-1}): 3441.3 (br), 3085.2 (m), 3062.2 (m), 3029.8 (m), 2973.7 (m), 2869.3 (s), 1954.1 (w), 1883.3 (w), 1810.7 (w), 1722.7 (m), 1652.5 (w), 1603.1 (w), 1585.5 (w), 1558.2 (w), 1493.0 (m), 1452.8 (s), 1398.0 (m), 1369.9 (m), 1346.1 (m), 1311.6 (m), 1278.5 (m), 1223.4 (m), 1197.5 (m), 1176.7 (m), 1156.8 (m), 1107.9 (vs), 1071.1 (vs), 1027.9 (s), 1001.9 (w), 943.2 (w), 915.1 (w), 892.9 (w), 861.2 (w), 758.5 (s), 701.0 (vs). **HRMS:** (M-CH_2=OH^+, $C_{17}H_{19}O_2$): cal.: 255.1379, found: 255.1381.

5.2.4. ^{1}H and ^{13}C NMR spectra



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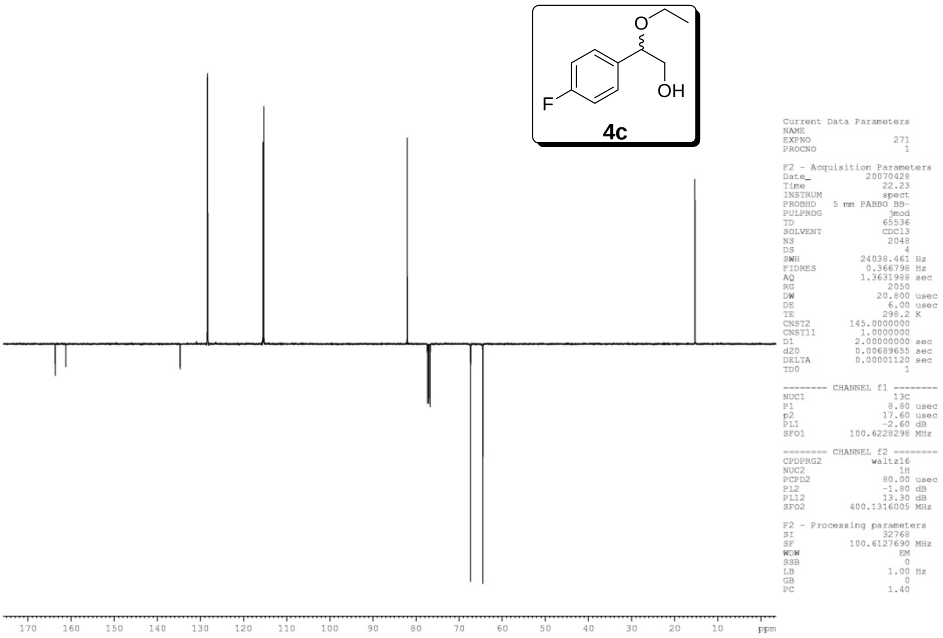

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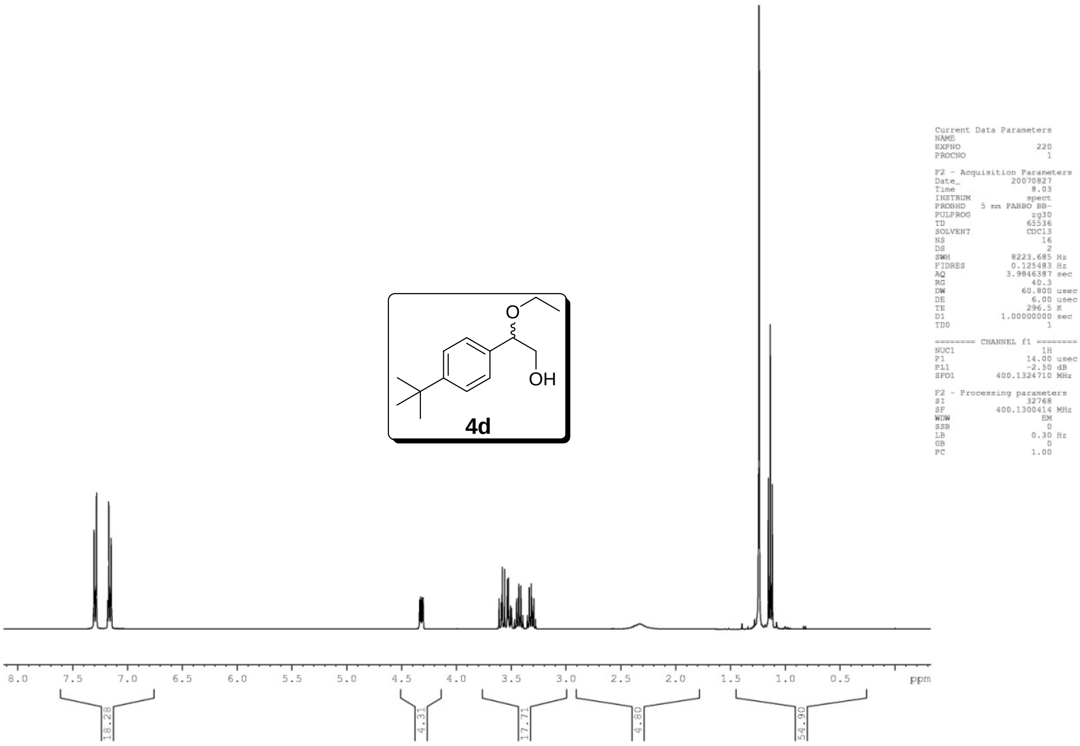

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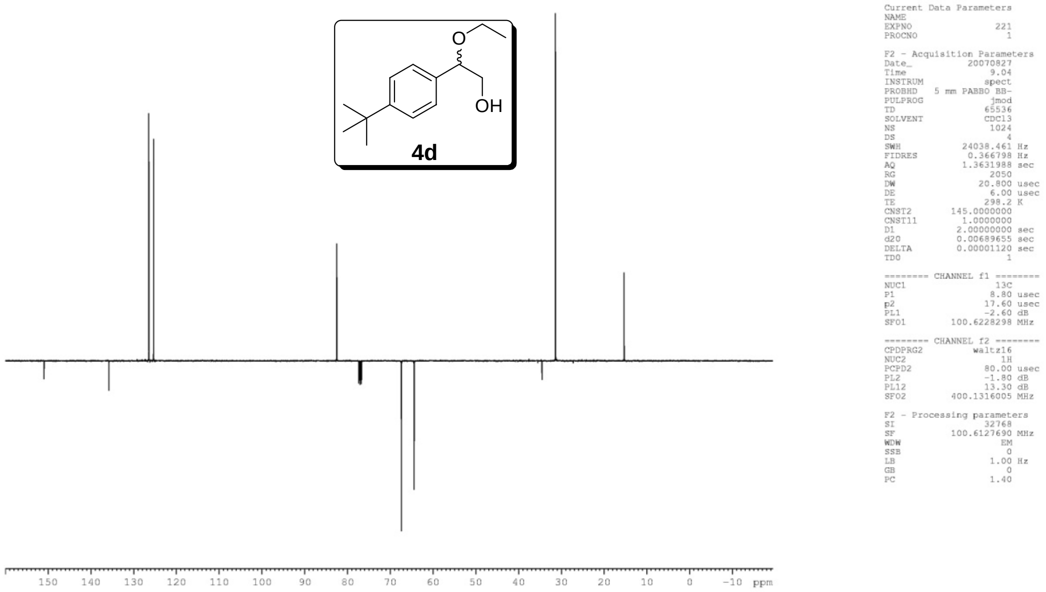

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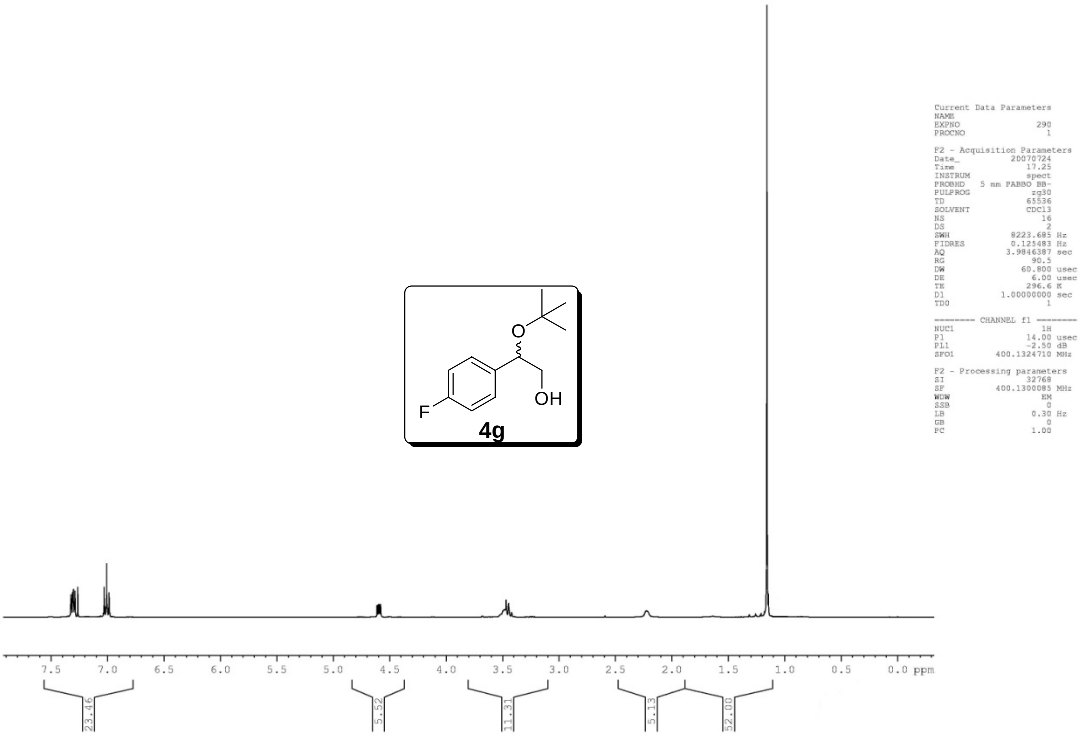
DE                     6.00 usec
TE                    298.2 K
CNST2           145.0000000
CNST11            1.0000000
D1               2.00000000 sec
d20              0.00689655 sec
DELTA            0.00001120 sec
TD0                       1

======== CHANNEL f1 ========
NUC1                    13C
P1                     8.80 usec
p2                    17.60 usec
PL1                   -2.60 dB
SFO1            100.6228298 MHz

======== CHANNEL f2 ========
CPDPRG2             waltz16
NUC2                     1H
PCPD2                 80.00 usec
PL2                   -1.80 dB
PL12                  13.30 dB
SFO2            400.1316005 MHz

F2 - Processing parameters
SI                    32768
SF              100.6127690 MHz
WDW                      EM
SSB                       0
LB                     1.00 Hz
GB                        0
PC                     1.40
```

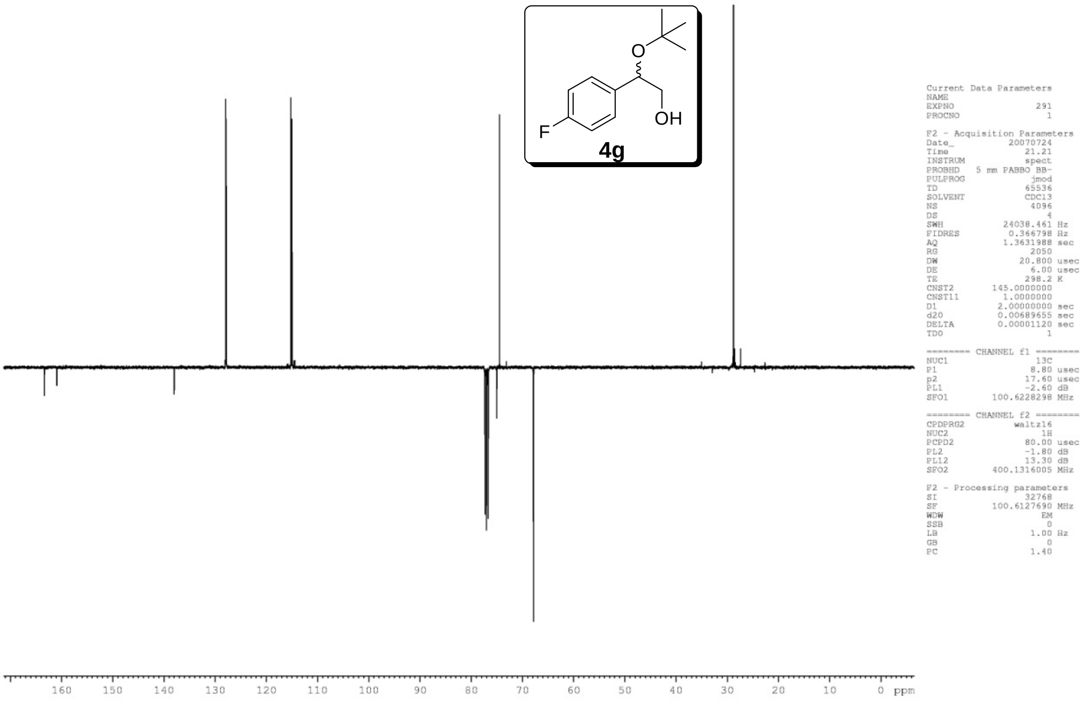


```
Current Data Parameters
NAME
EXPNO                290
PROCNO                 1

F2 - Acquisition Parameters
Date_           20070724
Time               17.25
INSTRUM            spect
PROBHD   5 mm PABBO BB-
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                    16
DS                     2
SWH             8223.685 Hz
FIDRES          0.125483 Hz
AQ             3.9846387 sec
RG                  90.5
DW                60.800 usec
DE                  6.00 usec
TE                 296.6 K
D1            1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                  1H
P1                 14.00 usec
PL1                -2.50 dB
SFO1         400.1324710 MHz

F2 - Processing parameters
SI                 32768
SF           400.1300085 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  1.00
```



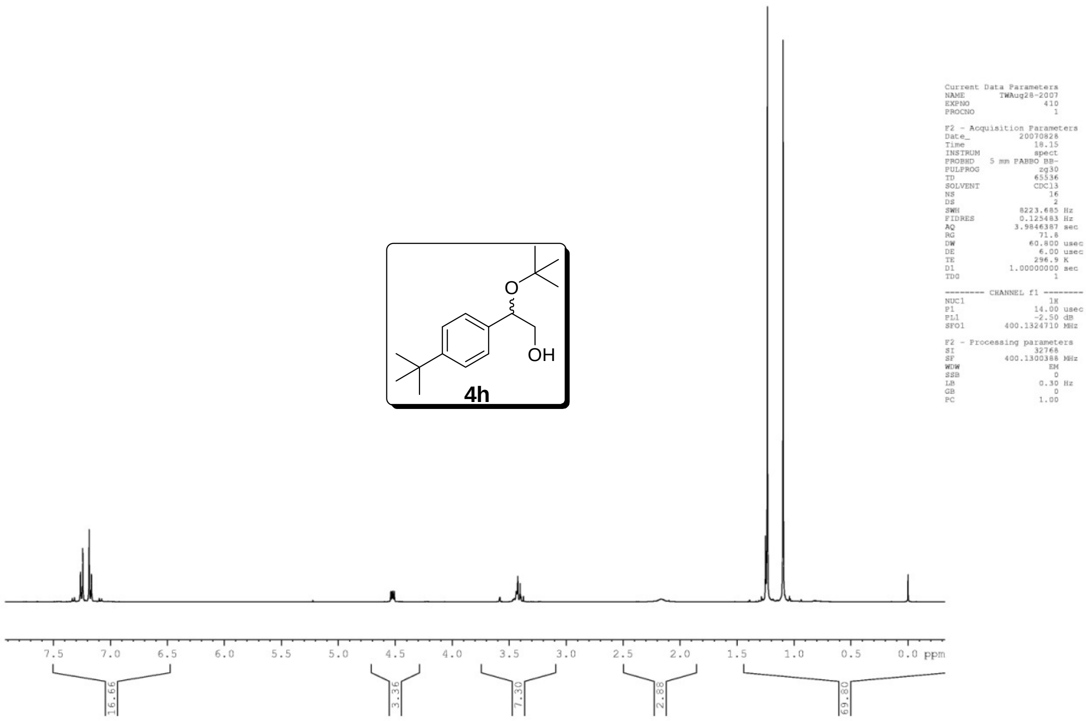
```
Current Data Parameters
NAME
EXPNO                291
PROCNO                 1

F2 - Acquisition Parameters
Date_           20070724
Time               21.21
INSTRUM            spect
PROBHD   5 mm PABBO BB-
PULPROG             jmod
TD                 65536
SOLVENT            CDCl3
NS                  4096
DS                     4
SWH            24038.461 Hz
FIDRES          0.366798 Hz
AQ             1.3631988 sec
RG                  2050
DW                20.800 usec
DE                  6.00 usec
TE                 298.2 K
CNST2        145.0000000
CNST11         1.0000000
D1            2.00000000 sec
d20           0.00689655 sec
DELTA         0.00001120 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                 13C
P1                  8.80 usec
p2                 17.60 usec
PL1                -2.60 dB
SFO1         100.6228298 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                  1H
PCPD2              80.00 usec
PL2                -1.80 dB
PL12               13.30 dB
SFO2         400.1316005 MHz

F2 - Processing parameters
SI                 32768
SF           100.6127690 MHz
WDW                   EM
SSB                    0
LB                  1.00 Hz
GB                     0
PC                  1.40
```

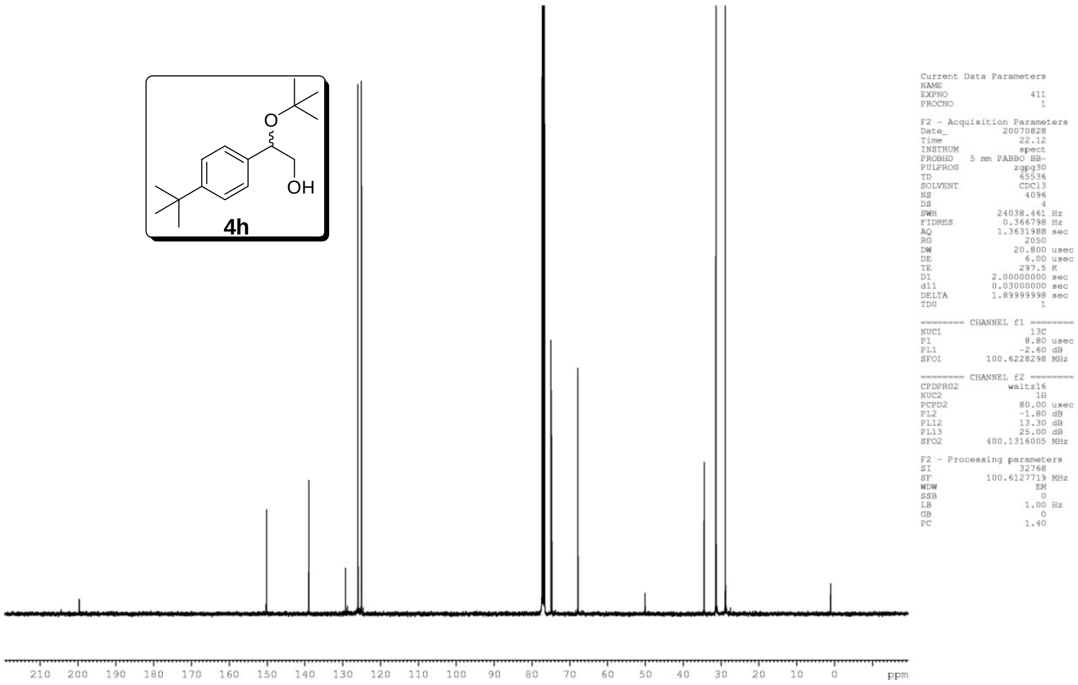


```
Current Data Parameters
NAME       TWAug28-2007
EXPNO               410
PROCNO                1

F2 - Acquisition Parameters
Date_          20070828
Time              18.15
INSTRUM           spect
PROBHD   5 mm PABBO BB-
PULPROG            zg30
TD                65536
SOLVENT           CDCl3
NS                   16
DS                    2
SWH            8223.685 Hz
FIDRES         0.125483 Hz
AQ            3.9846387 sec
RG                 71.8
DW               60.800 usec
DE                 6.00 usec
TE                296.9 K
D1           1.00000000 sec
TD0                   1

======== CHANNEL f1 ========
NUC1                 1H
P1                14.00 usec
PL1               -2.50 dB
SFO1        400.1324710 MHz

F2 - Processing parameters
SI                32768
SF          400.1300388 MHz
WDW                  EM
SSB                   0
LB                 0.30 Hz
GB                    0
PC                 1.00
```



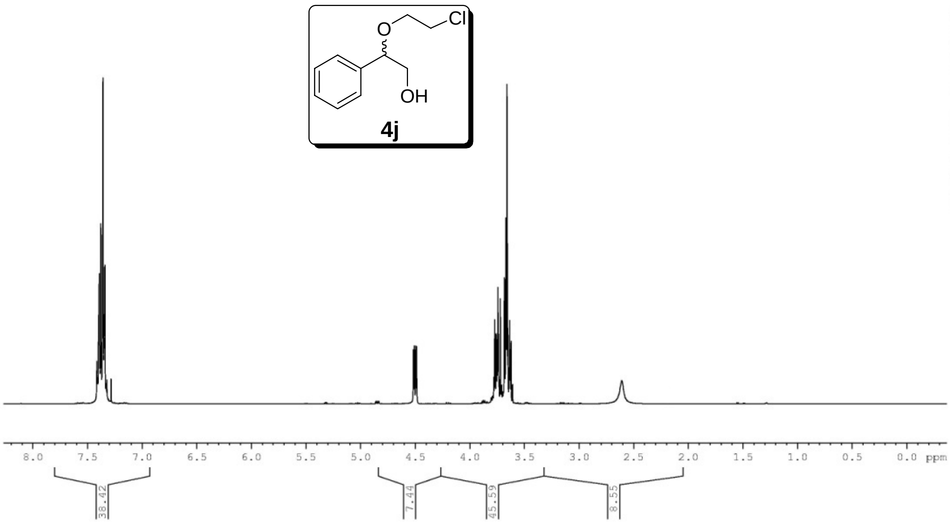
```
Current Data Parameters
NAME
EXPNO                411
PROCNO                 1

F2 - Acquisition Parameters
Date_           20070828
Time               22.12
INSTRUM            spect
PROBHD    5 mm PABBO BB-
PULPROG          zgpg30
TD                 65536
SOLVENT            CDCl3
NS                  4096
DS                     4
SWH            24038.461 Hz
FIDRES          0.366798 Hz
AQ             1.3631988 sec
RG                  2050
DW                20.800 usec
DE                  6.00 usec
TE                 297.5 K
D1            2.00000000 sec
d11           0.03000000 sec
DELTA         1.89999998 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                 13C
P1                  8.80 usec
PL1                -2.60 dB
SFO1         100.6228298 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                  1H
PCPD2              80.00 usec
PL2                -1.80 dB
PL12               13.30 dB
PL13               25.00 dB
SFO2         400.1316005 MHz

F2 - Processing parameters
SI                 32768
SF           100.6127719 MHz
WDW                   EM
SSB                    0
LB                  1.00 Hz
GB                     0
PC                  1.40
```



```
Current Data Parameters
NAME
EXPNO                 140
PROCNO                  1

F2 - Acquisition Parameters
Date_            20070313
Time                 8.07
INSTRUM             spect
PROBHD   5 mm PABBO BB-
PULPROG              zg30
TD                  65536
SOLVENT             CDCl3
NS                     16
DS                      2
SWH              8223.685 Hz
FIDRES           0.125483 Hz
AQ              3.9846387 sec
RG                   45.2
DW                 60.800 usec
DE                   6.00 usec
TE                  295.4 K
D1             1.00000000 sec
TD0                     1

======== CHANNEL f1 ========
NUC1                   1H
P1                  14.00 usec
PL1                 -2.50 dB
SFO1          400.1324710 MHz

F2 - Processing parameters
SI                  32768
SF            400.1300000 MHz
WDW                    EM
SSB                     0
LB                   0.30 Hz
GB                      0
PC                   1.00
```

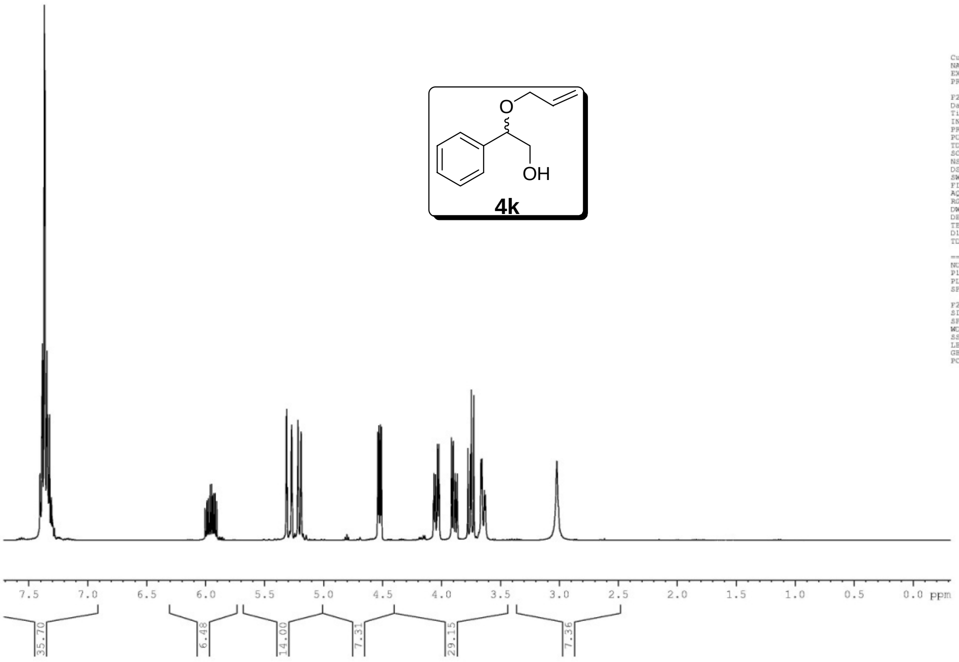
```
Current Data Parameters
NAME
EXPNO                 141
PROCNO                  1

F2 - Acquisition Parameters
Date_            20070313
Time                 8.21
INSTRUM             spect
PROBHD   5 mm PABBO BB-
PULPROG              jmod
TD                  65536
SOLVENT             CDCl3
NS                    204
DS                      4
SWH             24038.461 Hz
FIDRES           0.366798 Hz
AQ              1.3631988 sec
RG                   2050
DW                 20.800 usec
DE                   6.00 usec
TE                  297.2 K
CNST2         145.0000000
CNST11          1.0000000
D1             2.00000000 sec
d20            0.00689655 sec
DELTA          0.00001120 sec
TD0                     1

======== CHANNEL f1 ========
NUC1                  13C
P1                   8.80 usec
p2                  17.60 usec
PL1                 -2.60 dB
SFO1          100.6228298 MHz

======== CHANNEL f2 ========
CPDPRG2           waltz16
NUC2                   1H
PCPD2               80.00 usec
PL2                 -1.80 dB
PL12                13.30 dB
SFO2          400.1316005 MHz

F2 - Processing parameters
SI                  32768
SF            100.6127690 MHz
WDW                    EM
SSB                     0
LB                   1.00 Hz
GB                      0
PC                   1.40
```

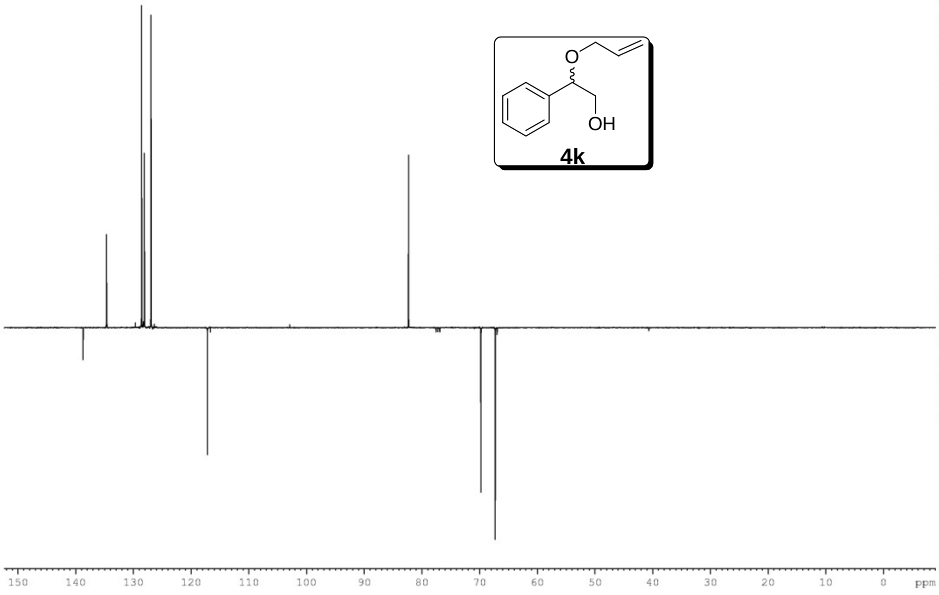


```
Current Data Parameters
NAME
EXPNO                  250
PROCNO                   1

F2 - Acquisition Parameters
Date_             20070207
Time                  9.21
INSTRUM              spect
PROBHD   5 mm PABBO BB-
PULPROG               zg30
TD                   65536
SOLVENT              CDCl3
NS                      16
DS                       2
SWH               8223.685 Hz
FIDRES            0.125483 Hz
AQ               3.9846387 sec
RG                    12.7
DW                  60.800 usec
DE                    6.00 usec
TE                   295.1 K
D1              1.00000000 sec
TD0                      1

======== CHANNEL f1 ========
NUC1                    1H
P1                   14.00 usec
PL1                  -2.50 dB
SFO1           400.1324710 MHz

F2 - Processing parameters
SI                   32768
SF             400.1300000 MHz
WDW                     EM
SSB                      0
LB                    0.30 Hz
GB                       0
PC                    1.00
```



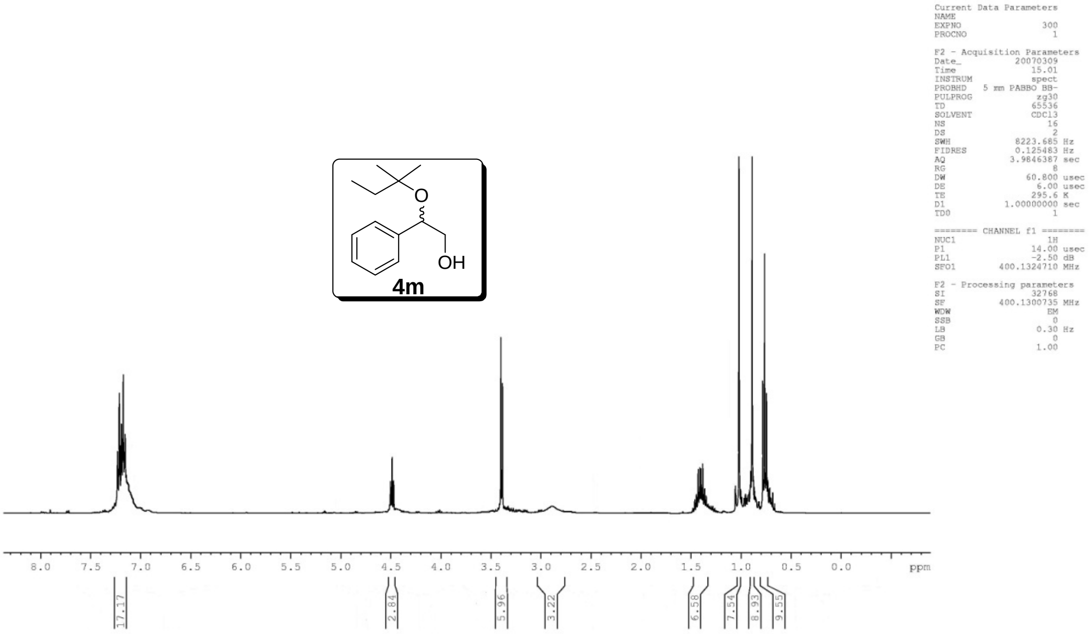
```
Current Data Parameters
NAME
EXPNO                  251
PROCNO                   1

F2 - Acquisition Parameters
Date_             20070207
Time                 11.04
INSTRUM              spect
PROBHD   5 mm PABBO BB-
PULPROG               jmod
TD                   65536
SOLVENT              CDCl3
NS                     204
DS                       4
SWH              24038.461 Hz
FIDRES            0.366798 Hz
AQ               1.3631988 sec
RG                    2050
DW                  20.800 usec
DE                    6.00 usec
TE                   296.6 K
CNST2          145.0000000
CNST11           1.0000000
D1              2.00000000 sec
d20             0.00689655 sec
DELTA           0.00001120 sec
TD0                      1

======== CHANNEL f1 ========
NUC1                   13C
P1                    8.80 usec
p2                   17.60 usec
PL1                  -2.60 dB
SFO1           100.6228298 MHz

======== CHANNEL f2 ========
CPDPRG2            waltz16
NUC2                    1H
PCPD2                80.00 usec
PL2                  -1.80 dB
PL12                 13.30 dB
SFO2           400.1316005 MHz

F2 - Processing parameters
SI                   32768
SF             100.6127690 MHz
WDW                     EM
SSB                      0
LB                    1.00 Hz
GB                       0
PC                    1.40
```

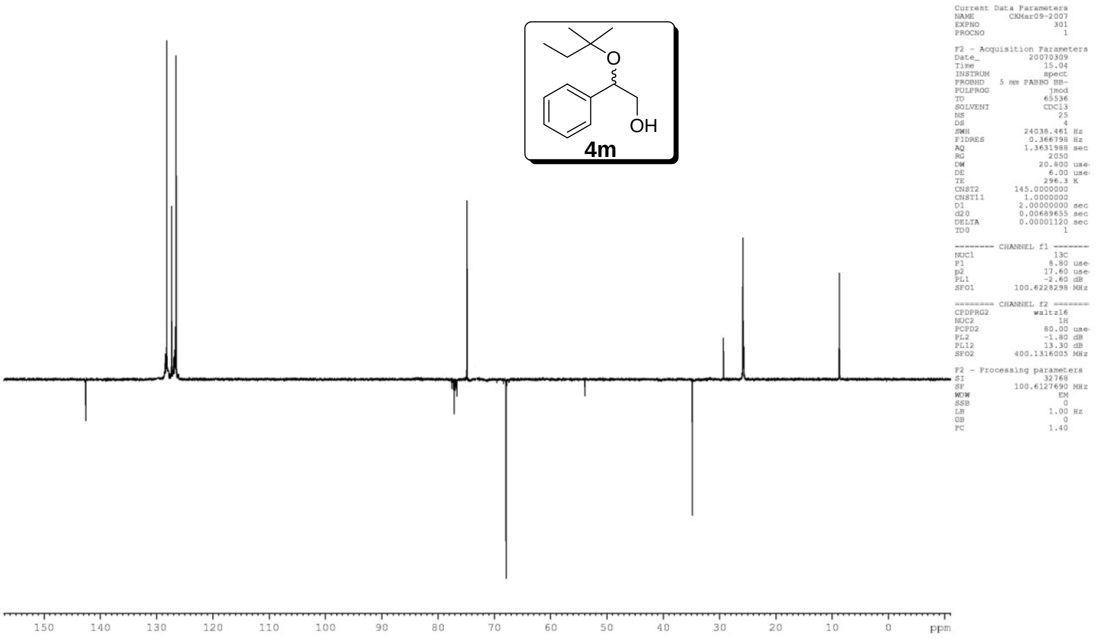


```
Current Data Parameters
NAME
EXPNO                 300
PROCNO                  1

F2 - Acquisition Parameters
Date_            20070309
Time                15.01
INSTRUM             spect
PROBHD   5 mm PABBO BB-
PULPROG              zg30
TD                  65536
SOLVENT             CDCl3
NS                     16
DS                      2
SWH              8223.685 Hz
FIDRES           0.125483 Hz
AQ              3.9846387 sec
RG                      8
DW                 60.800 usec
DE                   6.00 usec
TE                  295.6 K
D1             1.00000000 sec
TD0                     1

======== CHANNEL f1 ========
NUC1                   1H
P1                  14.00 usec
PL1                 -2.50 dB
SFO1          400.1324710 MHz

F2 - Processing parameters
SI                  32768
SF            400.1300735 MHz
WDW                    EM
SSB                     0
LB                   0.30 Hz
GB                      0
PC                   1.00
```



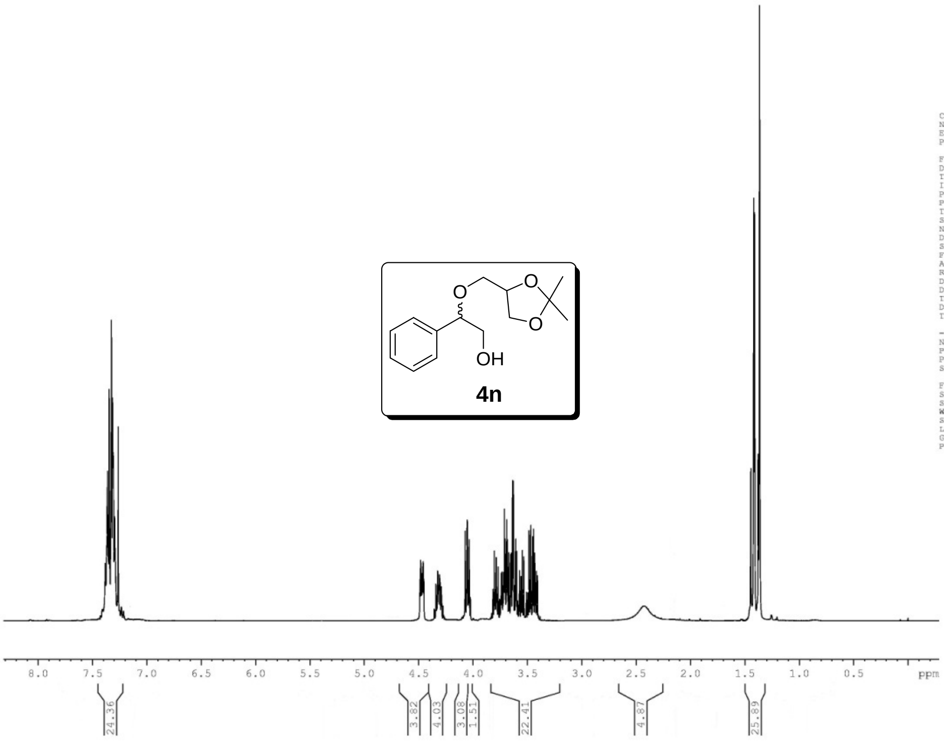
```
Current Data Parameters
NAME         CKMar09-2007
EXPNO                 301
PROCNO                  1

F2 - Acquisition Parameters
Date_            20070309
Time                15.04
INSTRUM             spect
PROBHD   5 mm PABBO BB-
PULPROG              jmod
TD                  65536
SOLVENT             CDCl3
NS                     25
DS                      4
SWH             24038.461 Hz
FIDRES           0.366798 Hz
AQ              1.3631988 sec
RG                   2050
DW                 20.800 use
DE                   6.00 use
TE                  296.3 K
CNST2         145.0000000
CNST11          1.0000000
D1             2.00000000 sec
d20            0.00689655 sec
DELTA          0.00001120 sec
TD0                     1

-------- CHANNEL f1 -------
NUC1                  13C
P1                   8.80 use
p2                  17.60 use
PL1                 -2.60 dB
SFO1          100.6228298 MHz

======== CHANNEL f2 =======
CPDPRG2           waltz16
NUC2                   1H
PCPD2               80.00 use
PL2                 -1.80 dB
PL12                13.30 dB
SFO2          400.1316005 MHz

F2 - Processing parameters
SI                  32768
SF            100.6127690 MHz
WDW                    EM
SSB                     0
LB                   1.00 Hz
GB                      0
PC                   1.40
```

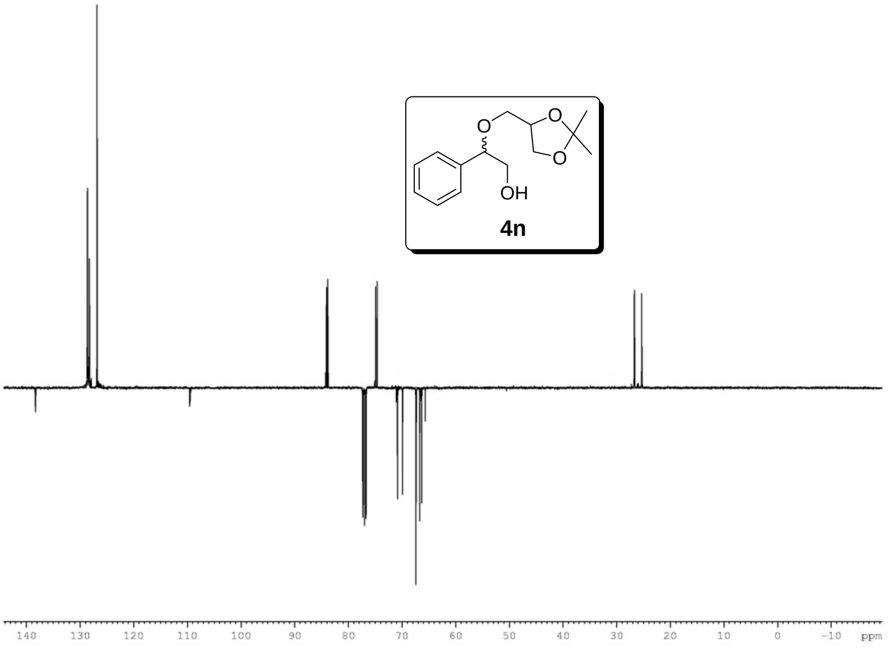


```
Current Data Parameters
NAME
EXPNO                  210
PROCNO                   1

F2 - Acquisition Parameters
Date_             20071002
Time                 10.40
INSTRUM              spect
PROBHD   5 mm PABBO BB-
PULPROG               zg30
TD                   65536
SOLVENT              CDCl3
NS                      16
DS                       2
SWH               8223.685 Hz
FIDRES            0.125483 Hz
AQ               3.9846387 sec
RG                    90.5
DW                  60.800 usec
DE                    6.00 usec
TE                   296.1 K
D1              1.00000000 sec
TD0                      1

======== CHANNEL f1 ========
NUC1                    1H
P1                   14.00 usec
PL1                  -2.50 dB
SFO1           400.1324710 MHz

F2 - Processing parameters
SI                   32768
SF             400.1300085 MHz
WDW                     EM
SSB                      0
LB                    0.30 Hz
GB                       0
PC                    1.00
```



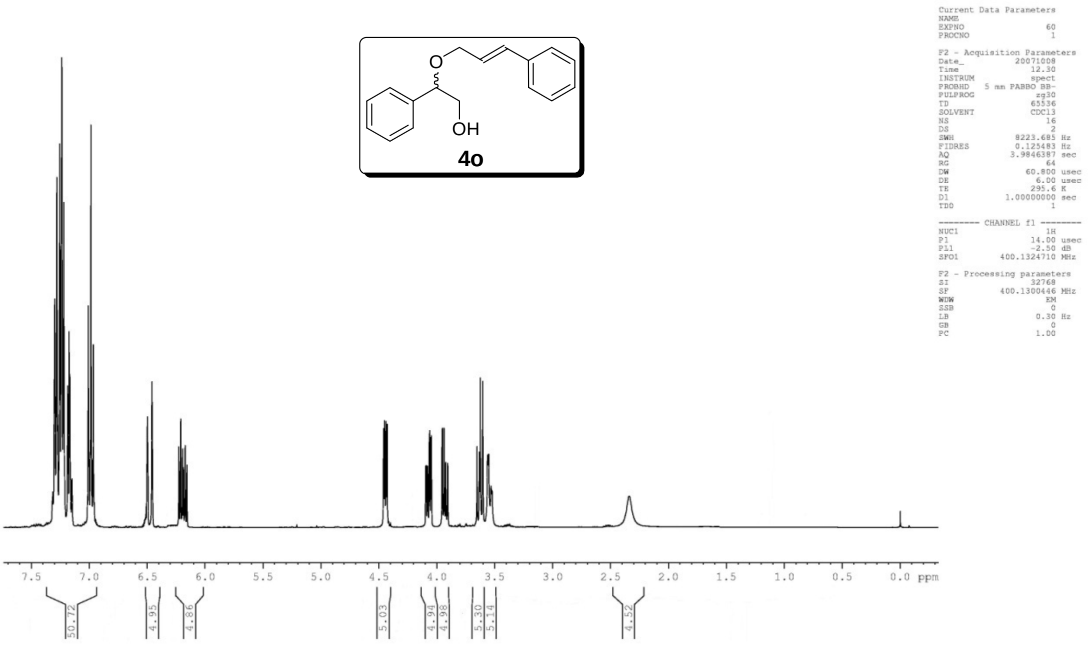
```
Current Data Parameters
NAME
EXPNO                  213
PROCNO                   1

F2 - Acquisition Parameters
Date_             20071003
Time                 13.23
INSTRUM              spect
PROBHD   5 mm PABBO BB-
PULPROG               jmod
TD                   65536
SOLVENT              CDCl3
NS                    8000
DS                       4
SWH              24038.461 Hz
FIDRES            0.366798 Hz
AQ               1.3631988 sec
RG                    2050
DW                  20.800 usec
DE                    6.00 usec
TE                   298.1 K
CNST2          145.0000000
CNST11           1.0000000
D1              2.00000000 sec
d20             0.00689655 sec
DELTA           0.00001120 sec
TD0                      1

======== CHANNEL f1 ========
NUC1                   13C
P1                    8.80 usec
p2                   17.60 usec
PL1                  -2.60 dB
SFO1           100.6228298 MHz

======== CHANNEL f2 ========
CPDPRG2            waltz16
NUC2                    1H
PCPD2                80.00 usec
PL2                  -1.80 dB
PL12                 13.30 dB
SFO2           400.1316005 MHz

F2 - Processing parameters
SI                   32768
SF             100.6127690 MHz
WDW                     EM
SSB                      0
LB                    1.00 Hz
GB                       0
PC                    1.40
```



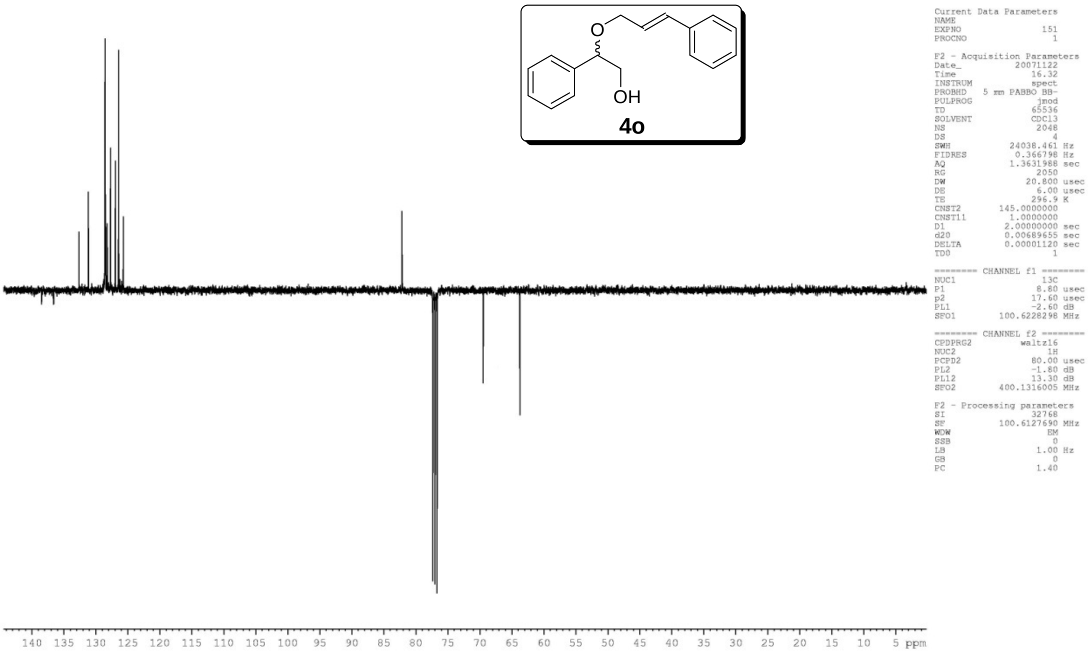
4o

```
Current Data Parameters
NAME
EXPNO                    60
PROCNO                    1

F2 - Acquisition Parameters
Date_              20071008
Time                  12.30
INSTRUM               spect
PROBHD   5 mm PABBO BB-
PULPROG                zg30
TD                    65536
SOLVENT               CDCl3
NS                       16
DS                        2
SWH            8223.685 Hz
FIDRES         0.125483 Hz
AQ            3.9846387 sec
RG                       64
DW               60.800 usec
DE                 6.00 usec
TE                  295.6 K
D1           1.00000000 sec
TD0                       1

======== CHANNEL f1 ========
NUC1                     1H
P1                14.00 usec
PL1               -2.50 dB
SFO1        400.1324710 MHz

F2 - Processing parameters
SI                    32768
SF          400.1300446 MHz
WDW                      EM
SSB                       0
LB                  0.30 Hz
GB                        0
PC                     1.00
```



4o

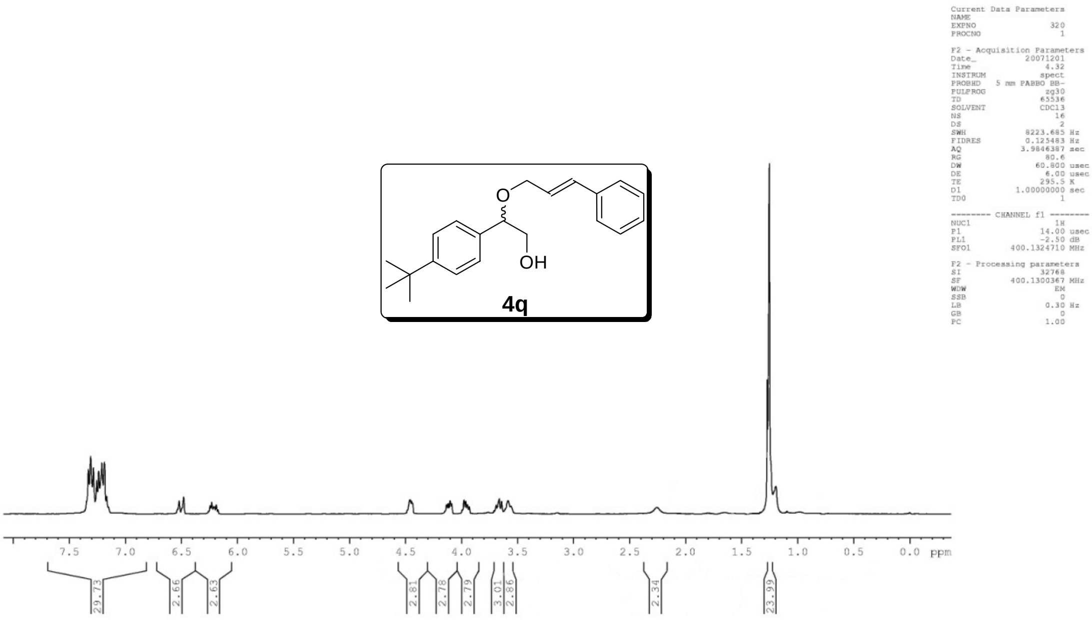
```
Current Data Parameters
NAME
EXPNO                   151
PROCNO                    1

F2 - Acquisition Parameters
Date_              20071122
Time                  16.32
INSTRUM               spect
PROBHD   5 mm PABBO BB-
PULPROG                jmod
TD                    65536
SOLVENT               CDCl3
NS                     2048
DS                        4
SWH           24038.461 Hz
FIDRES         0.366798 Hz
AQ            1.3631988 sec
RG                     2050
DW               20.800 usec
DE                 6.00 usec
TE                  296.9 K
CNST2       145.0000000
CNST11        1.0000000
D1           2.00000000 sec
d20          0.00689655 sec
DELTA        0.00001120 sec
TD0                       1

======== CHANNEL f1 ========
NUC1                    13C
P1                 8.80 usec
p2                17.60 usec
PL1               -2.60 dB
SFO1        100.6228298 MHz

======== CHANNEL f2 ========
CPDPRG2             waltz16
NUC2                     1H
PCPD2             80.00 usec
PL2               -1.80 dB
PL12              13.30 dB
SFO2        400.1316005 MHz

F2 - Processing parameters
SI                    32768
SF          100.6127690 MHz
WDW                      EM
SSB                       0
LB                  1.00 Hz
GB                        0
PC                     1.40
```

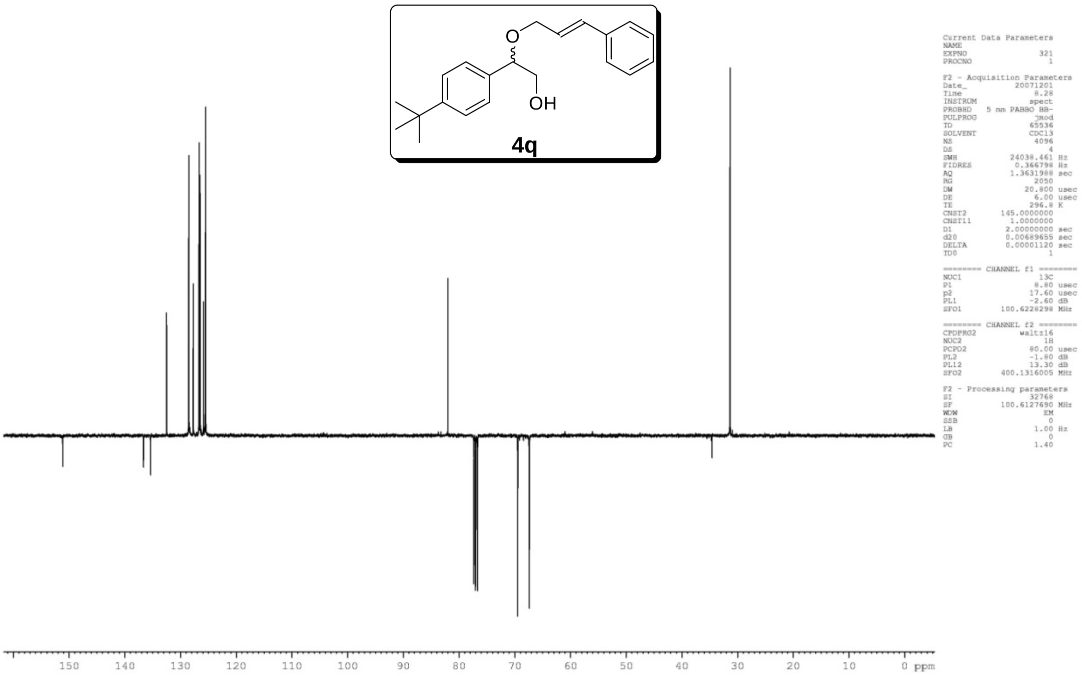


```
Current Data Parameters
NAME
EXPNO                 320
PROCNO                  1

F2 - Acquisition Parameters
Date_            20071201
Time                 4.32
INSTRUM             spect
PROBHD   5 mm PABBO BB-
PULPROG              zg30
TD                  65536
SOLVENT             CDCl3
NS                     16
DS                      2
SWH              8223.685 Hz
FIDRES           0.125483 Hz
AQ              3.9846387 sec
RG                   80.6
DW                 60.800 usec
DE                   6.00 usec
TE                  295.5 K
D1             1.00000000 sec
TD0                     1

======== CHANNEL f1 ========
NUC1                   1H
P1                  14.00 usec
PL1                 -2.50 dB
SFO1          400.1324710 MHz

F2 - Processing parameters
SI                  32768
SF            400.1300367 MHz
WDW                    EM
SSB                     0
LB                   0.30 Hz
GB                      0
PC                   1.00
```



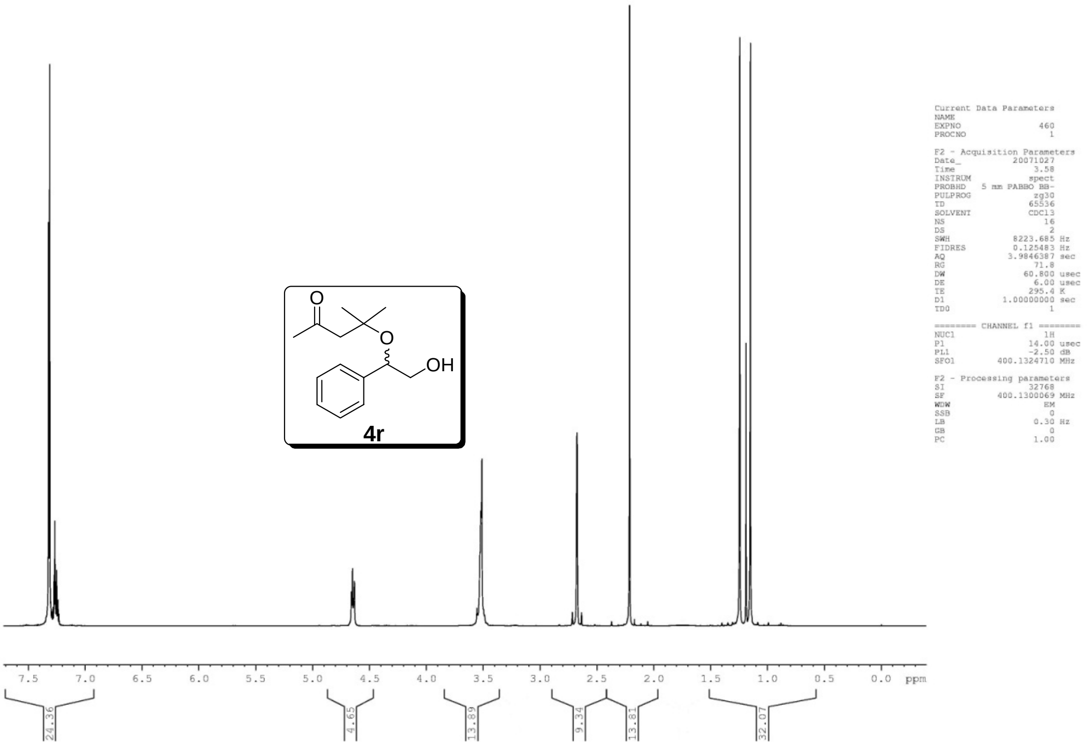
```
Current Data Parameters
NAME
EXPNO                 321
PROCNO                  1

F2 - Acquisition Parameters
Date_            20071201
Time                 8.28
INSTRUM             spect
PROBHD   5 mm PABBO BB-
PULPROG              jmod
TD                  65536
SOLVENT             CDCl3
NS                   4096
DS                      4
SWH             24038.461 Hz
FIDRES           0.366798 Hz
AQ              1.3631988 sec
RG                   2050
DW                 20.800 usec
DE                   6.00 usec
TE                  296.8 K
CNST2         145.0000000
CNST11          1.0000000
D1             2.00000000 sec
d20            0.00689655 sec
DELTA          0.00001120 sec
TD0                     1

======== CHANNEL f1 ========
NUC1                  13C
P1                   8.80 usec
p2                  17.60 usec
PL1                 -2.60 dB
SFO1          100.6228298 MHz

======== CHANNEL f2 ========
CPDPRG2           waltz16
NUC2                   1H
PCPD2               80.00 usec
PL2                 -1.80 dB
PL12                13.30 dB
SFO2          400.1316005 MHz

F2 - Processing parameters
SI                  32768
SF            100.6127690 MHz
WDW                    EM
SSB                     0
LB                   1.00 Hz
GB                      0
PC                   1.40
```

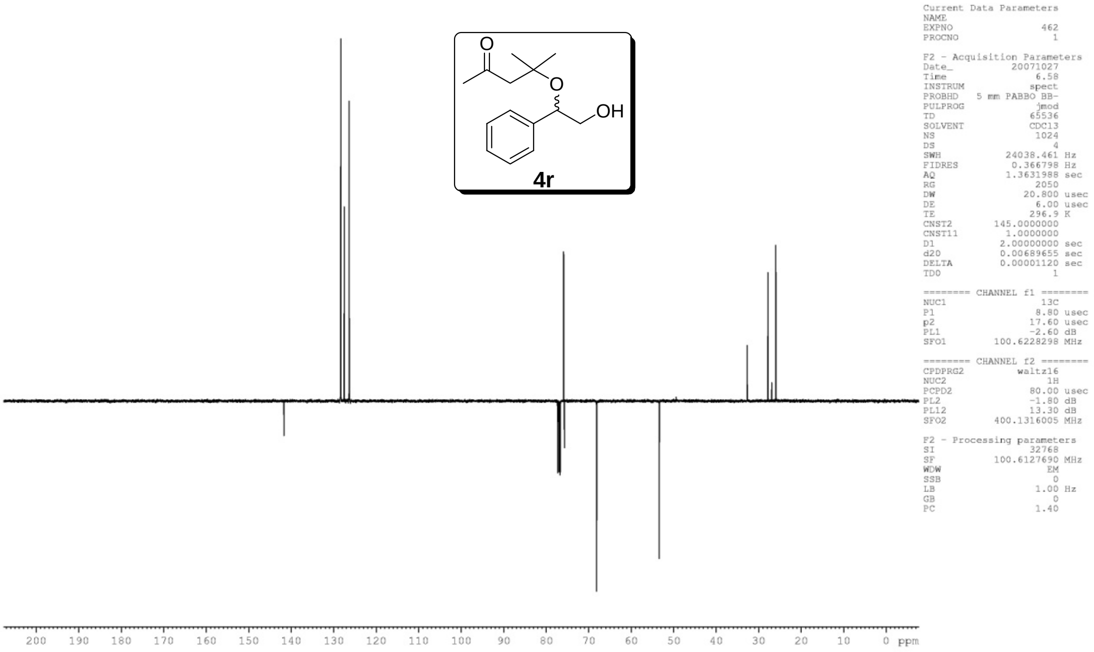


```
Current Data Parameters
NAME
EXPNO                 460
PROCNO                  1

F2 - Acquisition Parameters
Date_            20071027
Time                 3.58
INSTRUM             spect
PROBHD   5 mm PABBO BB-
PULPROG              zg30
TD                  65536
SOLVENT             CDCl3
NS                     16
DS                      2
SWH              8223.685 Hz
FIDRES           0.125483 Hz
AQ              3.9846387 sec
RG                   71.8
DW                 60.800 usec
DE                   6.00 usec
TE                  295.4 K
D1             1.00000000 sec
TD0                     1

======== CHANNEL f1 ========
NUC1                   1H
P1                  14.00 usec
PL1                 -2.50 dB
SFO1          400.1324710 MHz

F2 - Processing parameters
SI                  32768
SF            400.1300069 MHz
WDW                    EM
SSB                     0
LB                   0.30 Hz
GB                      0
PC                   1.00
```



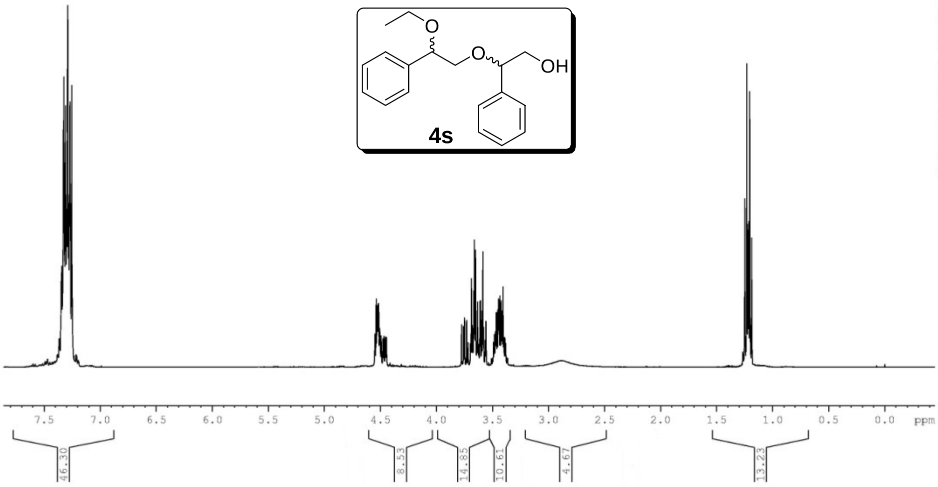
```
Current Data Parameters
NAME
EXPNO                 462
PROCNO                  1

F2 - Acquisition Parameters
Date_            20071027
Time                 6.58
INSTRUM             spect
PROBHD   5 mm PABBO BB-
PULPROG              jmod
TD                  65536
SOLVENT             CDCl3
NS                   1024
DS                      4
SWH             24038.461 Hz
FIDRES           0.366798 Hz
AQ              1.3631988 sec
RG                   2050
DW                 20.800 usec
DE                   6.00 usec
TE                  296.9 K
CNST2         145.0000000
CNST11          1.0000000
D1             2.00000000 sec
d20            0.00689655 sec
DELTA          0.00001120 sec
TD0                     1

======== CHANNEL f1 ========
NUC1                  13C
P1                   8.80 usec
p2                  17.60 usec
PL1                 -2.60 dB
SFO1          100.6228298 MHz

======== CHANNEL f2 ========
CPDPRG2           waltz16
NUC2                   1H
PCPD2               80.00 usec
PL2                 -1.80 dB
PL12                13.30 dB
SFO2          400.1316005 MHz

F2 - Processing parameters
SI                  32768
SF            100.6127690 MHz
WDW                    EM
SSB                     0
LB                   1.00 Hz
GB                      0
PC                   1.40
```



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Current Data Parameters
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EXPNO                190
PROCNO                 1

F2 - Acquisition Parameters
Date_           20071122
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INSTRUM            spect
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PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                    16
DS                     2
SWH             8223.685 Hz
FIDRES          0.125483 Hz
AQ             3.9846387 sec
RG                  90.5
DW                60.800 usec
DE                  6.00 usec
TE                 295.2 K
D1            1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                  1H
P1                 14.00 usec
PL1                -2.50 dB
SFO1         400.1324710 MHz

F2 - Processing parameters
SI                 32768
SF           400.1300103 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  1.00
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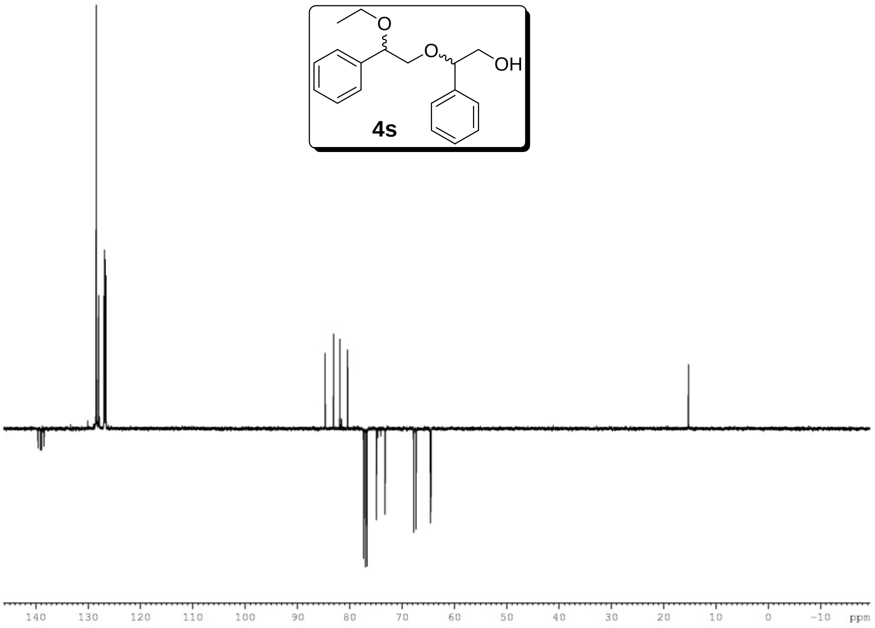

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Current Data Parameters
NAME
EXPNO                191
PROCNO                 1

F2 - Acquisition Parameters
Date_           20071122
Time               20.40
INSTRUM            spect
PROBHD   5 mm PABBO BB-
PULPROG             jmod
TD                 65536
SOLVENT            CDCl3
NS                  2048
DS                     4
SWH            24038.461 Hz
FIDRES          0.366798 Hz
AQ             1.3631988 sec
RG                  2050
DW                20.800 usec
DE                  6.00 usec
TE                 296.9 K
CNST2        145.0000000
CNST11         1.0000000
D1            2.00000000 sec
d20           0.00689655 sec
DELTA         0.00001120 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                 13C
P1                  8.80 usec
p2                 17.60 usec
PL1                -2.60 dB
SFO1         100.6228298 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                  1H
PCPD2              80.00 usec
PL2                -1.80 dB
PL12               13.30 dB
SFO2         400.1316005 MHz

F2 - Processing parameters
SI                 32768
SF           100.6127690 MHz
WDW                   EM
SSB                    0
LB                  1.00 Hz
GB                     0
PC                  1.40
```

5.2.5. Optimization experiments

5.2.5.1 To minimize formation of by-product **4s**, we studied a dilution series and optimized the reaction conditions (Figure S1). It turned out that a ratio of 1 equiv of styrene oxide and 12 eq. of ethanol avoids formation of the side product completely. Further dilution leads to reduced conversion.

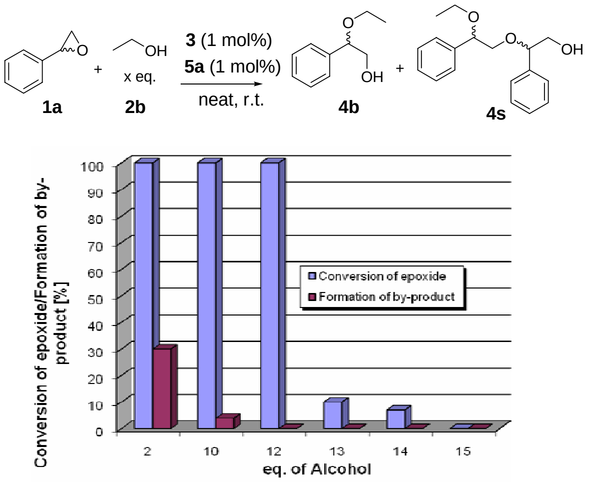

Figure S1. Optimization of the reaction conditions[a]
[a] Reaction time: 22 h

5.2.5.2 For further optimization of our dual catalyst system we also varied the ratio between **3** and **5a** (Figure S2). A loading of Brønsted acid **5a** in 1 mol% amount was kept constant in order to maintain mild reaction conditions. Surprisingly, reaction times in all cases are nearly equal, although GC/MS analysis after 15 h showed more than two times faster conversion in case of

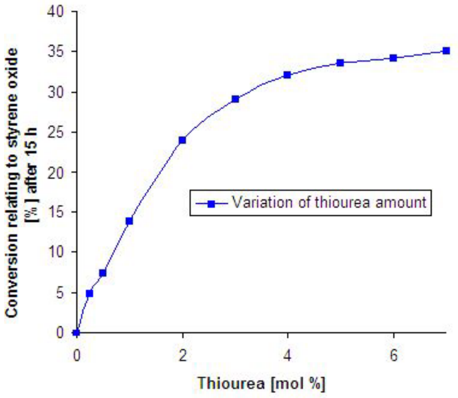

Figure S2. Variation of **3**

7 mol% of **3** than in case of our standard protocol (1 mol% **3**). These results are consistent with the observation of a non-linear catalytic effect with a dramatic rate enhancement in the second half of the reaction period when a 1:1 mixture of **3** and **5a** was utilized.

5.2.6. Table S1. Absolute energies (Hartree) and zero point vibrational energies (ZPVE, kcal/mol) at the B3LYP/6-31+G(d,p) level of theory.

Structure	**Absolute energy (Hartree)**	**ZPVE (kcal/mol)**
1a	-384.87389	87.0
3	-2358.57744	150.3
5a	-535.38169	92.9
1a·3	-2743.46792	238.5
5a·3	-2893.97976	244.3
1a·5a	-920.26586	180.8
1a·5a·3	-3278.86852	332.5

Table S2. Cartesian coordinates (B3LYP/6-31+G(d,p))

Structure 1a

C	-2.153232000	1.027993000	0.051952000
C	-0.787739000	1.303556000	-0.051506000
C	0.147133000	0.260621000	-0.103952000
C	0.306130000	-1.065560000	-0.070653000
C	-1.671351000	-1.340341000	0.028223000
C	-2.598933000	-0.295812000	0.093764000

H	-2.867158000	1.845677000	0.092731000
H	-0.446215000	2.335247000	-0.093203000
H	0.415167000	-1.873645000	-0.144132000
H	-2.012365000	-2.371618000	0.047182000
H	-3.660676000	-0.512018000	0.168508000
C	1.602837000	0.581398000	-0.187746000
C	2.601161000	0.004294000	0.737737000
O	2.494603000	-0.461948000	-0.613528000
H	1.833604000	1.557800000	-0.616556000
H	2.267172000	-0.700515000	1.498530000
H	3.511176000	0.557768000	0.968245000

Structure 3

C	2.941424000	0.248121000	0.975786000
C	4.304320000	0.536820000	1.076551000
C	5.224479000	0.020152000	0.164724000
C	4.760560000	-0.802624000	-0.864391000
C	3.402562000	-1.088248000	-0.990269000
C	2.486479000	-0.562281000	-0.069539000
H	2.245228000	0.644784000	1.701745000
H	6.279999000	0.246073000	0.258649000
H	3.056662000	-1.713063000	-1.806963000
C	5.758291000	-1.379655000	-1.837720000
C	4.773640000	1.450390000	2.183875000
F	6.644063000	-2.199932000	-1.216072000
F	6.487976000	-0.410333000	-2.442643000
F	5.165960000	-2.104843000	-2.816331000
F	6.091639000	1.293031000	2.449670000
F	4.100598000	1.229315000	3.339581000
F	4.587807000	2.756536000	1.866533000
N	1.130399000	-0.939124000	-0.197852000
H	0.987514000	-1.807062000	-0.700231000
C	0.000717000	-0.154565000	-0.027735000
S	0.006862000	1.490428000	0.201098000
N	-1.132979000	-0.948664000	-0.075973000
H	-0.991266000	-1.925057000	0.153506000
C	-2.488747000	-0.550044000	-0.090521000
C	-2.946629000	0.526132000	-0.857413000
C	-4.310403000	0.828765000	-0.869477000
C	-5.228657000	0.070471000	-0.144097000
C	-4.761535000	-1.011933000	0.605627000
C	-3.403114000	-1.319400000	0.641980000
H	-2.251853000	1.116646000	-1.438465000
H	-6.284211000	0.313371000	-0.166137000
H	-3.054575000	-2.150982000	1.245426000
C	-4.778063000	2.021628000	-1.669082000
C	-5.756070000	-1.856020000	1.363373000
F	-4.536738000	3.186062000	-1.015778000
F	-6.106815000	1.978199000	-1.922031000
F	-4.143122000	2.106082000	-2.864240000
F	-6.588625000	-1.097807000	2.116830000
F	-6.542508000	-2.575934000	0.521258000
F	-5.155208000	-2.740744000	2.194517000

Structure 5a

C	3.062821000	-0.045540000	-0.371008000
C	2.516287000	-0.953471000	0.537508000
C	1.173376000	-0.840391000	0.914621000

C	0.365698000	0.171598000	0.376816000
C	0.923316000	1.084784000	-0.528933000
C	2.264625000	0.976748000	-0.896982000
H	4.106450000	-0.125498000	-0.660253000
H	3.133245000	-1.737736000	0.966048000
H	0.762037000	-1.526670000	1.652558000
H	0.304544000	1.884325000	-0.922952000
H	2.689603000	1.691702000	-1.595429000
C	-1.107183000	0.243444000	0.739635000
H	-1.256581000	-0.308870000	1.684551000
C	-2.012780000	-0.471174000	-0.291448000
O	-3.084544000	-0.005823000	-0.608033000
O	-1.591323000	-1.653292000	-0.771816000
H	-0.666675000	-1.810548000	-0.513280000
O	-1.541846000	1.575017000	0.877916000
H	-2.447879000	1.610101000	0.522964000

Structure 1a·3

C	-3.364756000	-1.424607000	0.675913000
C	-4.759094000	-1.462096000	0.781553000
C	-5.572701000	-0.531968000	0.139373000
C	-4.959777000	0.463361000	-0.628258000
C	-3.576236000	0.516072000	-0.752485000
C	-2.759575000	-0.429595000	-0.103659000
H	-2.754820000	-2.157582000	1.183331000
H	-6.650508000	-0.578156000	0.231903000
H	-3.121766000	1.288215000	-1.364179000
C	-5.811808000	1.517098000	-1.287451000
C	-5.379297000	-2.573039000	1.595710000
F	-6.179598000	2.488392000	-0.407738000
F	-6.955373000	1.003823000	-1.797334000
F	-5.164366000	2.143487000	-2.303595000
F	-6.687174000	-2.344291000	1.864371000
F	-4.750083000	-2.740751000	2.784211000
F	-5.312405000	-3.764269000	0.947604000
N	-1.375848000	-0.254616000	-0.274517000
H	-1.142850000	0.644125000	-0.693279000
C	-0.299707000	-1.079421000	-0.028095000
S	-0.374329000	-2.647564000	0.542718000
N	0.879065000	-0.418149000	-0.319596000
H	0.806653000	0.579569000	-0.502826000
C	2.204145000	-0.895672000	-0.236271000
C	2.582446000	-2.174812000	-0.673038000
C	3.923203000	-2.550879000	-0.615388000
C	4.907907000	-1.675453000	-0.145743000
C	4.524156000	-0.402342000	0.268790000
C	3.182214000	-0.012795000	0.234258000
H	1.839208000	-2.858603000	-1.056749000
H	5.946937000	-1.978356000	-0.112564000
H	2.894808000	0.974427000	0.582619000
C	4.322672000	-3.943373000	-1.039379000
C	5.550074000	0.595493000	0.739061000
F	4.373242000	-4.793940000	0.018435000
F	5.553060000	-3.963011000	-1.611224000
F	3.457560000	-4.477012000	-1.932497000
F	6.764828000	0.040798000	0.939799000
F	5.720776000	1.601439000	-0.168193000
F	5.182469000	1.195158000	1.899810000
C	1.778123000	5.658911000	1.859761000

C	0.708809000	5.125808000	1.135363000
C	0.941116000	4.266201000	0.053671000
C	2.262694000	3.938655000	-0.287742000
C	3.329986000	4.463705000	0.440623000
C	3.089783000	5.327459000	1.514974000
H	1.584312000	6.323983000	2.695828000
H	-0.311373000	5.378152000	1.413528000
H	2.460803000	3.265099000	-1.116732000
H	4.347355000	4.194894000	0.173823000
H	3.922096000	5.733590000	2.081607000
C	-0.225222000	3.726969000	-0.700208000
C	-0.196996000	3.401706000	-2.137812000
O	-0.150845000	2.340155000	-1.159334000
H	-1.196888000	3.970959000	-0.272856000
H	0.725530000	3.541587000	-2.697078000
H	-1.115371000	3.446506000	-2.720369000

Structure 5a·3

C	2.345331000	-2.797030000	-0.137795000
C	3.676081000	-3.217886000	-0.242139000
C	4.731303000	-2.314108000	-0.319936000
C	4.432768000	-0.947040000	-0.296094000
C	3.119130000	-0.504806000	-0.202395000
C	2.055075000	-1.426151000	-0.120227000
H	1.541779000	-3.516661000	-0.073839000
H	5.755143000	-2.658811000	-0.397895000
H	2.907217000	0.558423000	-0.198035000
C	5.563766000	0.042829000	-0.403688000
C	3.952373000	-4.702595000	-0.217290000
F	6.167382000	-0.008012000	-1.619434000
F	6.532447000	-0.194749000	0.516313000
F	5.153217000	1.324217000	-0.223556000
F	5.221020000	-4.996328000	-0.590723000
F	3.123715000	-5.386886000	-1.040665000
F	3.779072000	-5.219494000	1.027959000
N	0.773194000	-0.861380000	-0.007857000
H	0.798574000	0.141616000	0.166908000
C	-0.492123000	-1.398038000	-0.117126000
S	-0.877123000	-3.021056000	-0.214305000
N	-1.424701000	-0.379612000	-0.158496000
H	-1.071714000	0.544501000	-0.400494000
C	-2.829534000	-0.462657000	-0.135083000
C	-3.533092000	-1.368879000	0.672421000
C	-4.927274000	-1.336398000	0.688638000
C	-5.646353000	-0.411380000	-0.073945000
C	-4.937059000	0.493960000	-0.861777000
C	-3.541837000	0.468185000	-0.902302000
H	-2.997489000	-2.082847000	1.281847000
H	-6.728455000	-0.394448000	-0.047789000
H	-3.001520000	1.166542000	-1.532867000
C	-5.671665000	-2.347101000	1.526644000
C	-5.661318000	1.552800000	-1.651113000
F	-5.857863000	-3.515276000	0.859665000
F	-6.901579000	-1.903079000	1.885665000
F	-5.007551000	-2.651245000	2.668313000
F	-6.973990000	1.277315000	-1.812932000
F	-5.587606000	2.770078000	-1.037779000
F	-5.127999000	1.722548000	-2.887812000
C	2.678805000	4.183678000	-0.106064000

C	3.735563000	5.085691000	-0.229499000
C	3.866924000	6.141638000	0.678684000
C	2.939979000	6.291155000	1.712289000
C	1.883523000	5.385195000	1.839383000
C	1.747034000	4.328263000	0.932545000
H	2.583861000	3.362605000	-0.811241000
H	4.455991000	4.963994000	-1.032469000
H	4.690847000	6.842072000	0.581260000
H	3.039030000	7.107406000	2.421362000
H	1.162367000	5.504365000	2.644000000
C	0.607344000	3.334423000	1.087973000
H	0.011585000	3.613563000	1.968747000
C	-0.357365000	3.362666000	-0.095865000
O	-0.602638000	2.424186000	-0.829342000
O	-0.932342000	4.565885000	-0.223022000
H	-1.546862000	4.535899000	-0.976999000
O	1.058097000	1.984666000	1.204059000
H	1.702586000	1.947469000	1.924747000

Structure 1a·5a

C	4.240734000	1.076692000	1.119024000
C	3.105159000	0.355481000	0.749188000
C	3.202868000	-0.680200000	-0.192279000
C	4.451140000	-0.972667000	-0.759039000
C	5.588893000	-0.255872000	-0.381151000
C	5.485648000	0.771195000	0.559507000
H	4.150692000	1.883070000	1.840624000
H	2.143871000	0.619369000	1.178324000
H	4.533628000	-1.764511000	-1.499599000
H	6.549818000	-0.494455000	-0.827295000
H	6.366779000	1.335733000	0.849706000
C	2.024951000	-1.495267000	-0.606238000
C	0.965251000	-1.940514000	0.320145000
O	0.708413000	-0.874794000	-0.617315000
H	2.189983000	-2.111680000	-1.489197000
H	1.011643000	-1.628484000	1.361847000
H	0.414778000	-2.857788000	0.121686000
C	-3.979993000	-2.233150000	0.902446000
C	-3.234835000	-2.374503000	-0.269970000
C	-2.652750000	-1.252401000	-0.868629000
C	-2.811089000	0.017766000	-0.304133000
C	-3.565137000	0.153054000	0.870781000
C	-4.143948000	-0.965126000	1.471309000
H	-4.436395000	-3.102201000	1.367649000
H	-3.114493000	-3.353745000	-0.725204000
H	-2.077571000	-1.363585000	-1.783890000
H	-3.705368000	1.136654000	1.310804000
H	-4.726035000	-0.848057000	2.380891000
C	-2.218328000	1.245646000	-0.990232000
H	-1.587398000	0.908352000	-1.823890000
C	-1.340619000	2.055111000	-0.016271000
O	-1.710943000	3.135832000	0.398569000
O	-0.177714000	1.524621000	0.367366000
H	0.040407000	0.670890000	-0.075712000
O	-3.226961000	2.093704000	-1.504795000
H	-3.204376000	2.904064000	-0.964076000

Structure 1a·5a·3

N	1.941342000	0.984338000	-0.056888000
C	1.259177000	2.181708000	-0.010396000
N	-0.047633000	1.987108000	-0.420820000
C	-1.202783000	2.780283000	-0.336208000
S	1.924625000	3.633365000	0.481147000
C	3.312936000	0.732168000	0.136395000
C	4.328044000	1.598679000	-0.290067000
C	5.664080000	1.232639000	-0.113915000
C	6.016421000	0.015679000	0.470858000
C	4.996931000	-0.848859000	0.875225000
C	3.657378000	-0.497818000	0.718403000
C	-2.390794000	2.178951000	-0.792665000
C	-3.598319000	2.870087000	-0.749003000
C	-3.663814000	4.173161000	-0.250732000
C	-2.482613000	4.763655000	0.197092000
C	-1.258269000	4.092182000	0.161614000
C	6.743788000	2.195894000	-0.542436000
F	6.985923000	3.136253000	0.407762000
F	6.411355000	2.864066000	-1.673949000
F	7.922603000	1.569516000	-0.779867000
C	5.355229000	-2.152018000	1.541886000
F	5.616272000	-1.987518000	2.866551000
F	6.462114000	-2.716115000	0.998824000
F	4.357444000	-3.067617000	1.455562000
C	-2.528566000	6.153083000	0.787535000
F	-1.401209000	6.855975000	0.539274000
F	-2.676748000	6.112485000	2.139569000
F	-3.569539000	6.876779000	0.305922000
C	-4.855037000	2.171374000	-1.194801000
F	-5.828603000	3.033669000	-1.561397000
F	-4.640104000	1.336793000	-2.242898000
F	-5.382630000	1.395985000	-0.197537000
H	1.368053000	0.137855000	-0.060411000
H	-0.228952000	1.079593000	-0.837708000
H	4.079174000	2.539937000	-0.758582000
H	7.057015000	-0.258686000	0.592416000
H	2.875451000	-1.178711000	1.036270000
H	-2.364202000	1.167669000	-1.184765000
H	-4.601645000	4.713283000	-0.225222000
H	-0.353188000	4.574946000	0.500195000
O	-2.226562000	-3.110096000	-1.929207000
C	-1.142748000	-3.197643000	-1.013945000
C	-0.485008000	-1.809122000	-0.899115000
O	0.313908000	-1.494086000	-0.037563000
O	-0.869805000	-0.934266000	-1.840525000
C	-0.118485000	-4.227469000	-1.481807000
C	0.921781000	-4.613127000	-0.624979000
C	1.871149000	-5.544031000	-1.048873000
C	1.787084000	-6.099666000	-2.329344000
C	0.747888000	-5.720387000	-3.181271000
C	-0.204206000	-4.786324000	-2.761534000
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H	-1.018549000	-4.500258000	-3.417278000
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C	-4.959029000	-2.068965000	0.736418000
C	-5.777742000	-2.135537000	-0.488847000
C	-4.639179000	-3.250498000	1.587294000
C	-4.447596000	-4.529823000	1.041937000
C	-4.152917000	-5.612644000	1.870697000
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H	-4.932510000	-1.109978000	1.251209000
H	-6.167765000	-3.098565000	-0.812605000
H	-6.331812000	-1.257516000	-0.812735000
H	-4.521181000	-4.681794000	-0.031321000
H	-4.003061000	-6.596937000	1.437115000
H	-3.821849000	-6.277068000	3.897572000
H	-4.155409000	-4.014037000	4.876240000
H	-4.661111000	-2.087843000	3.403881000

5.2.7. Full Reference Gaussian03

Gaussian 03, Revision C.02, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, Jr., J. A.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; and Pople, J. A.; Gaussian, Inc., Wallingford CT, 2004.

5.2.8. References

1. Robinson, M. W. C.; Buckle, R.; Mabbett, I.; Grant, G. M.; Graham, A. E., *Tetrahedron Lett.* **2007,** *48*, 4723-4725.

2. Kumar, G. D. K.; Baskaran, S., *J. Org. Chem.* **2005,** *70*, 4520-4523.

5.3 Organocatalytic Formation of 1,3-Dioxolanes

5.3.1 General Experimental Details

For general experimental details see **5.2.1** and **5.2.2**.

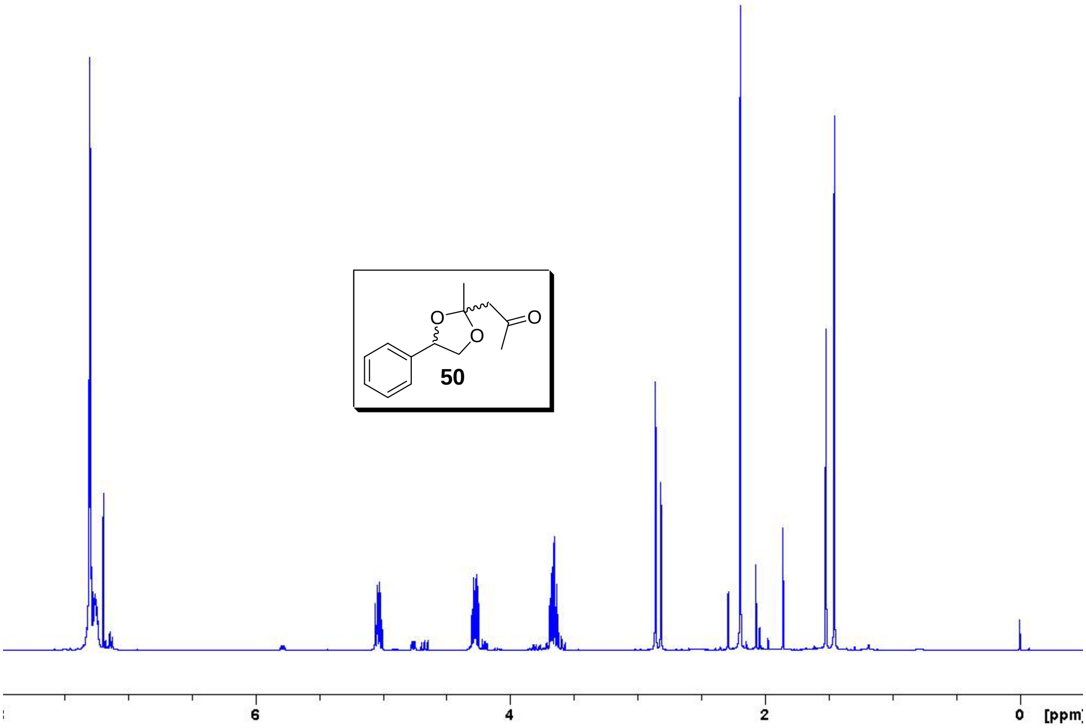
5.3.2 Compound Characterization

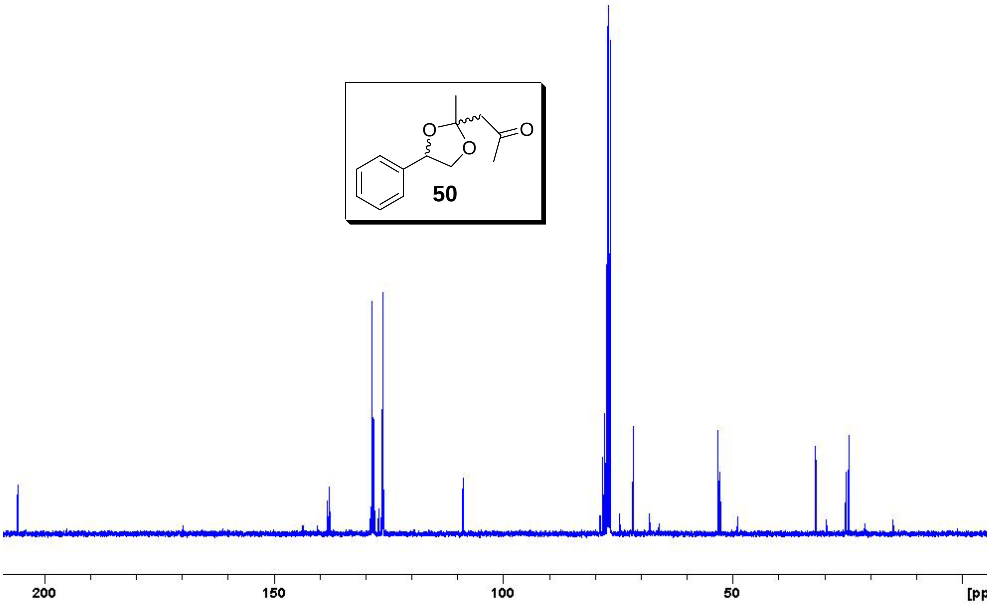
1-(2-Methyl-4-phenyl-1,3-dioxolan-2-yl)propan-2-one (**50**): HPLC afforded 62% (3.14 mmol) of the product as a colorless oil. **^{1}H NMR** (400 MHz,$CDCl_3$): δ 7.34-7.22 (m, 5H),5.06-5.00 (m, 1H), 4.29-4.24 (m, 1H, diastereotopic), 3.68-3.63 (m, 1H, diastereotopic), 2.86 (s, 1H, diastereotopic), 2.81 (s, 1H, diastereotopic), 2.19 (s, 3H), 1.52 (s, 1.5H, diastereotopic), 1.45 (s, 1.5 H, diastereotopic); **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 205.7, 137.9, 128.6, 128.5, 126.5, 108.9, 78.9 (diastereotopic), 78.4 (diastereotopic), 71.6, 53.0 (diastereotopic), 52.8 (diastereotopic), 31.8, 25.3 (diastereotopic), 24.8 (diastereotopic).

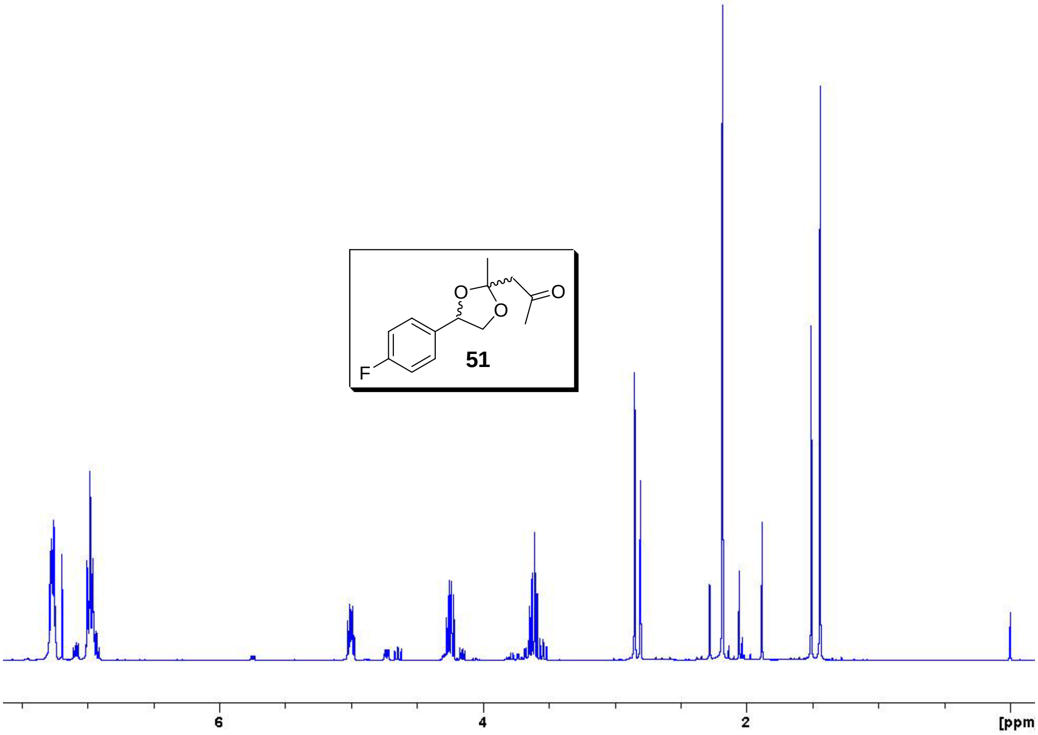
1-(4-(4-Fluorophenyl)-2-methyl-1,3-dioxolan-2-yl)propan-2-one (51): HPLC afforded 62% (3.14 mmol) of the product as a slightly yellowish oil. **^{1}H NMR** (400 MHz,$CDCl_3$): δ 7.30-7.24 (m, 2H), 7.01-6.94 (m, 2H), 5.02-4.98 (m, 1H), 4.27-4.22 (m, 1H, diastereotopic), 3.65-3.58 (m, 1H, diastereotopic), 2.85 (s, 1H, diastereotopic), 2.80 (s, 1H, diastereotopic), 2.18 (s, 3H), 1.51 (s, 1.5 H, diastereotopic), 1.44 (s, 1.5H, diastereotopic); **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 205.6, 163.8 (d, J=-245.4 Hz), 133.8 (d, J=2.9 Hz), 128.1, 115.6, 108.8, 78.8 (diastereotopic), 77.8 (diastereotopic), 71.6, 53.0 (diastereotopic), 52.6 (diastereotopic), 31.9 (diastereotopic), 31.7 (diastereotopic), 25.3 (diastereotopic), 24.7 (diastereotopic).

1-(4-(4-*tert*-Butylphenyl)-2-methyl-1,3-dioxolan-2-yl)propan-2-one (52): HPLC afforded 54% (2.70 mmol) of the product as a colorless oil. **^{1}H NMR** (400 MHz,$CDCl_3$): δ 7.26-7.22 (m, 2H), 7.09-7.06 (m, 2H), 5.01 (m, 1H), 4.25-4.22 (m, 1H, diastereotopic), 3.71-3.66 (m, 1H, diastereotopic), 2.85 (s, 1H, diastereotopic), 2.80 (s, 1H, diastereotopic), 2.19 (s, 1.5 H, diastereotopic), 2.18 (s, 1.5H, diastereotopic), 1.51 (s, 1.5 H, diastereotopic), 1.44 (s, 1.5H, diastereotopic).

5.3.3 ^{1}H and ^{13}C NMR spectra



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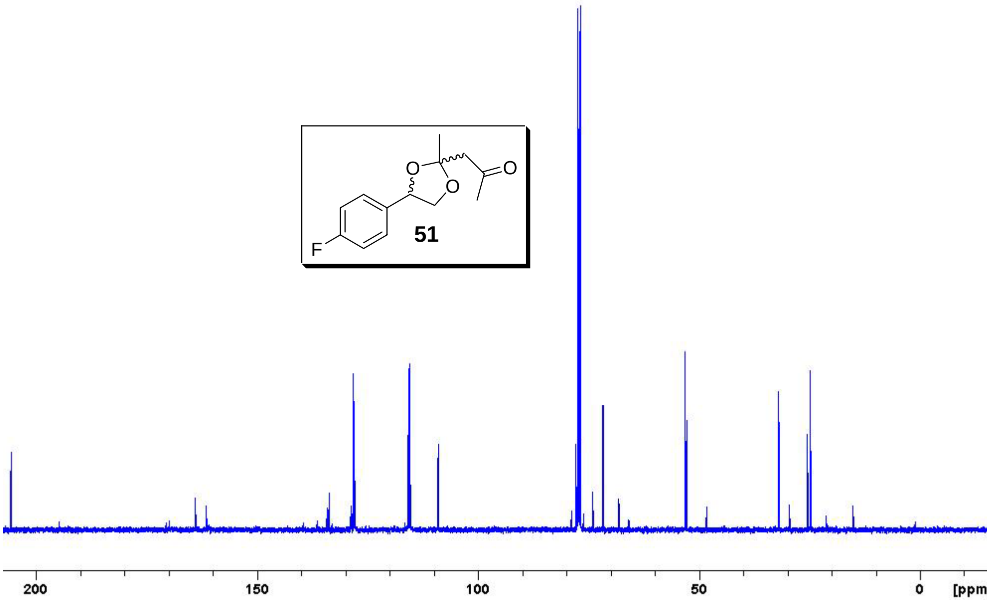
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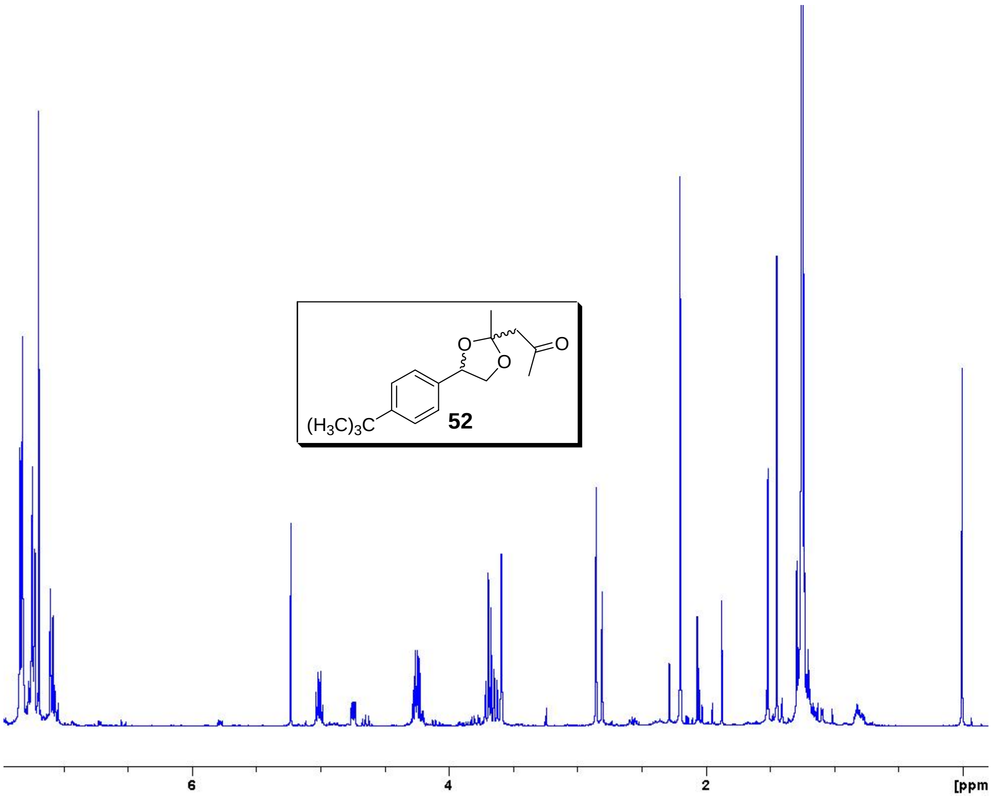
O
O
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(H3C)3C
52
6
4
2
[ppm

6. References

[1] K. Schulte, G. Rucker, *Progr. Drug. Res., Basel Stuttgart* **1970**, *14*, 387-563.

[2] J. Fried, C. Lin, M. Mehra, W. Kao, P. Dalven, *Annals of the New York Academy of Sciences* **1971**, *180*, 38-63.

[3] J. Fried, J. C. Sih, *Tetrahedron Lett.* **1973**, *14*, 3899-3902.

[4] K.-K. Chan, N. Cohen, J. P. De Noble, A. C. Specian, G. Saucy, *J. Org. Chem.* **1976**, *41*, 3497-3505.

[5] W. S. Johnson, R. S. Brinkmeyer, V. M. Kapoor, T. M. Yarnell, *J. Am. Chem. Soc.* **1977**, *99*, 8341-8343.

[6] K. C. Nicolaou, S. E. Webber, *J. Am. Chem. Soc.* **1984**, *106*, 5734-5736.

[7] E. J. Corey, K. Niimura, Y. Konishi, S. Hashimoto, Y. Hamada, *Tetrahedron Lett.* **1986**, *27*, 2199-2202.

[8] M. E. Pierce, R. L. Parsons, L. A. Radesca, Y. S. Lo, S. Silverman, J. R. Moore, Q. Islam, A. Choudhury, J. M. D. Fortunak, D. Nguyen, C. Luo, S. J. Morgan, W. P. Davis, P. N. Confalone, C.-Y. Chen, R. D. Tillyer, L. Frey, L. Tan, F. Xu, D. Zhao, A. S. Thompson, E. G. Corley, E. J. J. Grabowski, R. Reamer, P. J. Reider, *J. Org. Chem.* **1998**, *63*, 8536-8543.

[9] L. Tan, C. Y. Chen, R. D. Tillyer, E. J. J. Grabowski, P. J. Reider, *Angew. Chem. Int. Ed.* **1999**, *38*, 711-713.

[10] H. Stark, B. Sadek, M. Krause, A. Huls, X. Ligneau, C. R. Ganellin, J.-M. Arrang, J.-C. Schwartz, W. Schunack, *J. Med. Chem.* **2000**, *43*, 3987-3994.

[11] J. W. Corbett, S. S. Ko, J. D. Rodgers, L. A. Gearhart, N. A. Magnus, L. T. Bacheler, S. Diamond, S. Jeffrey, R. M. Klabe, B. C. Cordova, S. Garber, K. Logue, G. L. Trainor, P. S. Anderson, S. K. Erickson-Viitanen, *J. Med. Chem.* **2000**, *43*, 2019-2030.

[12] N. A. Magnus, P. N. Confalone, L. Storace, M. Patel, C. C. Wood, W. P. Davis, R. L. Parsons, *J. Org. Chem.* **2003**, *68*, 754-761.

[13] B. Jiang, Y. Si, *Adv. Synth. Catal.* **2004**, *346*, 669-674.

[14] P. A. Wender, D. A. Holt, S. M. Sieburth, *J. Am. Chem. Soc.* **1983**, *105*, 3348-3350.

[15] K. E. Stevens, L. A. Paquette, *Tetrahedron Lett.* **1981**, *22*, 4393-4396.

[16] P. E. Eaton, A. Srikrishna, F. Uggeri, *J. Org. Chem.* **1984**, *49*, 1728-1732.

[17] A. Hoffmann-Röder, N. Krause, *Helv. Chim. Acta* **2002**, *85*, 3176-3184.

[18] H. G. Viehe, M. Reinstein, *Chem. Ber.* **1962**, *95*, 2557-2562.

[19] L. Brandsma, *Preparative Acetylenic Chemistry*, Elsevier, Amsterdam, **1971**.

[20] Y. Shen, *Acc. Chem. Res.* **1998**, *31*, 584-592.

[21] J. H. Babler, V. P. Liptak, N. Phan, *J. Org. Chem.* **1996**, *61*, 416-417.

[22] D. Tzalis, P. Knochel, *Angew. Chem. Int. Ed.* **1999**, *38*, 1463-1465.

[23] D. Boyall, F. Lopez, H. Sasaki, D. Frantz, E. M. Carreira, *Org. Lett.* **2000**, *2*, 4233-4236.

[24] N. K. Anand, E. M. Carreira, *J. Am. Chem. Soc.* **2001**, *123*, 9687-9688.

[25] T. Ishikawa, T. Mizuta, K. Hagiwara, T. Aikawa, T. Kudo, S. Saito, *J. Org. Chem.* **2003**, *68*, 3702-3705.

[26] G. Lu, X. S. Li, X. Jia, W. L. Chan, A. S. C. Chan, *Angew. Chem. Int. Ed.* **2003**, *42*, 5057-5058.

[27] P. G. Cozzi, *Angew. Chem. Int. Ed.* **2003**, *42*, 2895-2898.

[28] B. Saito, T. Katsuki, *Synlett* **2004**, 1557-1560.

[29] A. E. Favorskii, *J. Russ. Phys. Chem. Soc.* **1905**, *37*, 643.

[30] T. Weil, P. R. Schreiner, *Eur. J. Org. Chem.* **2005**, 2213-2217.

[31] T. Harada, T. Fujiwara, K. Iwazaki, A. Oku, *Org. Lett.* **2000**, *2*, 1855-1857.

[32] C.-H. Ding, D.-D. Chen, Z.-B. Luo, L.-X. Dai, X.-L. Hou, *Synlett* **2006**, 1272-1274.

[33] J. R. Dunetz, R. L. Danheiser, *Org. Lett.* **2003**, *5*, 4011-4014.

[34] T. Baba, H. Kizuka, H. Handa, Y. Ono, *Appl. Catal., A* **2000**, *194-195*, 203-211.

[35] R. J. Tedeschi, *J. Org. Chem.* **1965**, *30*, 3045-3049.

[36] H. C. Brown, G. A. Molander, S. M. Singh, U. S. Racherla, *J. Org. Chem.* **1985**, *50*, 1577-1582.

[37] J. H. Ahn, M. J. Joung, N. M. Yoon, *J. Org. Chem.* **1995**, *60*, 6173-6175.

[38] J. H. Ahn, M. J. Joung, N. M. Yoon, D. C. Oniciu, A. R. Katritzky, *J. Org. Chem.* **1999**, *64*, 488-492.

[39] T. Imamoto, Y. Sugiura, N. Takiyama, *Tetrahedron Lett.* **1984**, *25*, 4233-4236.

[40] T. Hirao, D. Misu, T. Agawa, *Tetrahedron Lett.* **1986**, *27*, 933-934.

[41] P. Bertus, F. Fecourt, C. Bauder, P. Pale, *New J. Chem.* **2004**, *28*, 12-14.

[42] X. Yao, C.-J. Li, *Org. Lett.* **2005**, *7*, 4395-4398.

[43] S. P. Shahi, K. Koide, *Angew. Chem. Int. Ed.* **2004**, *43*, 2525-2527.

[44] M. Yamaguchi, A. Hayashi, T. Minami, *J. Org. Chem.* **1991**, *56*, 4091-4092.

[45] Y. Han, Y.-Z. Huang, *Tetrahedron Lett.* **1995**, *36*, 7277-7280.

[46] D. E. Frantz, R. Fassler, E. M. Carreira, *J. Am. Chem. Soc.* **1999**, *121*, 11245-11246.

[47] D. E. Frantz, R. Fassler, E. M. Carreira, *J. Am. Chem. Soc.* **2000**, *122*, 1806-1807.

[48] D. Boyall, D. E. Frantz, E. M. Carreira, *Org. Lett.* **2002**, *4*, 2605-2606.

[49] E. Tyrrell, K. Hunie Tesfa, A. Mann, K. Singh, *Synthesis* **2007**, 1491-1498.

[50] K. M. Nicholas, *Acc. Chem. Res.* **1987**, *20*, 207-214.

[51] A. Mann, C. Muller, E. Tyrell, *J. Chem. Soc., Perkin Trans. 1* **1998**, 1427-1438.

[52] B. Jiang, Z. Chen, X. Tang, *Org. Lett.* **2002**, *4*, 3451-3453.

[53] J. W. H. Watthey, J. L. Stanton, M. Desai, J. E. Babiarz, B. M. Finn, *J. Med. Chem.* **1985**, *28*, 1511-1516.

[54] D. P. G. Emmerson, W. P. Hems, B. G. Davis, *Org. Lett.* **2006**, *8*, 207-210.

[55] S. Niwa, K. Soai, *J. Chem. Soc., Perkin Trans. 1* **1990**, 937-943.

[56] M. Ishizaki, O. Hoshino, *Tetrahedron: Asymmetry* **1994**, *5*, 1901-1904.

[57] S. Dahmen, *Org. Lett.* **2004**, *6*, 2113-2116.

[58] M. Li, X.-Z. Zhu, K. Yuan, B.-X. Cao, X.-L. Hou, *Tetrahedron: Asymmetry* **2004**, *15*, 219-222.

[59] Z.-B. Li, L. Pu, *Org. Lett.* **2004**, *6*, 1065-1068.

[60] B. M. Trost, A. H. Weiss, A. J. von Wangelin, *J. Am. Chem. Soc.* **2006**, *128*, 8-9.

[61] M. G. Pizzuti, S. Superchi, *Tetrahedron: Asymmetry* **2005**, *16*, 2263-2269.

[62] J. Ruan, G. Lu, L. Xu, Y.-M. Li, A. S. C. Chan, *Adv. Synth. Catal.* **2008**, *350*, 76-84.

[63] S. Liebehentschel, J. Cvengro, A. J. von Wangelin, *Synlett* **2007**, 2574-2578.

[64] H. Li, Y. Huang, W. Jin, F. Xue, B. Wan, *Tetrahedron Lett.* **2008**, *49*, 1686-1689.

[65] J. Mao, B. Wan, F. Wu, S. Lu, *J. Mol. Catal. A-Chem.* **2005**, *237*, 126-131.

[66] R. Motoki, M. Kanai, M. Shibasaki, *Org. Lett.* **2007**, *9*, 2997-3000.

[67] R. F. Jordan, W. E. Dasher, S. F. Echols, *J. Am. Chem. Soc.* **1986**, *108*, 1718-1719.

[68] H. Maeta, T. Hashimoto, T. Hasegawa, K. Suzuki, *Tetrahedron Lett.* **1992**, *33*, 5965-5968.

[69] U. Rosenthal, P. Arndt, W. Baumann, V. V. Burlakov, A. Spannenberg, *J. Organomet. Chem.* **2003**, *670*, 84-96.

[70] P. K. Dhondi, J. D. Chisholm, *Org. Lett.* **2006**, *8*, 67-69.

[71] R. V. Lerum, J. D. Chisholm, *Tetrahedron Lett.* **2004**, *45*, 6591-6594.

[72] S. Serron, J. Huang, S. P. Nolan, *Organometallics* **1998**, *17*, 534-539.

[73] D. Moore, L. Pu, *Org. Lett.* **2002**, *4*, 1855-1857.

[74] Z. Xu, C. Chen, J. Xu, M. Miao, W. Yan, R. Wang, *Org. Lett.* **2004**, *6*, 1193-1195.

[75] R. Takita, Y. Fukuta, R. Tsuji, T. Ohshima, M. Shibasaki, *Org. Lett.* **2005**, *7*, 1363-1366.

[76] N. Sakai, R. Kanada, M. Hirasawa, T. Konakahara, *Tetrahedron* **2005**, *61*, 9298-9304.

[77] X. Jia, H. Yang, L. Fang, C. Zhu, *Tetrahedron Lett.* **2008**, *49*, 1370-1372.

[78] E. D. Bergmann, *The Chemistry of Acetylene and Related Compounds*, Interscience Publishers, Inc., New York, **1948**.

[79] P. R. Schreiner, O. Lauenstein, E. D. Butova, P. A. Gunchenko, I. V. Kolomitsin, A. Wittkopp, G. Feder, A. A. Fokin, *Chem. Eur. J.* **2001**, *7*, 4996-+.

[80] K. Bowden, R. S. Cook, *J. Chem. Soc., Perkin Trans. 2* **1972**, *48*, 1407-1411.

[81] M. Halpern, Y. Sasson, M. Rabinovitz, *J. Org. Chem.* **1983**, *48*, 1022-1025.

[82] F. G. Bordwell, *Acc. Chem. Res.* **1988**, *21*, 456-463.

[83] R. B. Lettan, K. A. Scheidt, *Org. Lett.* **2005**, *7*, 3227-3230.

[84] W. P. Weber, G. G. W. Gokel, *Phase-Transfer Catalysis in Organic Synthesis*, Springer, Berlin, **1977**.

[85] E. V. Dehmlow, S. S. Dehmlow, *Phase-Transfer Catalysis*, VCH, Weinheim, **1993**.

[86] C. Starks, C. Liotta, M. Halpern, *Phase-Transfer Catalysis: Fundamentals, Applications and Industrial Perspectives*, Chapman & Hall, New York, **1994**.

[87] M. Makosza, I. Krylowa, *Tetrahedron* **1999**, *55*, 6395-6402.

[88] T. Ooi, D. Sakai, M. Takeuchi, E. Tayama, K. Maruoka, *Angew. Chem. Int. Ed.* **2003**, *42*, 5868-5870.

[89] T. Ooi, Y. Uematsu, K. Maruoka, *Tetrahedron Lett.* **2004**, *45*, 1675-1678.

[90] C. Lemaire, S. Gillet, S. P. Guillouet, A. Plenevaux, J. L. Aerts, A. Luxen, *Eur. J. Org. Chem.* **2004**, 2899-2904.

[91] T. Ooi, K. Maruoka, *Angew. Chem. Int. Ed.* **2007**, *46*, 4222-4266.

[92] K. Maruoka, *Asymmetric Phase-Transfer Catalysis*, WILEY-VCH, Weinheim, **2008**.

[93] R. Schwesinger, H. Schlemper, C. Hasenfratz, J. Willaredt, T. Dambacher, T. Breuer, C. Ottaway, M. Fletschinger, J. Boele, H. Fritz, D. Putzas, H. W. Rotter,

F. G. Bordwell, A. V. Satish, G. Ji, E. Peters, K. Peters, H. G. Von Schnering, L. Walz, *Liebigs Ann. Chem.* **1996**, *1996*, 1055-1081.

[94] T. Imahori, C. Hori, Y. Kondo, *Adv. Synth. Catal.* **2004**, *346*, 1090-1092.

[95] B. S. Lane, K. Burgess, *Chem. Rev.* **2003**, *103*, 2457-2474.

[96] D. Yang, *Acc. Chem. Res.* **2004**, *37*, 497-505.

[97] Y. Shi, *Acc. Chem. Res.* **2004**, *37*, 488-496.

[98] E. M. McGarrigle, D. G. Gilheany, *Chem. Rev.* **2005**, *105*, 1563-1602.

[99] Q.-H. Xia, H.-Q. Ge, C.-P. Ye, Z.-M. Liu, K.-X. Su, *Chem. Rev.* **2005**, *105*, 1603-1662.

[100] A. K. Yudin, *Aziridines and Epoxides in Organic Synthesis*, Wiley-VCH, Weinheim, **2006**.

[101] A. O. Oyewale, R. A. Aitken, *Russian Chemical Bulletin* **1995**, *44*, 919-922.

[102] C. Schneider, *Synthesis* **2006**, 3919-3944.

[103] M. Moghadam, S. Tangestaninejad, V. Mirkhani, R. Shaibani, *Tetrahedron* **2004**, *60*, 6105-6111.

[104] H. Firouzabadi, N. Iranpoor, A. A. Jafari, S. Makarem, *J. Mol. Catal. A-Chem.* **2006**, *250*, 237-242.

[105] M. T. Reetz, C. Torre, A. Eipper, R. Lohmer, M. Hermes, B. Brunner, A. Maichele, M. Bocola, M. Arand, A. Cronin, Y. Genzel, A. Archelas, R. Furstoss, *Org. Lett.* **2004**, *6*, 177-180.

[106] M. H. Yang, C. J. Zhu, F. Yuan, Y. J. Huang, Y. Pan, *Org. Lett.* **2005**, *7*, 1927-1930.

[107] H. Desai, B. R. D'Souza, D. Foether, B. F. Johnson, H. A. Lindsay, *Synthesis* **2007**, 902-910.

[108] K. Arai, M. M. Salter, Y. Yamashita, S. Kobayashi, *Angew. Chem. Int. Ed.* **2007**, *46*, 955-957.

[109] J. S. Yadav, A. R. Reddy, A. V. Narsaiah, B. V. S. Reddy, *J. Mol. Catal. A: Chem.* **2007**, *261*, 207-212.

[110] R. V. Yarapathi, S. M. Reddy, S. Tammishetti, *React. Funct. Polym.* **2005**, *64*, 157-161.

[111] P. Vandeweghe, J. Collin, *Tetrahedron Lett.* **1995**, *36*, 1649-1652.

[112] M. L. Snapper, A. H. Hoveyda, *Angew. Chem. Int. Ed.* **1996**, *35*, 1995-1995.

[113] D. Albanese, D. Landini, M. Penso, *Tetrahedron* **1997**, *53*, 4787-4790.

[114] S. E. Schaus, E. N. Jacobsen, *Org. Lett.* **2000**, *2*, 1001-1004.

[115] E. Y. Lau, Z. E. Newby, T. C. Bruice, *J. Am. Chem. Soc.* **2001**, *123*, 3350-3357.

[116] G. Sabitha, R. S. Babu, M. Rajkumar, C. S. Reddy, J. S. Yadav, *Tetrahedron Lett.* **2001**, *42*, 3955-3958.

[117] M. A. Reddy, K. Surendra, N. Bhanumathi, K. R. Rao, *Tetrahedron* **2003**, *59*, 2363-2363.

[118] G. Smitha, C. S. Reddy, *J. Chem. Res., Synop.* **2004**, 300-301.

[119] Y. N. Belokon, D. Chusov, D. A. Borkin, L. V. Yashkina, A. V. Dmitriev, D. Katayev, M. North, *Tetrahedron: Asymmetry* **2006**, *17*, 2328-2333.

[120] B. Das, V. S. Reddy, F. Tehseen, M. Krishnaiah, *Synthesis* **2007**, 666-668.

[121] G. Prestat, C. Baylon, M. P. Heck, C. Mioskowski, *Tetrahedron Lett.* **2000**, *41*, 3829-3831.

[122] S. Chandrasekhar, C. R. Reddy, B. N. Babu, G. Chandrashekar, *Tetrahedron Lett.* **2002**, *43*, 3801-3803.

[123] M. L. Kantam, K. A. K. Jeyalakshmi, P. R. Likhar, *Catal. Lett.* **2003**, *89*, 95-97.

[124] D. Bradley, G. Williams, M. Lawton, *Org. Biomol. Chem.* **2005**, *3*, 3269-3272.

[125] J. M. R. Gallo, S. Teixeira, U. Schuchardt, *Appl. Catal., A* **2006**, *311*, 199-203.

[126] W. Solodenko, G. Jas, U. Kunz, A. Kirschning, *Synthesis* **2007**, 583-589.

[127] N. Iranpoor, I. Mohammadpour Baltork, *Tetrahedron Lett.* **1990**, *31*, 735-738.

[128] R. Garcia, M. Martinez, J. Aracil, *Chem. Eng. Technol.* **1999**, *22*, 987-990.

[129] S. Matsunaga, T. Ohshima, M. Shibasaki, *Adv. Synth. Catal.* **2002**, *344*, 3-15.

[130] M. W. C. Robinson, R. Buckle, I. Mabbett, G. M. Grant, A. E. Graham, *Tetrahedron Lett.* **2007**, *48*, 4723-4725.

[131] N. B. Chapman, J. Biggs, A. Finch, V. Wray, *J. Chem. Soc. (B)* **1971**, 55-63.

[132] J. M. Coxon, M. A. E. Townsend, *Tetrahedron* **2007**, *63*, 5665-5668.

[133] W. Reeve, I. Christoffel, *J. Am. Chem. Soc.* **1950**, *72*, 1480-1483.

[134] G. A. Olah, A. P. Fung, D. Meidar, *Synthesis* **1981**, 280-282.

[135] Y. Izumi, K. Hayashi, *Chem. Lett.* **1980**, 787-790.

[136] Y.-J. Liu, T.-Y. Chu, R. Engel, *Synth. Commun.* **1992**, *22*, 2367 - 2371.

[137] C. Moberg, L. Rakos, L. Tottie, *Tetrahedron Lett.* **1992**, *33*, 2191-2194.

[138] M. Korn, R. Wodarz, W. Schoknecht, H. Weichardt, E. Bayer, *Arch. Toxicol.* **1984**, *55*, 59-63.

[139] R. V. A. Orru, K. Faber, *Curr. Opin. Chem. Biol.* **1999**, *3*, 16-21.

[140] K. H. Hopmann, F. Himo, *Chem. Eur. J.* **2006**, *12*, 6898-6909.

[141] P. Moussou, A. Archelas, J. Baratti, R. Furstoss, *J. Mol. Catal. B: Enzym.* **1998**, *5*, 213-217.

[142] M. A. Argiriadi, C. Morisseau, M. H. Goodrow, D. L. Dowdy, B. D. Hammock, D. W. Christianson, *J. Biol. Chem.* **2000**, *275*, 15265-15270.

[143] T. Yamada, C. Morisseau, J. E. Maxwell, M. A. Argiriadi, D. W. Christianson, B. D. Hammock, *J. Biol. Chem.* **2000**, *275*, 23082-23088.

[144] Z. Liu, J. Michel, Z. Wang, B. Witholt, Z. Li, *Tetrahedron: Asymmetry* **2006**, *17*, 47-52.

[145] A. R. Gallimore, C. B. W. Stark, A. Bhatt, B. M. Harvey, Y. Demydchuk, V. Bolanos-Garcia, D. J. Fowler, J. Staunton, P. F. Leadlay, J. B. Spencer, *Chem. Biol.* **2006**, *13*, 453-460.

[146] P. R. Schreiner, A. Wittkopp, *Org. Lett.* **2002**, *4*, 217-220.

[147] P. R. Schreiner, *Chem. Soc. Rev.* **2003**, *32*, 289-296.

[148] A. Wittkopp, P. R. Schreiner, *Chem. Eur. J.* **2003**, *9*, 407-414.

[149] I. Vilotijevic, T. F. Jamison, *Science* **2007**, *317*, 1189-1192.

[150] C. M. Kleiner, P. R. Schreiner, *Chem. Commun.* **2006**, 4315-4317.

[151] T. Weil, M. Kotke, C. M. Kleiner, P. R. Schreiner, *Org. Lett.* **2008**, *10*, 1513-1516.

[152] R. E. Parker, N. S. Isaacs, *Chem. Rev.* **1959**, *59*, 737-799.

[153] I. Paterson, D. J. Berrisford, *Angew. Chem. Int. Ed.* **1992**, *31*, 1179-1180.

[154] E. N. Jacobsen, *Acc. Chem. Res.* **2000**, *33*, 421-431.

[155] Emerson, *This Journal* **1945**, *67*, 516.

[156] W. Kaminsky, A. Laban, *Appl. Catal., A* **2001**, *222*, 47-61.

[157] W. Kaminsky, *Catalysis Today* **2000**, *62*, 23-34.

[158] T. Takanami, R. Hirabe, M. Ueno, F. Hino, K. Suda, *Chem. Lett.* **1996**, *25*, 1031-1032.

[159] S. Tangestaninejad, V. Mirkhani, *Synth. Commun.* **1999**, *29*, 2079 - 2083.

[160] S. Tangestaninejad, M. H. Habibi, V. Mirkhani, M. Moghadam, *Synth. Commun.* **2002**, *32*, 1337 - 1343.

[161] T. P. Yoon, E. N. Jacobsen, *Science* **2003**, *299*, 1691-1693.

[162] J. F. Larrow, E. N. Jacobsen, *Top. Organomet. Chem.* **2003**, *6*, 123.

[163] J. M. Ready, E. N. Jacobsen, *J. Am. Chem. Soc.* **1999**, *121*, 6086-6087.

[164] Y. Masaki, T. Miura, M. Ochiai, *Synlett* **1993**, 847-849.

[165] J. E. Baldwin, *J. Chem. Soc., Chem. Commun.* **1976**, 734-736.

[166] G. A. Molander, J. P. Haar, *J. Am. Chem. Soc.* **1991**, *113*, 3608-3610.

[167] P. C. Boldt, M. H. M. G. Schumacher-Wandersleb, M. G. Peter, *Tetrahedron Lett.* **1991**, *32*, 1413-1416.

[168] B. N. Blackett, J. M. Coxon, M. P. Hartshorn, A. J. Lewis, G. R. Little, G. J. Wright, *Tetrahedron* **1970**, *26*, 1311-1313.

[169] V. G. Dryuk, V. I. Avramenko, V. N. Yandovsky, *J. Chem. Soc., Perkin Trans. 2* **1977**, 1526-1529.

[170] J. R. Vyvyan, J. A. Meyer, K. D. Meyer, *J. Org. Chem.* **2003**, *68*, 9144-9147.

[171] S. Tangestaninejad, M. H. Habibi, V. Mirkhani, M. Moghadam, *J. Chem. Res., Synop.* **2001**, 365-367.

[172] I. Mohammadpoor-Baltork, A. R. Khosropour, H. Aliyan, *Synth. Commun.* **2001**, *31*, 3411-3416.

[173] N. Iranpoor, B. Zeynizadeh, *J. Chem. Res., Synop.* **1998**, 466-467.

[174] N. Iranpoor, F. Kazemi, *Synth. Commun.* **1998**, *28*, 3189-3193.

[175] Z. Zhu, J. H. Espenson, *Organometallics* **1997**, *16*, 3658-3663.

[176] P. Krasik, M. Bohemier-Bernard, Q. Yu, *Synlett* **2005**, 0854-0856.

[177] A. Procopio, R. Dalpozzo, A. De Nino, L. Maiuolo, M. Nardi, B. Russo, *Adv. Synth. Catal.* **2005**, *347*, 1447-1450.

[178] J. M. Concellon, J. R. Suarez, S. Garcia-Granda, M. R. Diaz, *Org. Lett.* **2005**, *7*, 247-250.

[179] F. Kazemi, A. R. Kiasat, S. Ebrahimi, *Synth. Commun.* **2005**, *35*, 1441-1445.

[180] L. W. Zatorski, P. T. Wierzchowski, *Catal. Lett.* **1991**, *10*, 211-213.

[181] B. Rickborn, R. M. Gerkin, *J. Am. Chem. Soc.* **1971**, *93*, 1693-1700.

[182] D. S. Torok, J. J. Figueroa, W. J. Scott, *J. Org. Chem.* **1993**, *58*, 7274-7276.

[183] M. H. Habibi, S. Tangestaninejad, V. Mirkhani, B. Yadollahi, *Catal. Lett.* **2001**, *75*, 205-207.

[184] D. M. Clode, *Chem. Rev.* **1979**, *79*, 491-513.

[185] D. A. Evans, S. L. Bender, J. Morris, *J. Am. Chem. Soc.* **1988**, *110*, 2506-2526.

[186] D. A. Evans, R. P. Polniaszek, K. M. DeVries, D. E. Guinn, D. J. Mathre, *J. Am. Chem. Soc.* **1991**, *113*, 7613-7630.

[187] Y. Mori, K. Yaegashi, H. Furukawa, *J. Am. Chem. Soc.* **1996**, *118*, 8158-8159.

[188] Y. Mori, K. Yaegashi, H. Furukawa, *J. Org. Chem.* **1998**, *63*, 6200-6209.

[189] D. A. Evans, H. A. Rajapakse, A. Chiu, D. Stenkamp, *Angew. Chem. Int. Ed.* **2002**, *41*, 4573-4576.

[190] R. M. Hanson, *Chem. Rev.* **1991**, *91*, 437-475.

[191] R. P. Hanzlik, M. Leinwetter, *J. Org. Chem.* **1978**, *43*, 438-440.

[192] Y. N. Yandovskii, T. I. Temnikova, *J. Org. Chem. USSR 4* **1968**, 1695.

[193] M. Kotke, P. R. Schreiner, *Tetrahedron* **2006**, *62*, 434-439.

[194] M. Kotke, P. R. Schreiner, *Synthesis* **2007**, 779-790.

[195] M. J. T. Robinson, K. M. Rosen, J. D. B. Workman, *Tetrahedron* **1977**, *33*, 1655-1661.

[196] V. D. Delchev, *J. Struct. Chem.* **2003**, *44*, 574-580.

[197] I. Matanovic, N. Doslic, *J. Phys. Chem. A* **2005**, *109*, 4185-4194.

[198] A. Camerman, D. Mastropaolo, N. Camerman, *J. Am. Chem. Soc.* **1983**, *105*, 1584-1586.

[199] G. D. K. Kumar, S. Baskaran, *J. Org. Chem.* **2005**, *70*, 4520-4523.

7. Bibliography

This thesis is based on three publications (two already published and one in preparation):

1. Torsten Weil and Peter R. Schreiner; **Organocatalytic Alkynylation of Aldehydes and Ketones under Phase-Transfer Catalytic Conditions**, *Eur. J. Org. Chem*. **2005**, 2213-2217.

2. Torsten Weil, Mike Kotke, Christian M. Kleiner, and Peter R. Schreiner; **Cooperative Brønsted Acid-Type Organocatalysis: Alcoholysis of Styrene Oxides**, *Org. Lett*. **2008**, *10*, 1513-1516.

3. Christian M. Kleiner, Torsten Weil, Mike Kotke, and Peter R. Schreiner; **Organocatalytic Formation of 1,3-Dioxolanes**, manuscript in preparation.

Parts of the presented thesis have been presented as a poster:

Torsten Weil and Peter R. Schreiner
Organocatalytic Alkynylation of Aldehydes, Ketones and Imines under Phase-Transfer Catalytic Conditions
GdCh Jahrestagung, Düsseldorf
September 2005.

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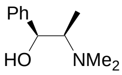
A. Abbreviations and Acronyms

1°	primary
18-C-6	18-crown 6 (1,4,7,10,13,16-hexaoxacyclooctadecane)
2°	secondary
3°	tertiary
A^2 coupling	alkyne-aldehyde coupling
acac	acetylacetonate
Alk	alkyl
aq.	aqueous
Ar	aryl
Asp	aspartate
B3LYP	Becke-3-Lee-Yang-Parr. A density functional theory method with three empirical parameters
BINOL	2,2´-Dihydroxy-1,1´-binaphthyl
Bn	benzyl
***t*Bu**	*tert*-butyl
BuLi	*n*-buthyllithium
***t*-Bu-P4**	(3-(*tert*-butylamino)-1,1,1,5,5,5-hexakis(dimethylamino)-3-{[tris-(dimethylamino) phosphoranylidene]amino}-$1\lambda^5$-$5\lambda^5$-triphosphazadien)
c	cyclic
C	celsius
cat.	catalyst
conc.	concentrated
cond.	conditions
Cp	cyclopentadienyl
Cy	cyclohexyl
δ	NMR chemical shift/ppm
d	day
DBU	1,8-diazabicyclo [5.4.0]undec-7-ene
DDQ	1,3-dichloro-5,6-dicyano-*p*-benzoquinone
DFT	density functional theory
DME	dimethoxyethane
DMSO	dimethyl sulfoxide
dr	diastereomeric ratio
ee	enantiomeric excess
equiv	equivalents
Et	ethyl
GC/MS	gas chromatography/mass spectroscopy
h	hour
His	histidine
HPA	heteropoly acid
IR	infrared
J	coupling constant/Hz
KHMDS	potassium bis(trimethylsilyl)amide
L*	chiral ligand
LDA	lithium diisopropylamide
LHMDS	lithium bis(trimethylsilyl)amide
m	meta
Me	methyl
MS	molecular sieve
Nafion-H	perfluoralkanesulfonic acid resin
NMR	nuclear magnetic resonance
o	ortho

OTf	triflate
p	para
Ph	phenyl
ppm	parts per million
***i*Pr**	*iso*-propyl
PTC	phase-transfer catalysis
pybox	pyridine bis(oxazoline)
rt	room temperature
SET	single-electron-transfer
sEH	soluable epoxide hydrolase
TBABr	tetra-*n*-butyl ammonium bromide
TBDMS	*tert*-butyl-dimethylsilylether
TBME	*tert*-butyl-methylether
TCNE	tetracyanoethylene
THF	tetrahydrofuran
THP	tetrahydropyrane
TMS	trimethylsilyl
Triton B™	benzyl-trimethyl ammonium hydroxide
Ts	tosyl
TsOH	*p*-toluenesulphonic acid
Tyr	tyrosine
xantphos	4,5-bis(diphenylphosphino)-9,9-dimethylxanthene

B. Compound Index



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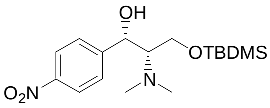

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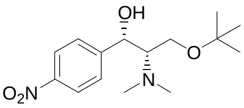

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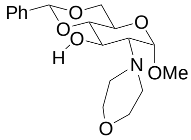

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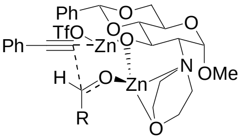

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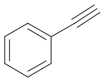

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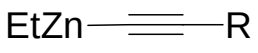

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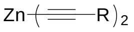

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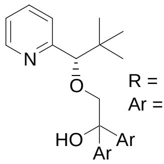

R = phenyl
Ar = α-naphthyl

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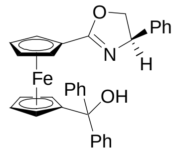

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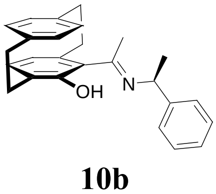

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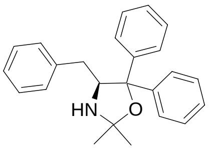

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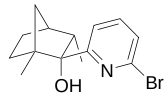

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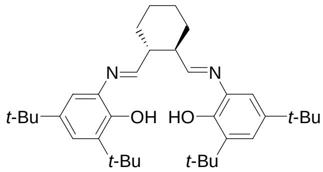

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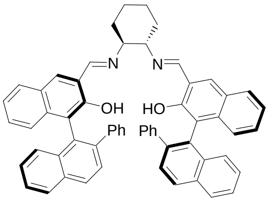

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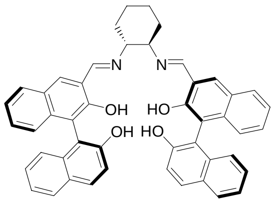

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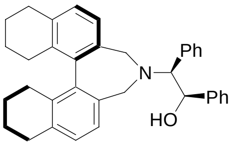

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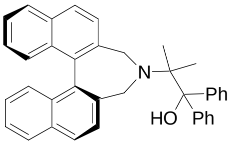

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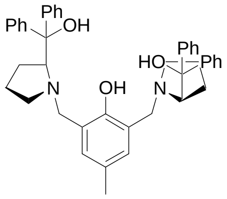

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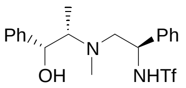

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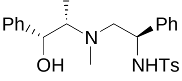

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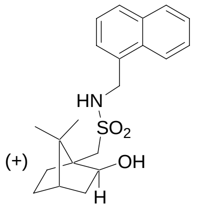

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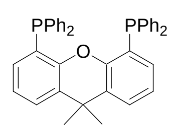

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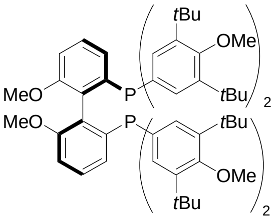

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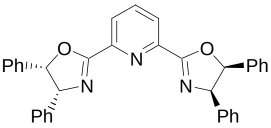

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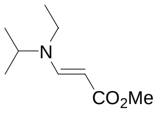

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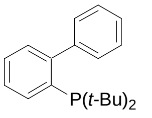

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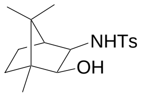

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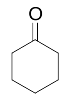

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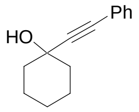

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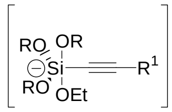

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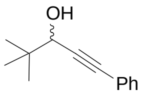

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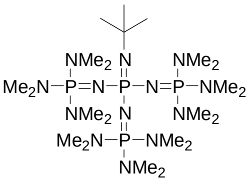

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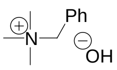

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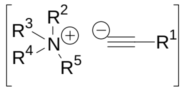

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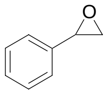

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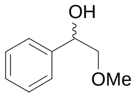

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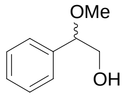


26b

$H_3PW_{12}O_{40}$

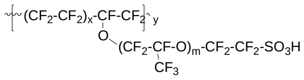
27

$H_3PMo_{12}O_{40}$

28

$H_4SiW_{12}O_{40}$

29



$\sim[(CF_2\text{-}CF_2)_x\text{-}CF\text{-}CF_2]_y$ $\text{O}\text{-}(CF_2\text{-}CF(CF_3)\text{-}O)_m\text{-}CF_2\text{-}CF_2\text{-}SO_3H$

30

$SnCl_4$

31

$TiCl_4$

32

$BF_3{\cdot}OEt_2$

33

$B(C_6F_5)_3$

34

$Al(OTf)_3$

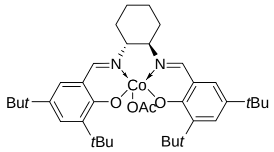
35

$AlPW_{12}O_{40}$

36

Cp_2ZrCl_2

37



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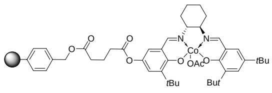

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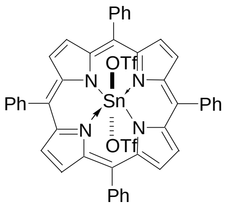

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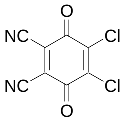

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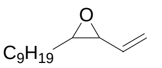

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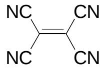

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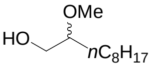

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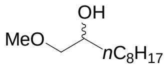

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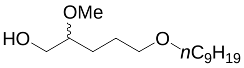

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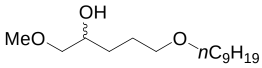

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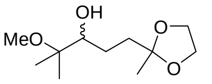

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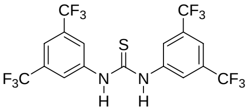

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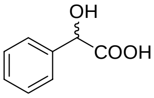

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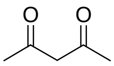

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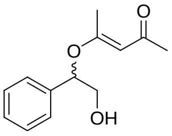

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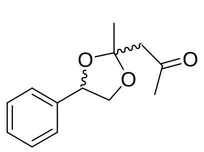

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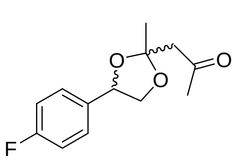

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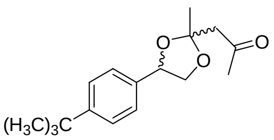

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Hiermit versichere ich an Eides statt, dass ich die vorliegende
Arbeit selbstständig ausgeführt, verfasst und keine anderen als
die aufgeführten Hilfsmittel und Quellen benutzt habe.

Gießen, den 03.09.2008

Torsten Weil