COOPERATIVE DUAL CATALYSIS WITH THIOUREA ORGANOCATALYSTS

By

CHENFEI ZHAO

A dissertation submitted to the

Graduate School-New Brunswick

Rutgers, The State University of New Jersey

In partial fulfillment of the requirements

For the degree of

Doctor of Philosophy

Graduate Program in Chemistry and Chemical Biology

Written under the direction of

Professor Daniel Seidel

And approved by

_____

_____

_____

_____

New Brunswick, New Jersey

October, 2017

ABSTRACT OF THE DISSERTATION

Cooperative Dual Catalysis with Thiourea Organocatalysts

by CHENFEI ZHAO

Dissertation Director:

Professor Daniel Seidel

Thiourea organocatalysis represents a versatile activation strategy in synthetic organic chemistry. By hydrogen-bonding interactions with neutral or anionic substrates and/or intermediates, thiourea organocatalysts can often direct the reaction pathways with promising levels of stereochemical control.

This dissertation demonstrates the cooperative use of thiourea organocatalysts in combination with other types of catalysts in addressing challenging synthetic problems that are not realized by either type alone. Specifically, cooperative catalysis of thiourea and iminium organocatalysts enabled the first highly enantioselective direct oxa-Pictet–Spengler reactions under weakly acidic conditions. In combination with a transition metal catalyst, an acid–thiourea catalyst afforded highly enantioselective A^3 reactions with secondary amines. Strong Brønsted acid was also applied cooperatively with thiourea organocatalyst, furnishing the direct reductive etherification reactions with a wide variety of substrates.

ACKNOWLEDGEMENTS

Parts of chapter II were adapted from the article “Direct Formation of Oxocarbenium Ions under Weakly Acidic Conditions: Catalytic Enantioselective Oxa-Pictet–Spengler Reactions” (*J. Am. Chem. Soc.* **2016**, *138*, 9053). Parts of chapter III were adapted from the article “Enantioselective A^3 Reactions of Secondary Amines with a Cu(I)/Acid-Thiourea Catalyst Combination” (*J. Am. Chem. Soc.* **2015**, *137*, 4650). Parts of chapter IV were adapted from the article “Reductive Etherification via Anion-Binding Catalysis” pending publication.

I’d like to express my great gratitude to my advisor Professor Daniel Seidel, for his guidance and support throughout my graduate studies. I really appreciate his patience and the great amount of time he has spent on me, not only in helping me excel in research but also in acquiring opportunities for my future development. It has been highly enjoyable and encouraging to work for Professor Seidel, whose goals and priorities often align with my own. I also want to thank my committee members Professor Lawrence Williams, Professor Alan Goldman, Professor Kai Hultzsch and my outside committee member Dr. Blair Wood, for their invaluable time and advices, which have significantly inspired my ways of thinking and carrying out research. I am also grateful to the Seidel group members from the past and present, for their support throughout my graduate studies. I would like to especially thank Dr. Longle Ma, for teaching me and familiarizing me with the lab in many aspects during my very early days here. My progress in research is also inseparable from the help provided by Dr. Tom Emge, Dr. Nagarajan Murali and Dr. Alexei Ermakov and I deeply appreciate their professionalism and passion.

I deeply thank my parents, for their love, support and understanding of me pursuing my career far away from home.

Table of Contents

Chapter I Introduction to Cooperative Multiple Catalysis

1.1 Organocatalysis

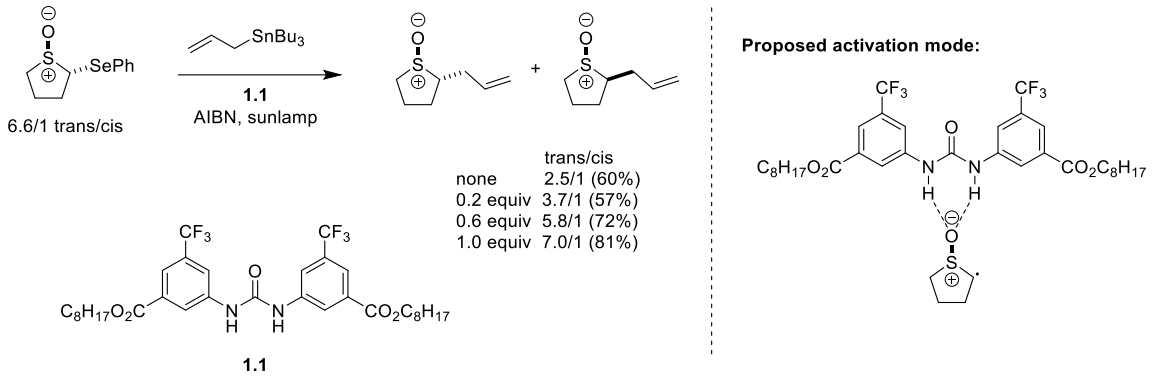
Organocatalysis refers to the use of organic molecules in substoichiometric amounts to accelerate chemical reactions.[1] Although organocatalysis has been applied by chemists for over a century, this area only started to grow considerably since the late 1990s and soon became a major branch in synthetic methodology.[2] Compared with traditional metal catalysis, organocatalysis offers several advantages such as simple reaction set-up, stability towards air and moisture, and cheap and abundant catalyst building blocks. New activation modes enabled by organocatalysis have been applied in various chemical transformations, many of which have not been realized in traditional metal catalysis. Specifically, organocatalysis has been developed for electrophilic activation, such as iminium catalysis,[3] chiral Brønsted acid catalysis[4] and multi-hydrogen bonding catalysis,[5] and for nucleophilic activation, such as enamine catalysis,[6] phase transfer catalysis[7] and Lewis base catalysis.[8] The combination of discrete activation modes within and beyond the scope of organocatalysis also widely exists,[9] either unexpectedly or intentionally. In short, organocatalysis has become a powerful tool that has infiltrated many aspects of modern synthetic organic chemistry.

1.1.1 Thiourea Organocatalysis

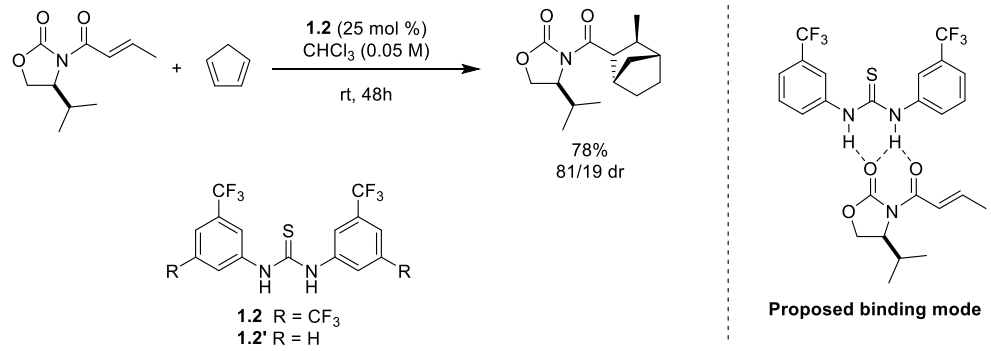
In 1994, Curran reported a simple urea molecule **1.1** as a dual hydrogen-bond donor catalyst in accelerating the allylation reactions of α-sulfinyl radicals (Scheme 1.1).[10] Besides the reaction rate, stereochemical outcome is also affected by the presence of **1.1** favoring the trans product. The authors proposed that catalyst **1.1** associates with the sulfoxide radical through double hydrogen bonding. The resulted complex is considered more electrophilic than the uncomplexed radical intermediate. The proposed activation mode is supported by a number of control experiments. Inhibition of the catalytic effect was observed in the

presence of tetrahydrothiophene oxide as a competing hydrogen-bond acceptor. Moreover, when the urea nitrogen atoms are methylated, the catalytic behavior is rendered absent. Subsequently, catalyst **1.1** was also shown to accelerate Claisen rearrangement reactions where the proposed activation mode also involves a dual hydrogen-bonding interaction.[11]

Scheme 1.1 Urea catalyzed allylation reactions of α-sulfinyl radicals.



Scheme 1.2 Thiourea acts like Lewis acid.

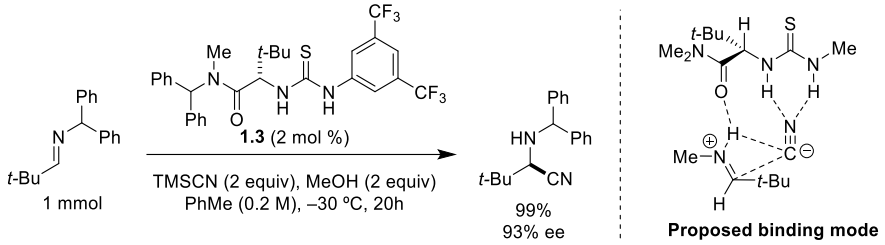


In 2002, Schreiner demonstrated that simple thiourea molecules can act as Lewis acids to activate oxazolidinones via complexation.[12] Dynamic NMR, low-temperature IR and DFT calculations indicate that a preferred binding mode involves the complexation of both thiourea N–H protons with both carbonyl groups of oxazolidinone (Scheme 1.2). The Gibbs free energy of such complexation was determined to be $\Delta G_{298} = -3.4 \pm 0.2$ kcal mol^{-1} ($\Delta H_{298} = -6.5 \pm 1.3$ kcal mol^{-1}, $\Delta S_{298} = -9.6 \pm 2.6$ kcal mol^{-1} K^{-1}). The catalytic behavior of these

thiourea catalysts was also revealed in a Diels–Alder reaction that was similarly catalyzed by traditional Lewis acids.

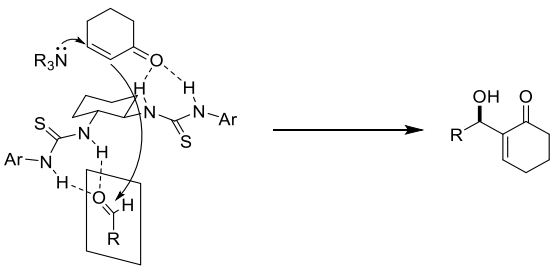
In 1998, Jacobsen described a chiral Schiff base catalyst **1.3** for the enantioselective Strecker reaction.[13] Although it was later clarified via mechanistic studies that the key interaction between thiourea N–H protons and cyanide was responsible for the stereochemical outcome (Scheme 1.3),[14] this and Schreiner's seminal work spurred the flourish of thiourea catalysis as a general strategy for electrophile activation.[5]

Scheme 1.3 Thiourea catalyzed enantioselective Strecker reaction.



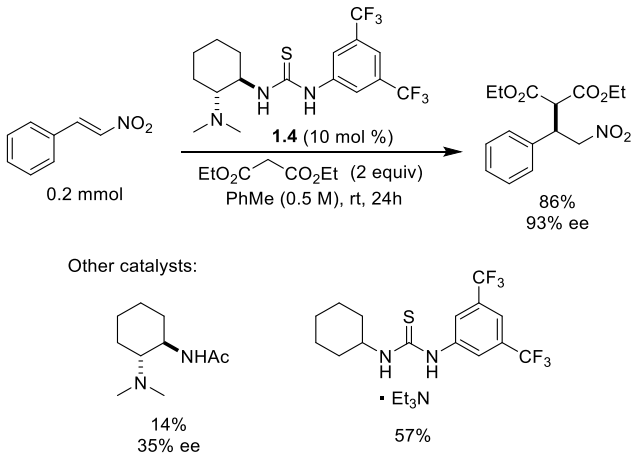
Direct activation of neutral electrophiles by thiourea moiety generally relies on its interaction with carbonyl compounds and nitroalkenes.[5] For example, Nagasawa demonstrated the application of a readily accessible bis-thiourea catalyst in the asymmetric Baylis–Hillman reactions with the designing notion that the catalyst can simultaneously activate aldehyde and promote enolate formation.[15] The proposed transition state matches the stereochemical outcome of the reaction (Figure 1.1).

Figure 1.1 Proposed transition state for the organocatalytic asymmetric Baylis-Hillman reaction.

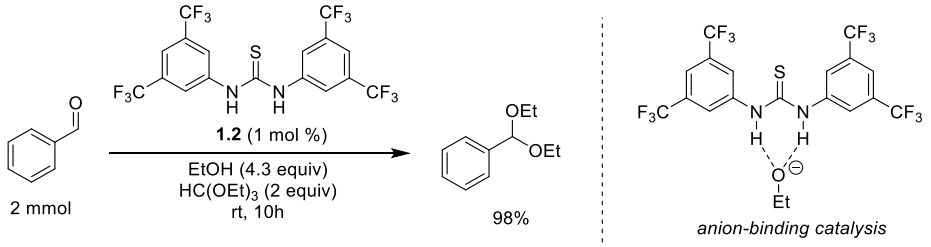


A more profound synergetic effect is exemplified by Takemoto's bifunctional catalyst **1.4** where an extra tertiary amino group is attached to the thiourea catalyst.[16] Control experiments in the enantioselective Michael reactions show that high reactivity and enantioselectivity require the presence of both the thiourea and tertiary amine moieties within the catalyst structure (Scheme 1.4). This is most likely the result of simultaneous activation of the electrophile and the nucleophile.

Scheme 1.4 Bifunctional aminothiourea catalyzed Michael reaction.



Scheme 1.5 Thiourea catalyzed acetalization reactions via anion binding.

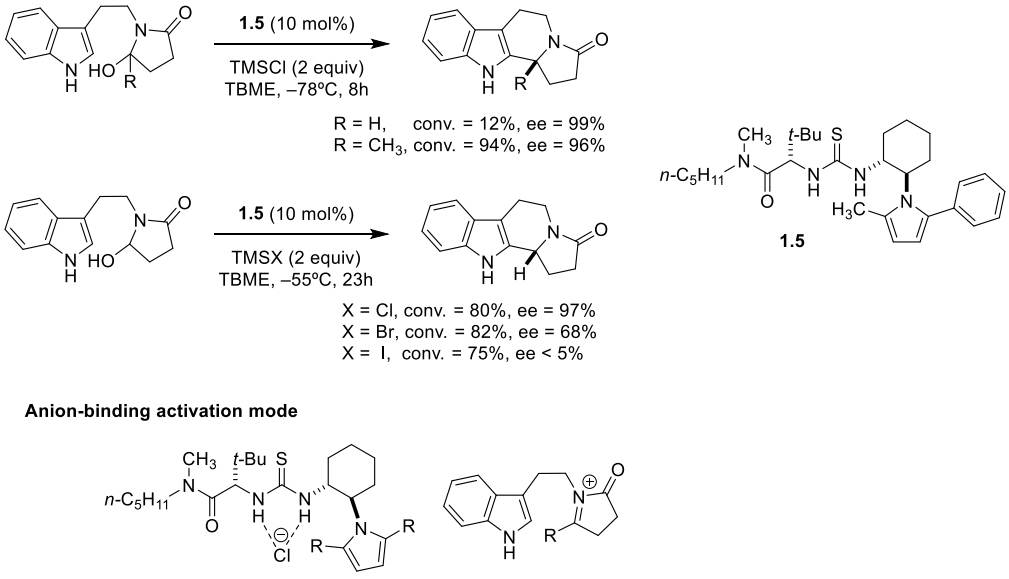


In 2006, Schreiner described the use of simple thiourea catalyst **1.2** for the acetalization of aldehydes and ketones (Scheme 1.5).[17] Control experiment in the presence of thiol and triethyl orthoester only resulted in the formation of the corresponding diethyl acetal,

which is in accord with the proposed role of the thiourea catalyst in stabilizing the alkoxide anion. This is the first time thiourea catalysis was recognized through anion abstraction.

In 2007, Jacobsen first proposed an anion-binding mechanism as a key step in the context of asymmetric catalysis (Scheme 1.6).[18] In the thiourea catalyzed Pictet–Spengler-type cyclization reactions, a profound halide effect was found, as switching from chloride to iodide resulted in complete loss of enantioselectivity. Moreover, enhanced reactivity was observed with an additional α-Me group with regard to the amide nitrogen. These results strongly suggest the mechanism involves chloride binding by the thiourea catalyst and the S_N-1 nature of the cyclization step.

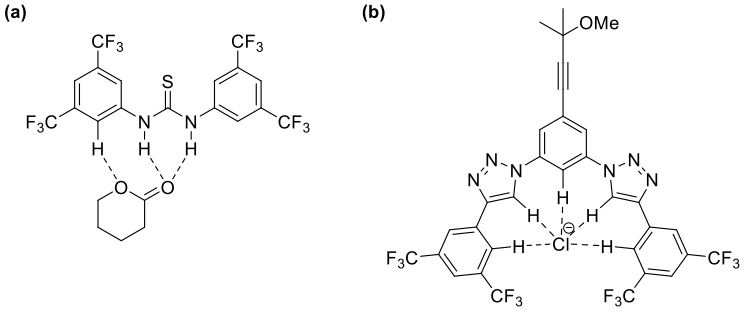
Scheme 1.6 Thiourea catalyzed Pictet–Spengler-type cyclization reactions via anion binding.



The 3,5-bis(trifluoromethyl)phenyl moiety is frequently incorporated in thiourea organocatalysts and is termed as the "privileged" structure.[19] A number of mechanistic studies from IR, NMR, ESI-MS and computations suggest that the *ortho* C–H bond also serves as a hydrogen-bond donor site (Figure 1.2 a). This is in accord with the fact that electron-deficient arenes and heterocyclic compounds can form strong hydrogen bonds with

anions.[20] For example, Mancheno demonstrated that bis-triazole compounds could serve as neutral anion receptor organocatalysts enabled by C–H bonds (Figure 1.2 b).[21] Computational studies indicate a binding energy (ΔE_0) in acetone to be –9.1 kcal mol^{-1} with a Gibbs free energy (ΔG_{298}) of –1.6 kcal mol^{-1}.

Figure 1.2 C_{sp2}–H bonds as hydrogen-bond donors.



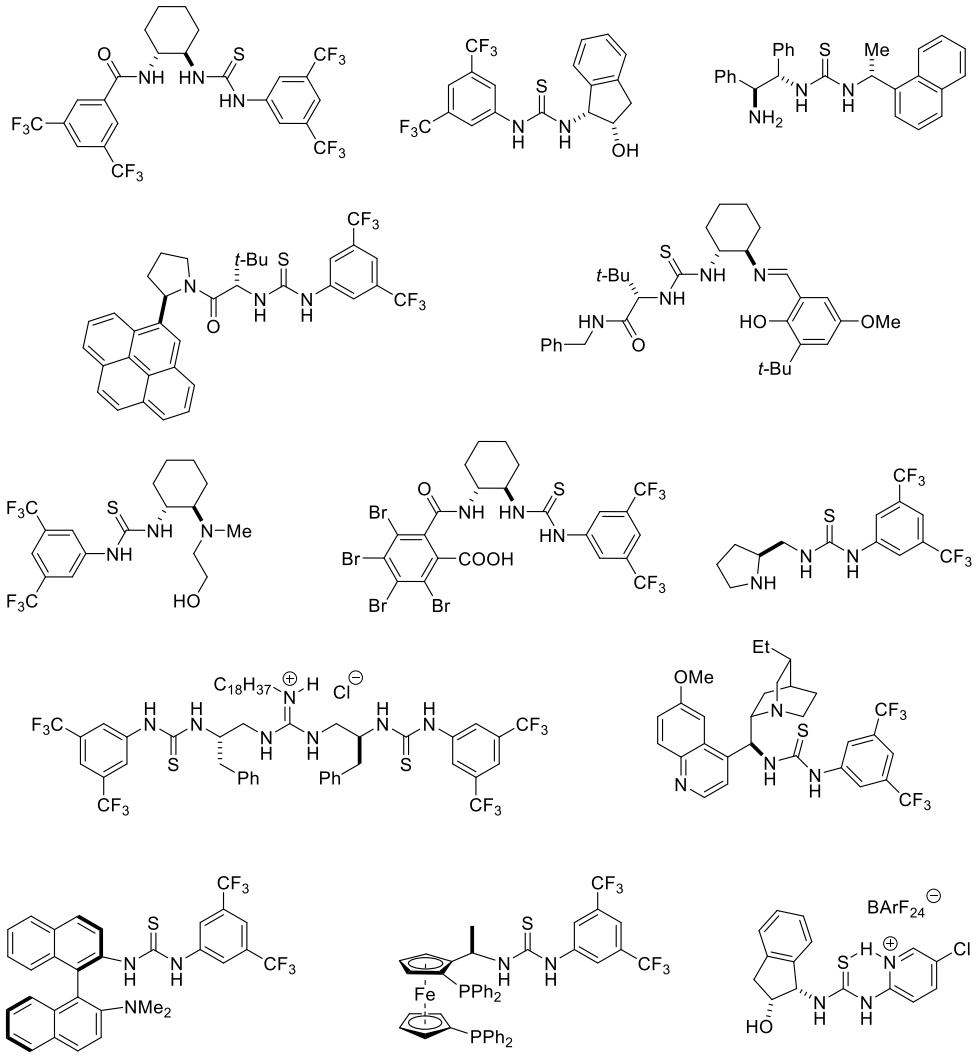
Following the seminal work by Schreiner and Jacobsen, thiourea catalysis has drawn immense attention from the synthetic organic chemistry community and has become one of the main strategies in electrophile activation, either through binding with neutral electrophiles or anions. Thiourea moieties have been incorporated in many catalyst structures that often contain secondary functionalities varying from acid to base (Figure 1.3).[5,22–24] It has also been incorporated in ligands[22] and solid supports[23]. The versatility of thiourea catalysis has enabled numerous chemical transformations with high levels of reactivity and selectivity.[19]

1.2 Cooperative Multiple Catalysis

Traditionally, catalytic reactions only involve the interactions between one catalyst and one substrate. Modern synthetic chemistry, on the contrary, has found enormous advantages in cooperative catalysis when more than one catalyst are used to activate multiple reacting partners and/or steps.[9] Combination between various types of metal catalysts, such as Lewis acids, transition metals, photoredox catalysts, and organocatalysts, such as amino

catalysts, chiral Brønsted acids, anion-binding catalysts have enabled many unprecedented reactions with high levels of chemo-, regio- and stereo-chemical control.[9,27–32]

Figure 1.3 Selected examples of thiourea-containing catalysts.



1.2.1 Cooperative Multiple Catalysis with Organocatalysts and Transition Metal Catalysts

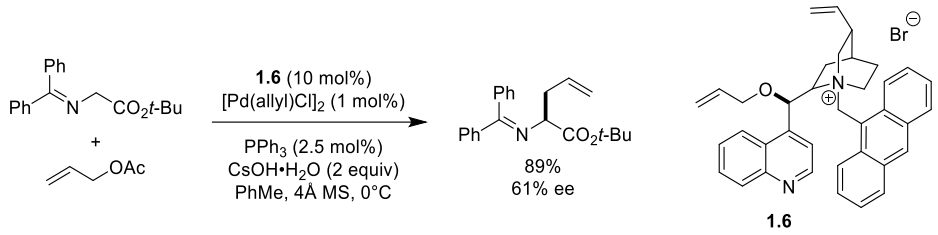
Despite the surge of organocatalysis since the beginning of this century and the immense amount of new reactions developed thereof, the unique reactivity of transition metals in cleaving many inert chemical bonds has not been realized by organocatalysts.[31] On the other hand, transition metal catalysis, especially within the context of asymmetric catalysis, has frequently relied on the judicious choice of ligands, which are often complex and require multi-step synthesis and/or resolution. To this end, and in a simplified model, it will be highly desirable if a simple metal source is used for bond cleavage and/or formation, with a readily available organocatalyst to dictate the stereochemical outcome. Moreover, the presence of organocatalysts in combination with transition metals often provides additional activation of the reaction partners and/or intermediates, resulting in both increased reactivity and selectivity. Therefore, a productive application of the two types of catalysts in a single reaction has significant potential towards novel chemical transformations that have not been realized by each of them alone.

In 2001, Gong first reported the asymmetric allylation of glycine imino esters with a combination of a palladium complex and a cinchona alkaloid type phase-transfer catalyst **1.6** (Scheme 1.7).[33] The palladium complex serves to cleave the allylic C–O bond while the phase-transfer catalyst **1.6** delivers enantiomeric control via ion pairing with deprotonated imino ester.

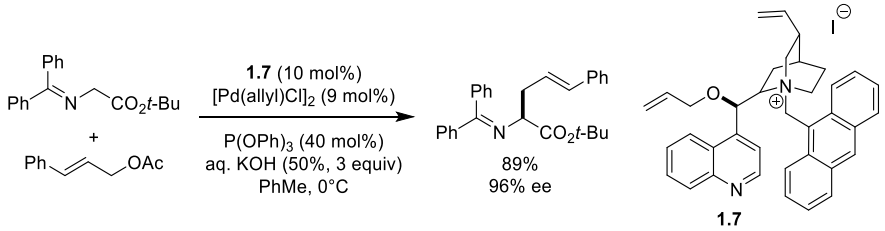
A highly similar work was reported by Takemoto almost simultaneously (Scheme 1.8).[34] Replacing PPh_3 with $P(OPh)_3$ affords a boost in the enantioselectivity while more α-donating ligands such as 1,2-bis(diphenylphosphino)ethane (DPPE) and P(*n*-Bu)$_3$ are disadvantageous. The authors proposed that the more α-donating ligands would favor the

formation of a highly reactive cationic palladium complex, allowing for considerable background reaction that led to racemic product.

Scheme 1.7 Asymmetric allylation of imino ester with Pd/PTC combination by Gong.



Scheme 1.8 Asymmetric allylation of imino ester with Pd/PTC combination by Takemoto.

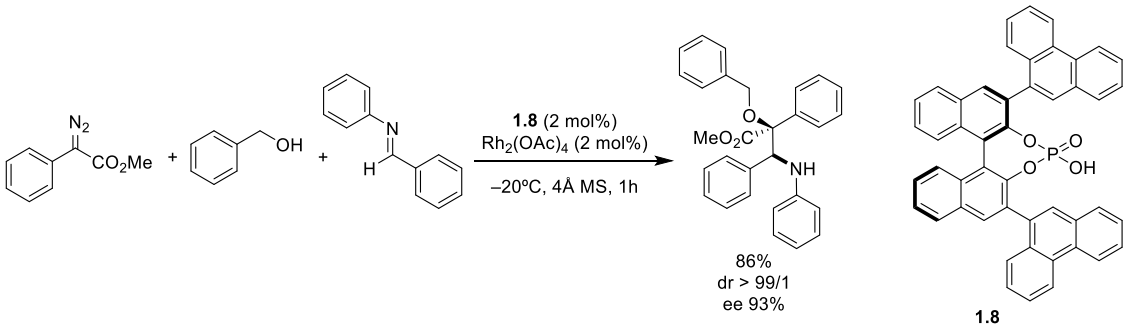


Hu and Gong reported an example of cooperative catalysis with chiral phosphoric acid **1.8** and $Rh_2(OAc)_4$ for the enantioselective reactions between diazoacetate, benzyl alcohol and aromatic imine (Scheme 1.9).[35] The key intermediate oxonium ylide is generated via rhodium carbene O–H insertion while the chiral phosphoric acid controls the stereochemical outcome through multiple hydrogen bonding interactions. The full recovery of the starting material was observed in the absence of $Rh_2(OAc)_4$.

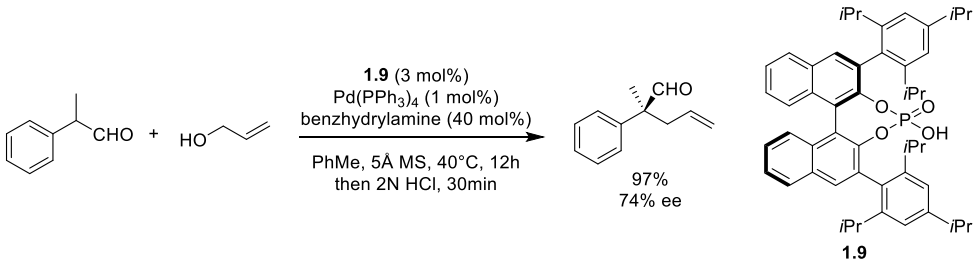
Cooperative asymmetric catalysis with three catalysts was demonstrated by List in the asymmetric α-allylation reactions of aldehydes with allylic alcohols (Scheme 1.10).[36] The palladium complex is essential for the reactivity as no reaction occurred in its absence. Benzhydrylamine serves to facilitate enamine formation and suppress the enol pathway, which leads to low enantioselectivity. The amine cocatalyst is used in a relatively high

loading due to product inhibition. Lastly, the chiral phosphoric acid **1.9** facilitates the oxidative addition of the allylic alcohol to palladium and direct the subsequent stereodetermining step via ion pairing and multiple hydrogen bonding.

Scheme 1.9 Enantioselective coupling of diazoacetate, benzyl alcohol and aromatic imine.



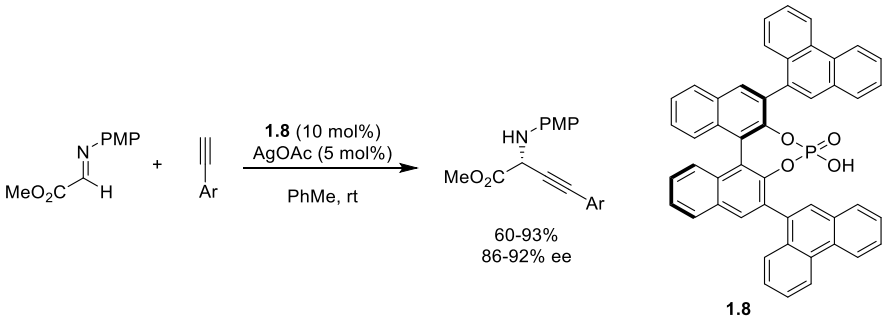
Scheme 1.10 Asymmetric α-allylation of aldehydes with allylic alcohols with three catalysts.



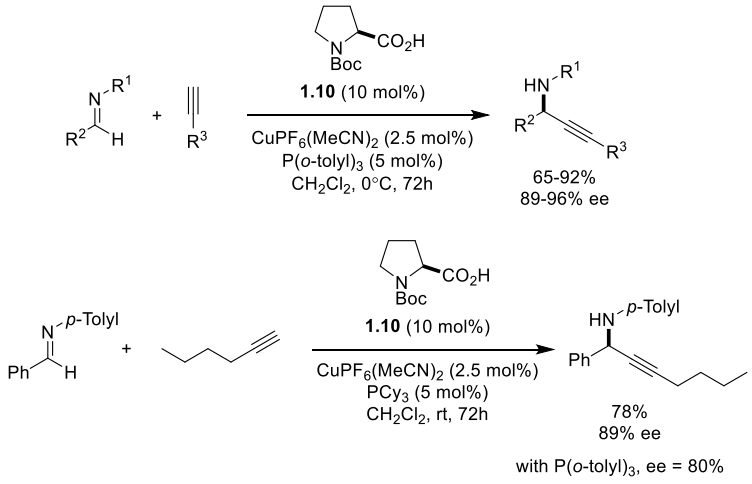
Rueping reported the enantioselective alkynylation reactions of α-imino esters with dual catalytic system of AgOAc and chiral phosphoric acid 1.8 (Scheme 1.11).[37] Best enantioselectivities were observed when α-imino methyl esters and *para*-methoxyphenylimino groups were implemented. Various substituents on the aryl alkyne are well tolerated with good to excellent yields and ee's. Although the initially proposed working hypothesis involves the direct protonation of imine substrate by the chiral phosphoric acid, it's unclear if an initial anion exchange between AgOAc and the phosphoric acid is involved.

Arndtsen elegantly exemplified the easy tunability of cooperative catalysis between amino acid derivative **1.10** and transition metal catalyst with the highly enantioselective alkynylation reactions of imines (Scheme 1.12).[38] The reaction features a system of readily available catalytic components. Various aromatic and aliphatic variants on all three groups (R_1, R_2 and R_3) can be tolerated with satisfactory results. The high modularity of this process also allows for easy adjustment of the reaction conditions aiming for different substrates. For example, switching to a readily available PCy_3 ligand increases the ee of the challenging substrate 1-hexyne to 89%.

Scheme 1.11 Enantioselective alkynylation reactions of α-imino esters via dual catalysis.

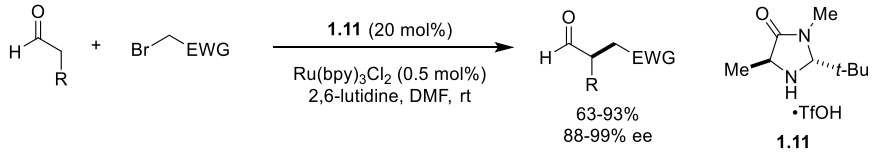


Scheme 1.12 Enantioselective alkynylation reactions of imines with *N*-Boc proline and Cu.



The groundbreaking merger of photoredox catalysis and organocatalysis reported by Nicewicz and MacMillan resulted in the highly enantioselective intermolecular α-alkylation reactions of aldehydes (Scheme 1.13).[39] The enamine species, generated from the organocatalytic cycle, reacts smoothly with the electron-deficient radical species. The latter is presumably generated from reductive cleavage of the carbon–halogen bond enabled by photoredox catalysis. Following this seminal work, photoredox chemistry soon became a vibrant area in synthetic organic chemistry and has been successfully applied cooperatively with various organocatalysts.[40]

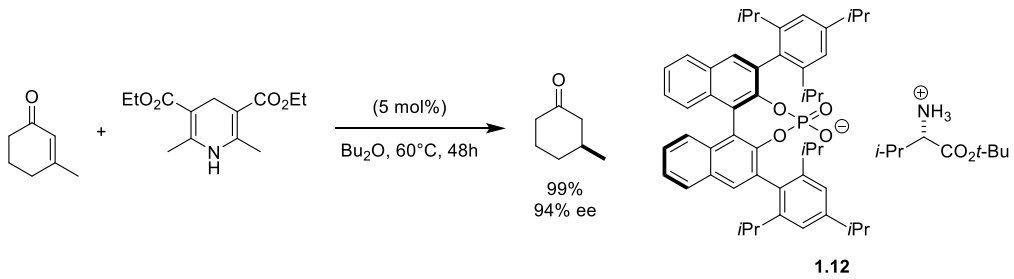
Scheme 1.13 Enantioselective α-alkylation of aldehydes.



1.2.2 Cooperative Multiple Catalysis with Organocatalysts

Similar to the cooperative multiple catalysis combining transition metals and organocatalysts, different types of organocatalysts featuring different activation modes are often required to work in concert to realize chemical transformations that are impossible with either one alone.[9] On the other hand, it is common for an organocatalyst to interact with molecules, intermediates and transition states via multiple interacting sites that are covalently linked within the catalyst.[5,22,41] Although many of such multifunctional catalysts have been developed, it would be highly desirable if the requisite functionalities are incorporated in multiple readily available compounds that can work in concert without being chemically integrated beforehand.[42] Moreover, covalently linking two discrete organocatalysts can jeopardize their structure integrity necessary for efficient catalysis, thus requiring a labor-intensive trial-and-error process.

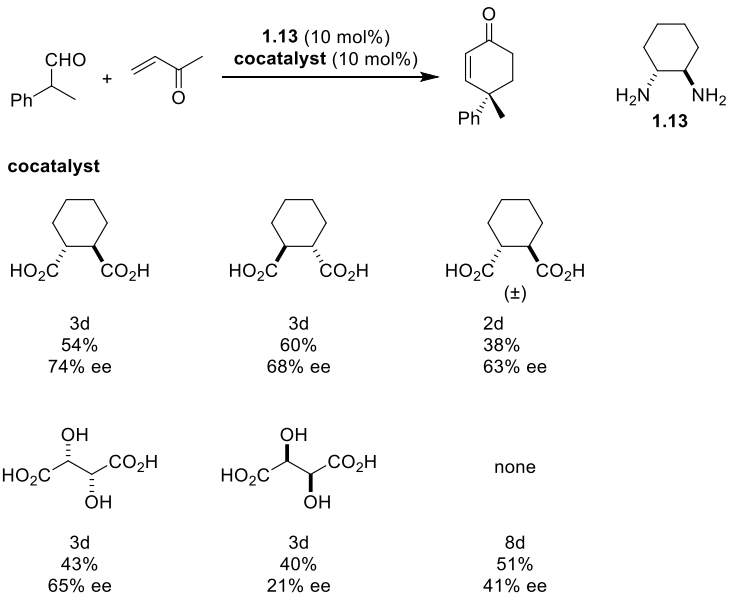
Scheme 1.14 Enantioselective hydrogenation of α,β-unsaturated ketones.



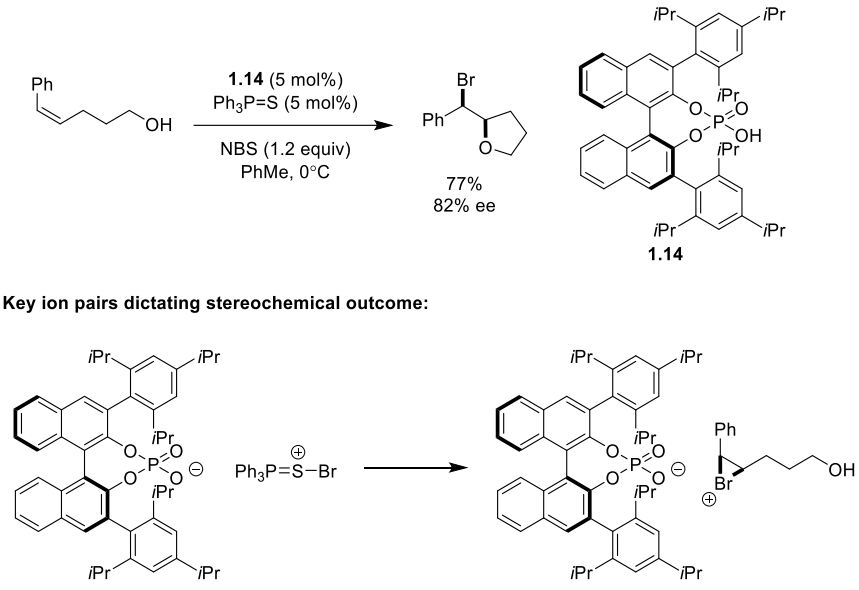
An important example of cooperative catalysis using two organocatalysts was demonstrated by List in the enantioselective hydrogenation of α,β-unsaturated ketones (Scheme 1.14).[43] Previously established chiral acid or aminocatalysis approach alone is ineffective towards this transformation in a highly enantioselective fashion. But the combination of the two, a readily available Valine derivative and a commonly used chiral phosphoric acid affords the hydrogenated α,β-unsaturated ketones in satisfactory results. The reaction efficiency is vastly attenuated in the absence of either catalyst, and a strong match/mismatch behavior was observed. Although the catalyst is premade from two, the simple acid/base chemistry used is at a different level compared to the synthesis of new catalysts via covalent chemistry.

Kotsuki reported the enantioselective construction of quaternary carbon stereogenic centers via Robinson-type annulation reactions (Scheme 1.15).[44] The method features an enamine-iminium dual activation mode using a chiral primary diamine catalyst. The reaction outcome is highly dependent on the structure of the carboxylic acid cocatalysts. Match/mismatch effects were observed with cyclohexane dicarboxylic acids and tartaric acids, thus stressing the judicious choice of both catalytic components towards an efficient process.

Scheme 1.15 Enantioselective Robinson-type annulation.



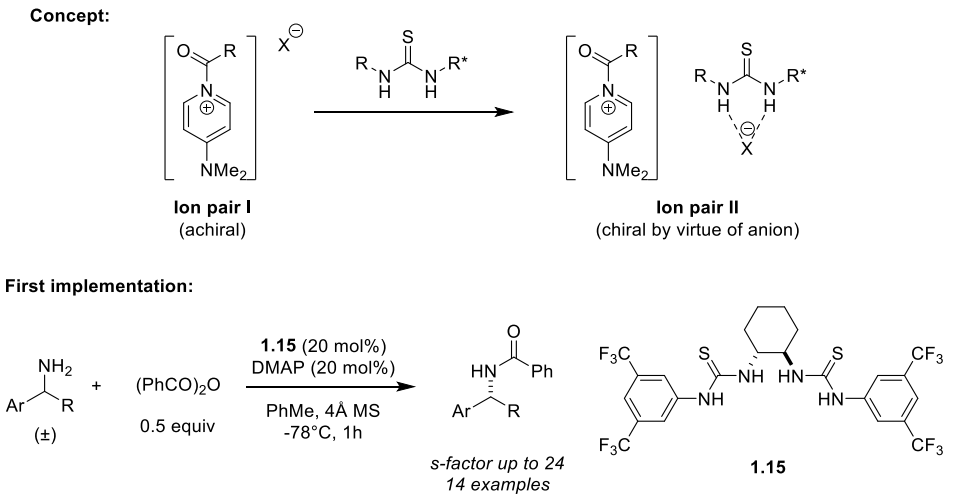
Scheme 1.16 Lewis base catalyzed bromocycloetherification assisted by chiral Brønsted acid.



Denmark reported a dual catalytic approach towards the enantioselective bromocycloetherification of 5-arylpentenols (Scheme 1.16).[45] The reaction works presumably via achiral Lewis base activation of a bromonium ion assisted by a chiral phosphoric acid **1.14**. The ion pairs between the bromonium cationic complexes along the

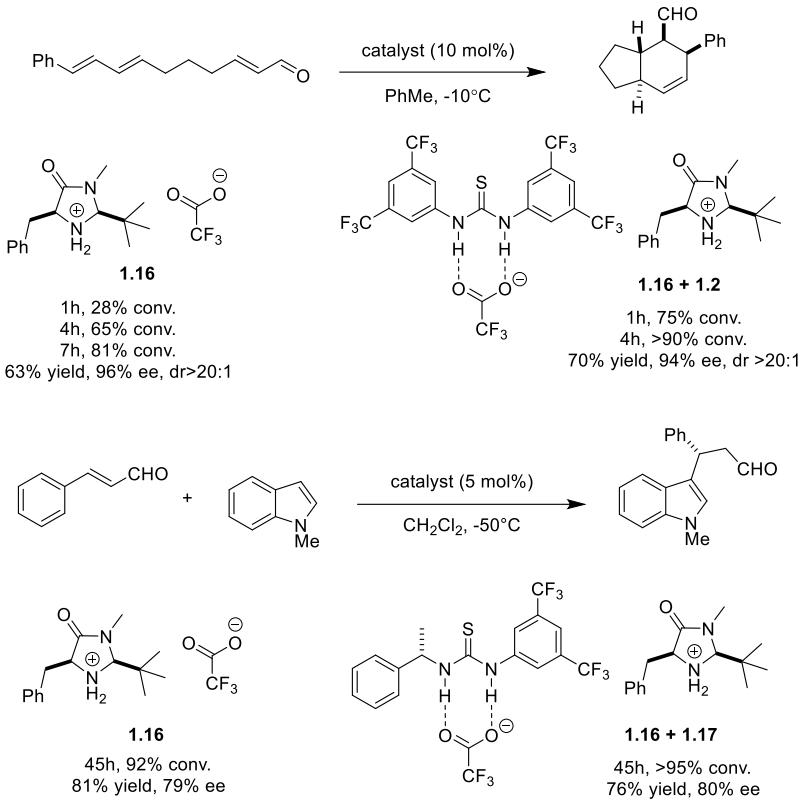
mechanistic pathway and the conjugate base of chiral Brønsted acid are responsible for the stereochemical outcome of the reaction. On the other hand, efforts in using a chiral Lewis base towards this transformation were not successful.

Scheme 1.17 Merging nucleophilic and hydrogen bonding.



In 2009, our group developed a cooperative dual catalysis concept merging nucleophilic catalysis and anion recognition (Scheme 1.17).[46] Specifically, an achiral ion pair I is generated from simple nucleophilic catalyst DMAP and an acylating reagent. Upon anion binding to a chiral receptor, ion pair II is rendered chiral with enhanced electrophilicity and solubility. This concept was first applied to the kinetic resolution of benzylic amines. The versatility of this concept is underscored in subsequent work in the kinetic resolution of propargylic amines,[47] allylic amines,[48] racemic diamines,[49] and desymmetrization of *meso*-diamines.[50] Other types of acyl transfer reactions such as the Steglich reaction and the addition of *O*-acylated azlactones to isoquinolines are also catalyzed enantioselectively with this approach.[51]

Scheme 1.18 Thiourea assisted iminium catalysis.

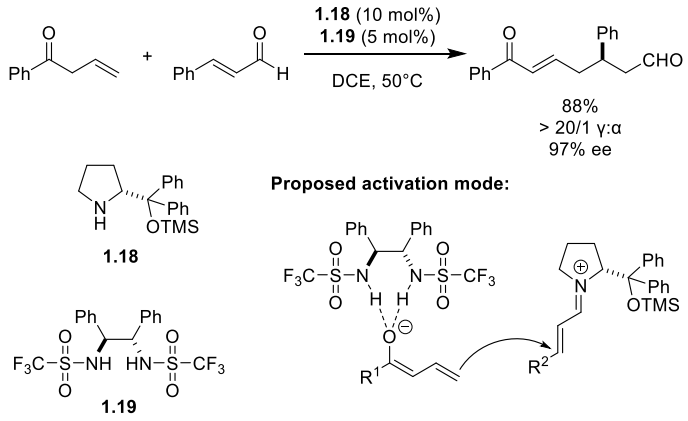


Using a similar approach, Xu reported the thiourea assisted iminium catalysis of widely used diphenylprolinol trimethylsilyl ether and imidazolinone catalysts.[52] NMR and ESI-MS studies suggest the propensity of iminium ion formation is sharply increased in the presence of thiourea anion-binding catalysts. This idea is corroborated in the intramolecular Diels–Alder reactions and the Friedel–Crafts alkylation reactions where a drastic acceleration effect is observed in both reactions with various thiourea catalysts (Scheme 1.18).

Subsequently, the same group extended this strategy to the enantioselective direct vinylogous Michael addition reactions (Scheme 1.19).[53] While the iminium catalyst **1.18** alone can provide high enantioselectivity, satisfactory yield and regioselectivity calls for the combination with an anion-binding catalyst **1.19**. A match/mismatch effect was also observed as the use enantiomer of iminium catalyst resulted in dramatic loss of reactivity.

The anion-binding catalyst **1.19** is proposed to both promote iminium ion formation and stabilize the nucleophilic dienoxide intermediate. Upon association with the dienoxide nucleophile, the anion-binding catalyst presumably serves to block the α position so as to ensure a high regioselectivity favoring the γ attack.

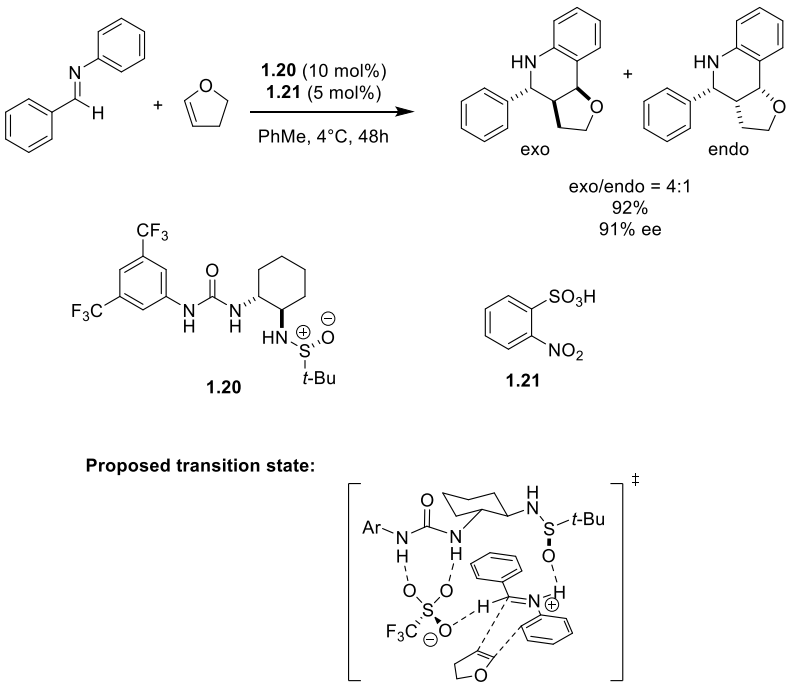
Scheme 1.19 Enantioselective direct vinylogous Michael addition via thiourea assisted iminium catalysis.



Chiral Brønsted acid catalysts have been largely explored by variation of the conjugate base structures, among which chiral phosphoric acid analogs have been most popular and realized a wide variety of asymmetric transformations with high efficiency. On the other hand, chiral Brønsted acid catalysis has also been explored via "medium effects",[54] which was exemplified by Jacobsen using achiral Brønsted acids in combination with chiral anion-binding catalysts.[22] When the achiral Brønsted acids are used in catalytic amounts, this strategy can be regarded as cooperative catalysis. Jacobsen demonstrated highly enantioselective Povarov reactions using cooperative catalysis between a strong Brønsted acid **1.21** and a chiral urea catalyst **1.20** (Scheme 1.20).[54] Mechanistic studies show that the strong Brønsted acid **1.21** protonates the imine starting material quantitatively to form the resting state as a sparingly soluble salt in nonpolar organic solvents. Upon interaction with a

simple urea catalyst, both solubility and charge separation are enhanced for the salt complex. However, when the optimized sulfinamidourea catalyst **1.21** was used, although improved solubility was observed, the iminium formyl proton shows a down-field shift corresponding to a tighter association through hydrogen bonding. Kinetic studies indicate that the sulfonamidourea catalyzed enantioselective reaction is considerably slower than both the reaction catalyzed by simple achiral urea and the background reaction. Computational analyses depict the transition state structure for the cycloaddition step as shown in Scheme 1.20, where multiple noncovalent interactions together account for the high enantioselectivity.

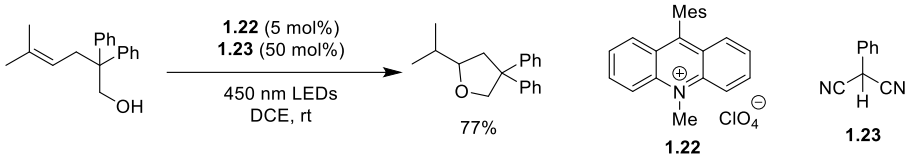
Scheme 1.20 Cooperative catalysis with Strong Brønsted acid and chiral urea.



Cooperative catalysis has also been applied with organic photoredox catalysis. Nicewicz reported direct anti-Markovnikov hydroetherification reactions of alkenols (Scheme 1.21).[55] While 9-mesityl-10-methylacridinium perchlorate **1.22** was identified as an optimal organic photoredox catalyst affording high conversion, the yield of the desired product is only 36% with many unidentified side products. Successfully identified the

problem to be a slow reduction of the radical species generated from the cyclization step, the authors discovered the use of a second catalyst as the hydrogen atom donor significantly increased the overall yield. Although the H-donor catalyst **1.23** is used at a relatively high loading (50 mol %), the dual catalytic concept has been further extended to many other transformations with lower loadings of this component.[56]

Scheme 1.21 Cooperative catalysis with organic photoredox catalyst and H-atom donor.



1.3 Objectives

The elegant examples described above clearly suggest the advantage and versatility of cooperative catalysis. Given the presence of numerous activation modes enabled by enormous catalysts developed so far, it is highly desirable to combine catalysts of different types cooperatively towards challenging synthetic problems that are yet to be addressed.

As a continuing interest of our group in thiourea catalysis, this dissertation aims to develop its combination with catalysts capable of other activation modes towards novel chemical transformations. Chapter II will demonstrate the application of a bifunctional thiourea catalyst in combination with an amine catalyst for the generation and stereochemical control of elusive oxocarbenium ions under mild conditions. This methodology allows for the first highly enantioselective oxa-Pictet–Spengler reactions. Chapter III will describe the combination of an acid-thiourea catalyst and a transition metal for the enantioselective A^3 reactions with secondary amines. Chapter IV will cover the activation of strong Brønsted acids via anion binding of thiourea catalysts, which allows for a direct reductive etherification process that accommodates a wide range of substrates.

References

(1) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004,** *43,* 5138.
(2) MacMillan, D. W. C. *Nature* **2008,** *455,* 304.
(3) Erkkilä, A.; Majander, I.; Pihko, P. M. *Chem. Rev.* **2007,** *107,* 5416.
(4) Akiyama, T.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2006,** *348,* 99.
(5) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007,** *107,* 5713.
(6) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007,** *107,* 5471.
(7) Ooi, T.; Maruoka, K. *Angew. Chem., Int. Ed.* **2007,** *46,* 4222.
(8) Denmark, S. E.; Beutner, G. L. *Angew. Chem., Int. Ed.* **2008,** *47,* 1560.
(9) Allen, A. E.; MacMillan, D. W. C. *Chem. Sci.* **2012,** *3,* 633.
(10) Curran, D. P.; Kuo, L. H. *J. Org. Chem.* **1994,** *59,* 3259.
(11) Curran, D. P.; Kuo, L. H. *Tetrahedron Lett.* **1995,** *36,* 6647.
(12) Schreiner, P. R.; Wittkopp, A. *Org. Lett.* **2002,** *4,* 217.
(13) Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998,** *120,* 4901.
(14) Zuend, S. J.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2009,** *131,* 15358.
(15) Sohtome, Y.; Tanatani, A.; Hashimoto, Y.; Nagasawa, K. *Tetrahedron Lett.* **2004,** *45,* 5589.
(16) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003,** *125,* 12672.
(17) Kotke, M.; Schreiner, P. R. *Tetrahedron* **2006,** *62,* 434.
(18) Raheem, I. T.; Thiara, P. S.; Peterson, E. A.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2007,** *129,* 13404.
(19) Lippert, K. M.; Hof, K.; Gerbig, D.; Ley, D.; Hausmann, H.; Guenther, S.; Schreiner, P. R. *Eur. J. Org. Chem.* **2012,** 5919.
(20) Nagorny, P.; Sun, Z. *Beilstein J. Org. Chem.* **2016,** *12,* 2834.
(21) Beckendorf, S.; Asmus, S.; Mück-Lichtenfeld, C.; Mancheño, O. G. *Chem.–Eur. J.* **2013,** *19,* 1581.
(22) Brak, K.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2013,** *52,* 534.
(23) Min, C.; Mittal, N.; Sun, D. X.; Seidel, D. *Angew. Chem., Int. Ed.* **2013,** *52,* 14084.
(24) Ganesh, M.; Seidel, D. *J. Am. Chem. Soc.* **2008,** *130,* 16464.
(25) Zhao, Q.; Li, S.; Huang, K.; Wang, R.; Zhang, X. *Org. Lett.* **2013,** *15,* 4014.
(26) Luan, Y.; Zheng, N.; Qi, Y.; Tang, J.; Wang, G. *Catal. Sci. Technol.* **2014,** *4,* 925.
(27) Paull, D. H.; Abraham, C. J.; Scerba, M. T.; AldenDanforth, E.; Lectka, T. *Acc. Chem. Res.* **2008,** *41,* 655.
(28) Rueping, M.; Koenigs, R. M.; Atodiresei, I. *Chem.—Eur. J.* **2010,** *16,* 9350.
(29) Piovesana, S.; Scarpino Schietroma, D. M.; Bella, M. *Angew. Chem., Int. Ed.* **2011,** *50,* 6216.
(30) Lv, F.; Liu, S.; Hu, W. *Asian J. Org. Chem.* **2013,** *2,* 824.
(31) Chen, D.; Han, Z.; Zhou, X.; Gong, L. *Acc. Chem. Res.* **2014,** *47,* 2365.
(32) Lang, X.; Zhao, J.; Chen, X. *Chem. Soc. Rev.* **2016,** *45,* 3026.
(33) Chen, G.; Deng, Y.; Gong, L.; Mi, A.; Cui, X.; Jiang, Y.; Choi, M. C. K.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2001,** *12,* 1567.
(34) Nakoji, M.; Kanayama, T.; Okino, T.; Takemoto, Y. *Org. Lett.* **2001,** *3,* 3329.
(35) Hu, W.; Xu, X.; Zhou, J.; Liu, W.-J.; Huang, H.; Hu, J.; Yang, L.; Gong, L.-Z. *J. Am. Chem. Soc.* **2008,** *130,* 7782.
(36) Jiang, G.; List, B. *Angew. Chem., Int. Ed.* **2011,** *50,* 9471.
(37) Rueping, M.; Antonchick, A. P.; Brinkmann, C. *Angew. Chem., Int. Ed.* **2007,** *46,* 6903.
(38) Lu, Y.; Johnstone, T. C.; Arndtsen, B. A. *J. Am. Chem. Soc.* **2009,** *131,* 11284.
(39) Nicewicz, D. A.; MacMillan, D. W. C. *Science* **2008,** *322,* 77.
(40) Shaw, M. H.; Twilton, J.; MacMillan, D. W. C. *J. Org. Chem.* **2016,** *81,* 6898.

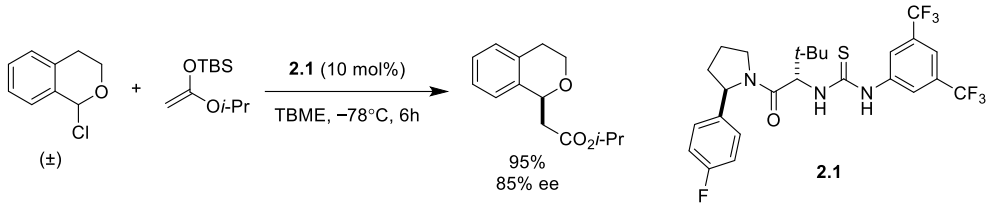
(41) Briere, J.-F.; Oudeyer, S.; Dalla, V.; Levacher, V. *Chem. Soc. Rev.* **2012,** *41,* 1696.
(42) Piovesana, S.; Scarpino Schietroma, D. M.; Bella, M. *Angew. Chem., Int. Ed.* **2011,** *50,* 6216.
(43) Martin, N. J. A.; List, B. *J. Am. Chem. Soc.* **2006,** *128,* 13368.
(44) Inokoishi, Y.; Sasakura, N.; Nakano, K.; Ichikawa, Y.; Kotsuki, H. *Org. Lett.* **2010,** *12,* 1616.
(45) Denmark, S. E.; Burke, M. T. *Org. Lett.* **2012,** *14,* 256.
(46) De, C. K.; Klauber, E. G.; Seidel, D. *J. Am. Chem. Soc.* **2009,** *131,* 17060.
(47) Klauber, E. G.; De, C. K.; Shah, T. K.; Seidel, D. *J. Am. Chem. Soc.* **2010,** *132,* 13624.
(48) Klauber, E. G.; Mittal, N.; Shah, T. K.; Seidel, D. *Org. Lett.* **2011,** *13,* 2464.
(49) Min, C.; Mittal, N.; De, C. K.; Seidel, D. *Chem. Commun.* **2012,** *48,* 10853.
(50) De, C. K.; Seidel, D. *J. Am. Chem. Soc.* **2011,** *133,* 14538.
(51) De, C. K.; Mittal, N.; Seidel, D. *J. Am. Chem. Soc.* **2011,** *133,* 16802.
(52) Wang, Y.; Yu, T.-Y.; Zhang, H.-B.; Luo, Y.-C.; Xu, P.-F. *Angew. Chem., Int. Ed.* **2012,** *51,* 12339.
(53) Gu, Y.; Wang, Y.; Yu, T.-Y.; Liang, Y.-M.; Xu, P.-F. *Angew. Chem., Int. Ed.* **2014,** *53,* 14128.
(54) Xu, H.; Zuend, S. J.; Woll, M. G.; Tao, Y.; Jacobsen, E. N. *Science* **2010,** *327,* 986.
(55) Hamilton, D. S.; Nicewicz, D. A. *J. Am. Chem. Soc.* **2012,** *134,* 18577.
(56) Margrey, K. A.; Nicewicz, K. A. *Acc. Chem. Res.* **2016,** *49,* 199.

Chapter II Cooperative Dual Catalysis Enables Direct Formation of Oxocarbenium Ions

2.1 Background

Oxocarbenium ions are key intermediates in a range of synthetically important transformations. Because of their generally high reactivities and lack of basic sites suitable for interaction with chiral Lewis acids or hydrogen bond donors, the development of catalytic enantioselective methods involving oxocarbenium intermediates poses significant challenges. Nevertheless, a number of creative approaches have been reported, the majority of which rely on the formation of oxocarbenium ions from acetals[1–18] or enol ethers.[19–24] Oxidative methods are also known.[25,26] Most catalytic enantioselective transformations reported to date feature cyclic and relatively stable (iso)pyrylium or (iso)chroman-type oxocarbenium ions. Jacobsen reported the catalytic enantioselective addition of silyl ketene acetals to isochroman derived oxocarbenium ions (Scheme 2.1).[4] The chloroisochroman starting material is prepared from the corresponding isochroman acetal and unreactive towards silyl ketene acetal in the absence of anion binding catalyst at –78 °C in TBME. However, the presence of an optimized thiourea organocatalyst **2.1** furnishes the reaction with high reactivity and selectivity, indicating a dynamic kinetic resolution process.

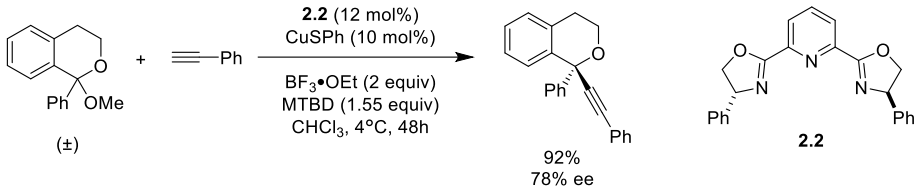
Scheme 2.1 Thiourea catalyzed enantioselective additions to oxocarbeniums.



Watson reported the enantioselective alkynylation reactions with isochroman ketals to afford tetrasusbstituted isochroman products in high yields and ee's (Scheme 2.2).[15] While

chloroform as solvent and BF_3 etherate as Lewis acid are important for high yields, the identification of pybox ligand **2.2** and CuSPh as the metal complex is crucial to differentiate the prochiral faces of a diaryl-substituted oxocarbenium ion to a satisfactory extent. The resulting alkynylated product can undergo various derivatization reactions with retention of the ee.

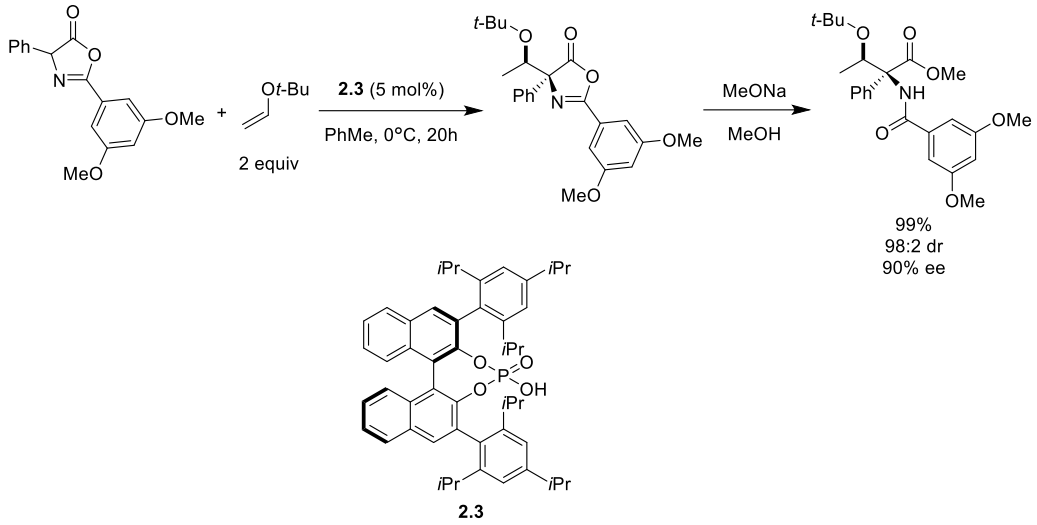
Scheme 2.2 Enantioselective alkynylation of oxocarbenium ions.



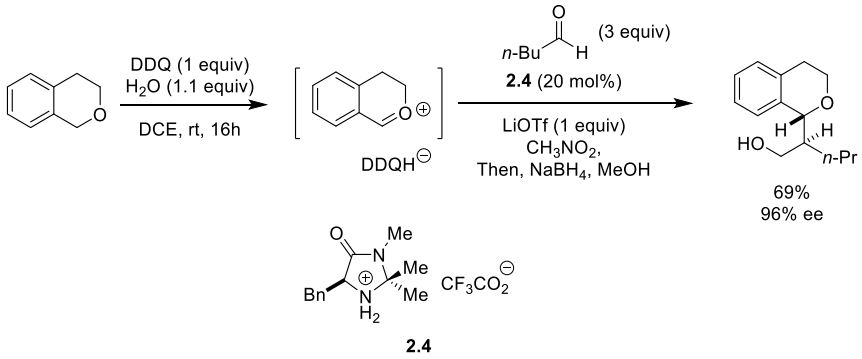
Using an alternative approach to generate oxocarbenium ions, Terada reported enantioselective Aldol-type additions of azlactones to vinyl ethers (Scheme 2.3).[20] The key oxocarbenium ion is generated via protonation of vinyl ether enabled by chiral phosphoric acid **2.3**. The anionic conjugate base presumably interacts with the oxocarbenium ion through multiple hydrogen bonding interactions to dictate the stereochemical outcome of the reaction.

Another method to generate oxocarbenium ions in the context of asymmetric catalysis is through oxidation. Liu reported the oxidative coupling between cyclic benzylethers with aliphatic aldehydes enabled by enamine catalysis (Scheme 2.4).[26] Mechanistic studies show that the incipient oxocarbenium ion is not electrophilic enough to be attacked by enamine, while the synergic use of H_2O and $LiClO_4$ presumably generates a counteranion with more delocalized negative charge, thus enhancing the electrophilicity of the oxocarbenium ion.

Scheme 2.3 Enantioselective Aldol-type additions of azlactones to vinyl ethers.



Scheme 2.4 Enantioselective oxidative coupling between isochroman and aliphatic aldehyde.

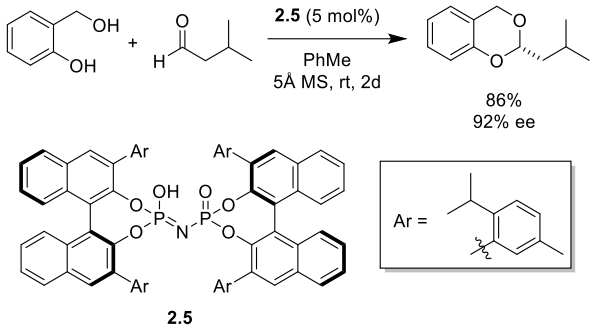


Direct condensation of an alcohol with an aldehyde has only rarely been applied in the context of asymmetric catalysis.[27–30] Although highly acidic chiral Brønsted acids are effective towards certain transformations, their syntheses are typically nontrivial. List reported the application of a highly confined chiral Brønsted acid to the long standing goal of direct asymmetric acetalization of aldehydes and alcohols (Scheme 2.5).[27] The *C*$_2$-symmetric imidophophoric acid **2.5** outperforms other classes of chiral phosphoric acids reported before and allows for a broad substrate scope encompassing both aliphatic and aromatic aldehydes.

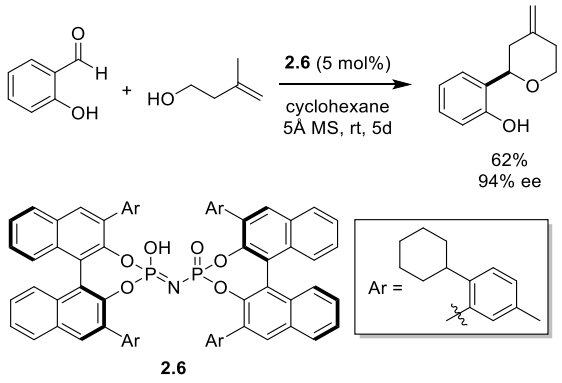
Control experiments using mixed acetals as starting materials indicate the condensation of the primary alcohol proceeds prior to the oxocarbenium formation and subsequent ring closure.

The highly confined chiral phosphoric acid has also been successfully applied in the asymmetric Prins cyclization using aldehydes and alcohols (Scheme 2.6).[30] The *ortho* hydroxyl group is indispensable for both high reactivity and enantioselectivity, presumably through hydrogen bonding interaction with the catalyst. Derivatization can also take advantage of the existing hydroxyl group as exemplified by triflation followed by detriflation and Suzuki coupling reactions.

Scheme 2.5 Enantioselective acetalization from aldehyde and alcohol.



Scheme 2.6 Aymmetric Prins cyclization from aldehyde and alcohol.

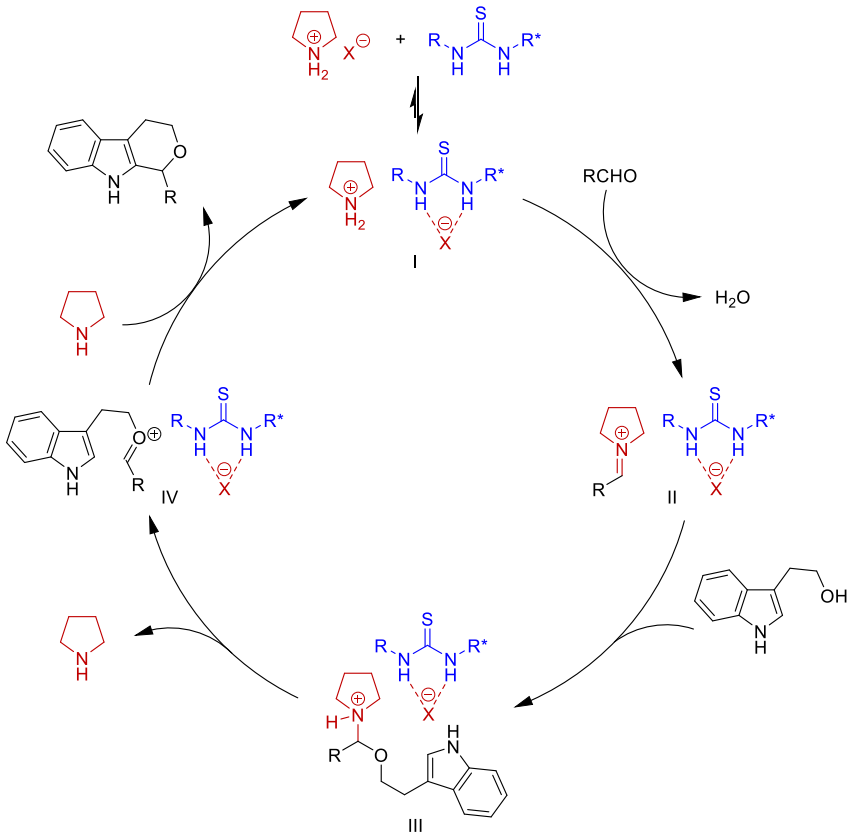


Despite the progress realized with chiral phosphoric acids, various reactions capable of providing valuable products via the intermediacy of oxocarbenium ions have not yet been

realized in catalytic enantioselective fashion. Therefore, novel activation methods towards this challenge is highly desired.

2.2 Concept

Figure 2.1 Proposed catalytic cycle.



We envisioned a new dual catalysis approach for the generation of oxocarbenium ions under weakly acidic conditions. Our strategy is outlined in Figure 2.1, using the oxa-Pictet–Spengler reaction as an example and a pyrrolidinium salt and a generic, chiral thiourea as model catalysts. With proper choice of X^- in an apolar solvent, the catalysts likely interact and exist predominantly as ion pair **I**. Condensation with an aldehyde results in the formation of iminium ion pair **II** which is subsequently attacked by an alcohol to generate *N*,*O*-acetal intermediate **III**. Elimination of the neutral amine catalyst furnishes

oxocarbenium intermediate **IV** which cyclizes to product. In this scenario, the enantiodetermining step is controlled entirely by the thiourea catalyst which acts as a chiral anion receptor.

The amine catalyst has to fulfill several crucial requirements. First, the amine must be sufficiently nucleophilic to generate the requisite iminium ion. Second, the iminium ion must possess the necessary electrophilicity to facilitate 1,2-attack by a weakly nucleophilic alcohol. Finally, the amine must be an excellent leaving group. Although common in achiral settings[31–33] and harking back to classic work by Knoevenagel,[34,35] examples of asymmetric iminium catalysis in which turnover of the catalyst is achieved by elimination are rare.[36–40] The anion binding catalyst, while primarily responsible for controlling the stereochemical outcome, is likely enhancing the electrophilicity of iminium ion **II**.[41] It may further increase the leaving group aptitude of the amine.

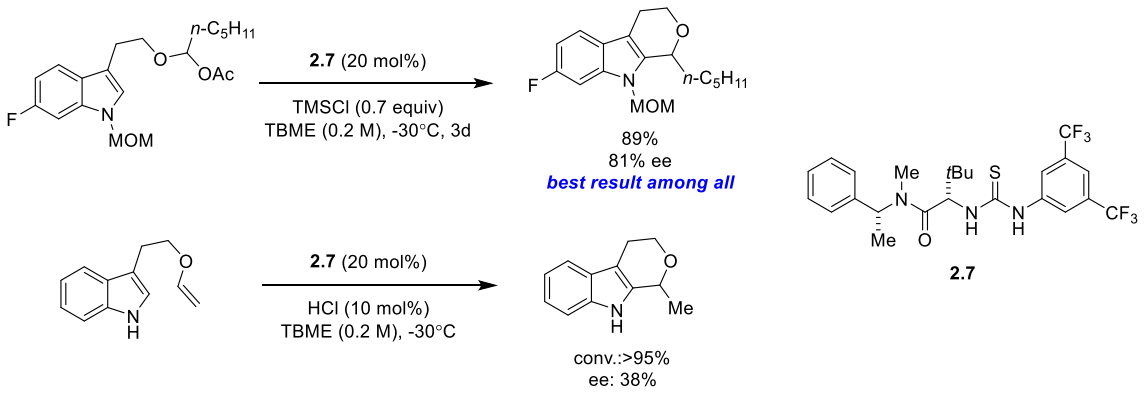
2.3 Catalytic Enantioselective Oxa-Pictet–Spenger Reactions

2.3.1 Background

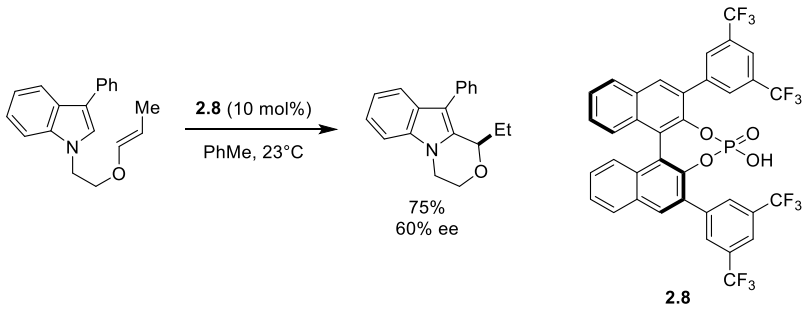
Progress in developing catalytic enantioselective oxa-Pictet–Spengler reactions has remained limited.[42–47] No highly enantioselective variants exist, and no direct approach from tryptophols and aldehydes has emerged. A thorough study on the enantioselective oxa-Pictet–Spengler reactions from the Jacobsen group reveals a system where a chiral thiourea catalyst **2.7** is used in combination with trimethylsilyl chloride (Scheme 2.7).[42] Meanwhile, the starting material requires a pre-installed acetoxy leaving group because the alternative direct approach using alcohols and aldehydes results in unsatisfactory enantioselectivities, presumably because the conditions required to generate oxocarbenium ions are incompatible with efficient stereochemical control. Evaluation of different protecting groups on the indole nitrogen reveals methoxymethyl acetal (MOM) to be optimal. The best result obtained

among various substrates is 89% yield with 81% ee. An alternative approach using enol ether as starting material in combination with hydrochloric acid proved to be highly reactive, albeit with moderate enantioselectivity.

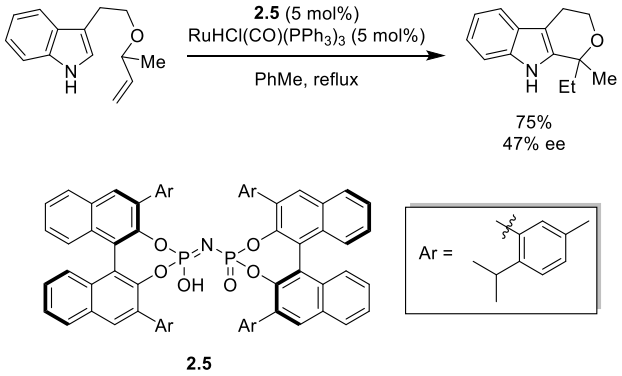
Scheme 2.7 Thiourea catalyzed enantioselective oxa-Pictet–Spengler reactions.



Scheme 2.8 Enantioselective oxa-Pictet–Spenger reaction by Scheidt.



Scheme 2.9 Enantioselective oxa-Pictet–Spenger reaction by Nielsen.

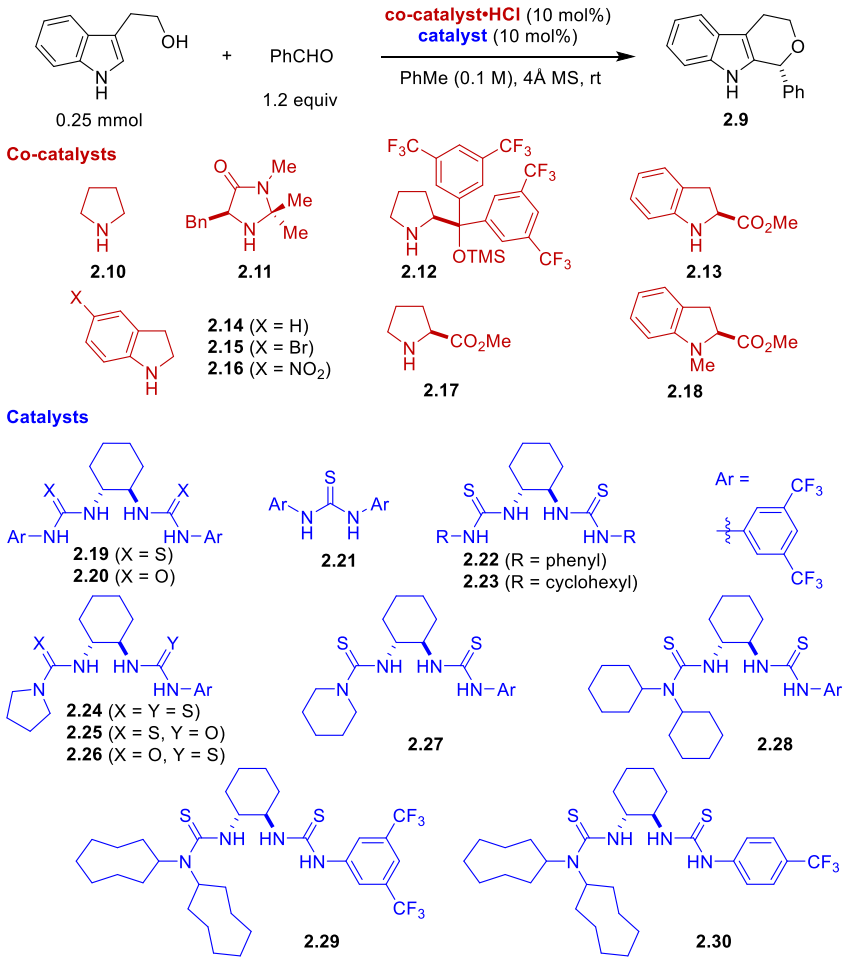


Subsequently, other sporadic attempts on the enantioselective oxa-Pictet–Spenger reactions also emerged, however, with unsatisfactory levels of enantioselectivity. For example, Scheidt reported the enantioselective oxa-Pictet–Spengler reactions with the enol ether substrate.[48] After an extensive screening of the reaction conditions, the highest ee obtained was 60% with a chiral phosphoric acid catalyst **2.8** (Scheme 2.8). Nielsen reported a highly similar isomerization/cyclization approach without isolating the enol ether intermediate, where the imidophosphoric acid **2.5** afforded the best ee of 47% (Scheme 2.9).[49]

2.3.2 Optimization

Tryptophol and benzaldehyde were selected as model substrates to test the proposed oxa-Pictet–Spengler reaction (Table 2.1). As expected, no reaction was observed in the absence of any additives. The Nagasawa catalyst **2.19**[50] was initially tested in combination with various amine HCl salts. No reaction was observed with **2.10**•HCl or widely used catalysts **2.11**•HCl[51] and **2.12**•HCl[52] (entries 2–4). The failure of **2.11** and **2.12** is not necessarily surprising, considering that they were specifically designed to minimize 1,2-addition. Remarkably, indoline-2-carboxylic acid ester **2.13**•HCl used in concert with **2.19** facilitated rapid formation of desired product **2.9** in excellent yield and notable ee (entry 5). Virtually identical results were obtained with the same catalyst prepared in situ (entry 6). A number of other amine HCl salts were tested but none provided further improvements (entries 7–11). Interestingly, (±)**2.13** provided results very similar to enantiopure **2.13** (entry 7). Achiral 5-nitroindoline (**2.16**) performed almost at the same level (entry 10). These results indicate that the amine catalyst is not involved in the enantiodetermining step of the reaction. Catalyst **2.18**, which is incapable of forming iminium ions, was tested to rule out

Table 2.1 Optimization of reaction conditions.



entry	co-catalyst •HCl	catalyst	time [h]	yield (%)	ee (%)
1	-	-	24	0	-
2[a]	**2.10**	**2.19**	24	0	-
3	**2.11**	**2.19**	24	trace	ND
4[a]	**2.12**	**2.19**	24	0	-
5	**2.13**	**2.19**	1	91	33
6[a]	**2.13**	**2.19**	1	90	33
7	**(±)2.13**	**2.19**	2	85	34
8[a]	**2.14**	**2.19**	24	0	-
9[a]	**2.15**	**2.19**	24	8	31
10[a]	**2.16**	**2.19**	1	82	26
11	**2.17**	**2.19**	24	trace	ND

12	**2.18**	**2.19**	48	13	29
13	**2.13**	**-**	24	14	0
14	**2.13**	**2.21**	1	88	0
15	**2.13**	**2.20**	3	39	–8
16	**2.13**	**2.22**	2	90	50
17	**2.13**	**2.23**	2	90	61
18	**2.13**	**2.24**	2	88	66
19	**2.13**	**2.25**	2	88	55
20	**2.13**	**2.26**	24	34	–24
21	**2.13**	**2.27**	2	90	66
22	**2.13**	**2.28**	2	91	70
23	**2.13**	**2.29**	2	88	75
24	**2.13**	**2.30**	2	90	79
25[b]	**2.13**	**2.30**	3	91	84
26[b,c]	**2.13**	**2.30**	48	90	91
27[b]	**-**[d]	**2.30**	24	64	81

[a] **co-catalyst•**HCl was prepared in situ from **co-catalyst** and HCl (4 M in dioxane). [b] Reaction was run at 0.05 M concentration. [c] Reaction was run at –30 °C. [d] 10 mol % of HCl (4 M in dioxane) was used as the cocatalyst.

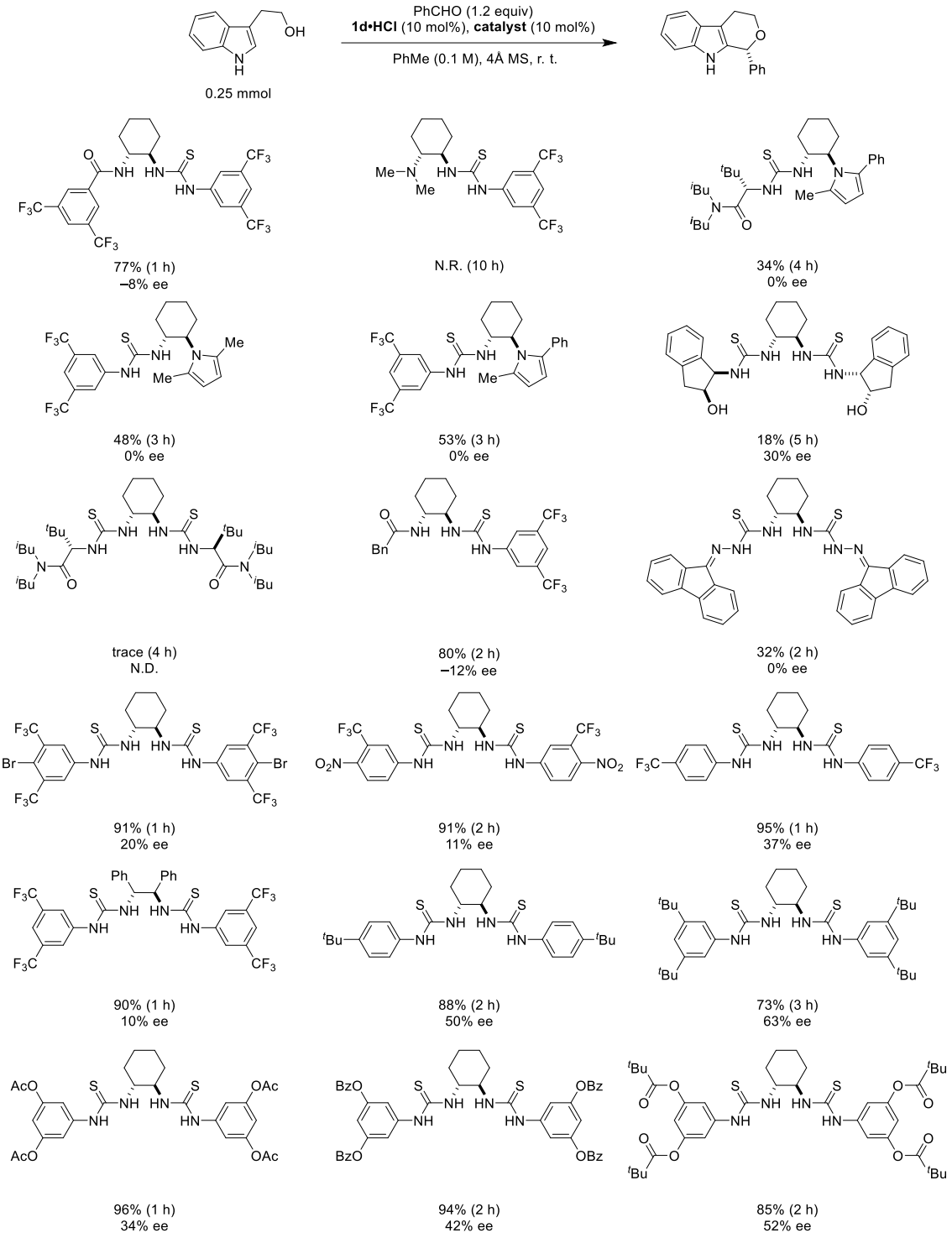
the possibility of the amine salt simply acting as a buffered source of HCl. Indeed, while a small amount of **2.9** was obtained in 29% ee, the reaction was extremely sluggish (entry 12). Use of **2.13•**HCl as the only catalyst resulted in an extremely slow reaction and racemic **2.9** (entry 13). A rapid, albeit racemic reaction, was observed in the presence of the achiral Schreiner catalyst **2.21** (entry 14).[53] Entries 1–14 clearly highlight the need for both, an electronically fine-tuned amine catalyst and a chiral anion receptor catalyst.

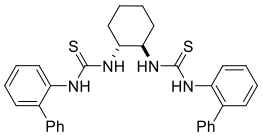
Consistent with the well-known tendency of ureas to be poorer anion receptors than the corresponding thioureas,[54,55] catalyst **2.20** provided a reduced reaction rate and low ee (entry 15). Surprisingly, **2.22** and **2.23**, both substantially more electron-rich than **2.19** and thus expected to be poorer anion receptors, provided significant improvements in ee (entries 16, 17). This might be rationalized with one thiourea acting as an anion receptor while the

other is engaged in interactions with the substrate. These considerations and results from a broad screen of other anion receptors (Scheme 2.8, 2.9) led us to the realization that the most efficient catalysts combine an electron-deficient with an electron-rich thiourea. The presence of two N–H protons on the electron-rich thiourea is not required as catalyst **2.24** afforded further improvements (entry 18). Replacement of either thiourea in **2.24** for a urea provided inferior results. However, while exchange of the electron-deficient thiourea (anion binding site) for a urea (catalyst **2.25**) only had a minor effect (entry 19), dramatic loss of reactivity and selectivity ensued when the electron-rich thiourea was replaced. Moreover, the sense of enantioinduction with **2.26** was opposite to that with **2.24** (entry 20). Increasing the size of the secondary amine component proved beneficial (entries 21–23) as did the exchange of the 3,5-bis-trifluoromethylphenyl group for 4-trifluoromethylphenyl (entry 24). Further increase in enantioselectivity was achieved at lower substrate concentration (entry 25). At –30 °C, **2.9** was obtained in 90% yield and 91% ee (entry 26). While **2.30** is capable of promoting the title reaction using only HCl as the cocatalyst, the reaction rate is dramatically reduced (entry 27). In addition, the formation of unidentified byproducts was noted.

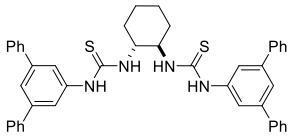
Further optimization of the catalyst structure (scheme 2.10) as well as acid source of the cocatalyst (scheme 2.11) was also performed, albeit with no improvement of the reaction efficiency.

Scheme 2.10 Evaluation of other anion binding catalysts.

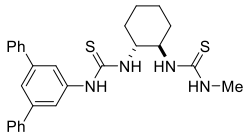




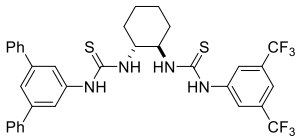
39% (5 h)
26% ee



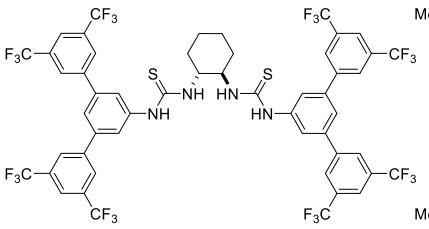
90% (3 h)
63% ee



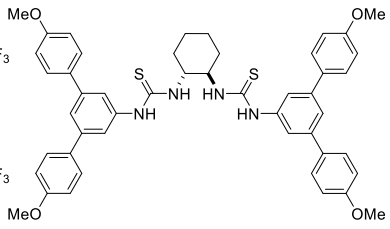
84% (2 h)
55% ee



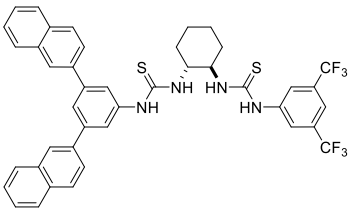
92% (1.5 h)
58% ee



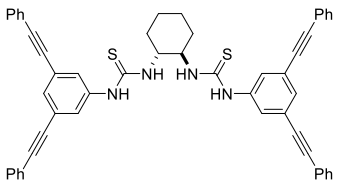
88% (1 h)
49% ee



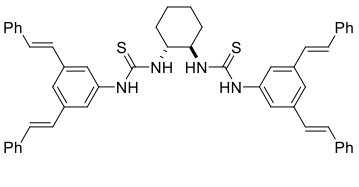
35% (5 h)
62% ee



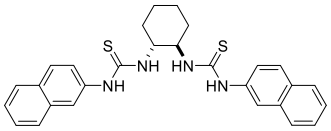
95% (1 h)
59% ee



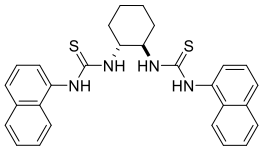
93% (3 h)
56% ee



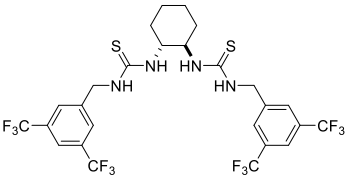
80% (2 h)
55% ee



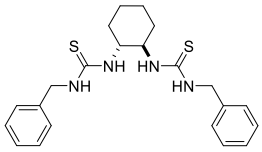
86% (2 h)
49% ee



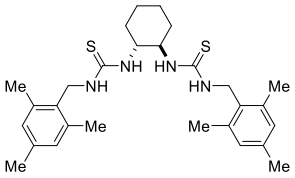
56% (3 h)
36% ee



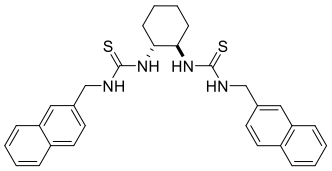
85% (1 h)
45% ee



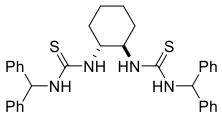
43% (4 h)
46% ee



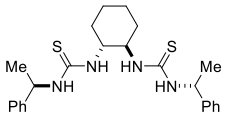
19% (3 h)
47% ee



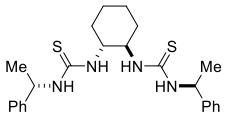
trace (10 h)
N.D.



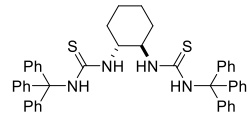
80% (2 h)
52% ee



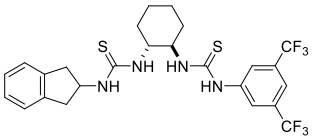
87% (2 h)
47% ee



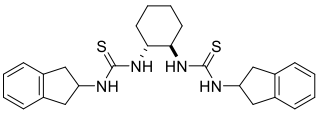
84% (2 h)
57% ee



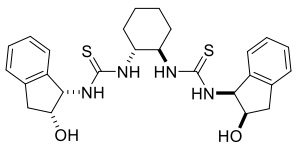
trace (4 h)
N.D.



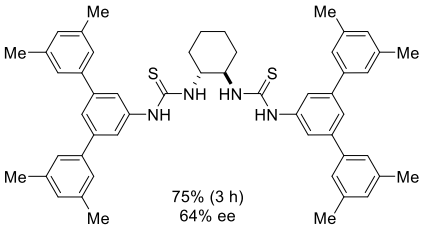
88% (3 h)
52% ee



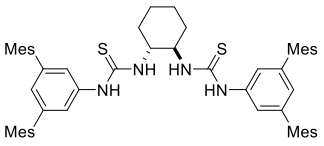
51% (24 h)
59% ee



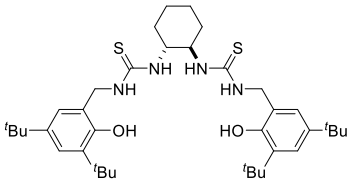
trace (3 h)
N.D.



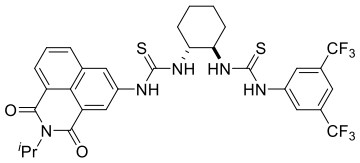
75% (3 h)
64% ee



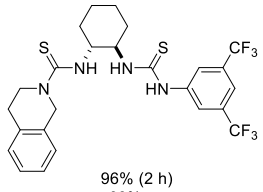
76% (3 h)
57% ee



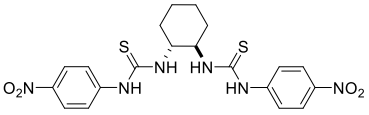
90% (4 h)
50% ee



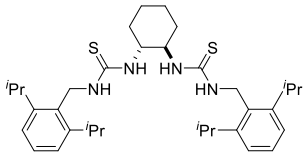
91% (3 h)
50% ee



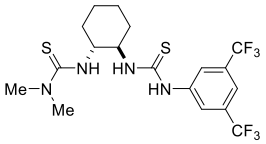
96% (2 h)
60% ee



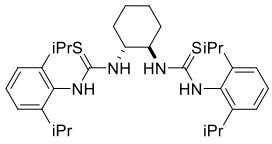
82% (3 h)
23% ee



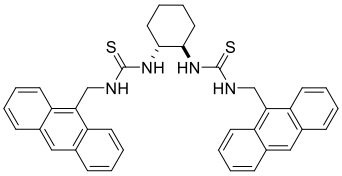
13% (3 h)
0% ee



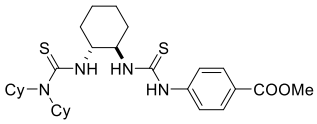
91%(2 h)
56% ee



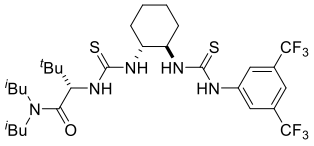
53% (4 h)
0% ee



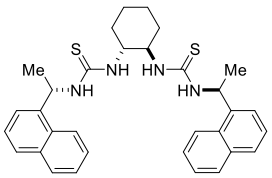
trace (10 h)
N.D.



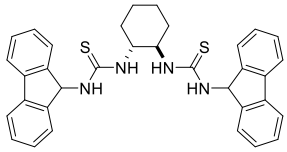
53% (12 h)
70% ee



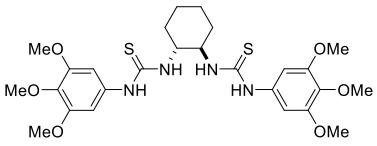
44% (12 h)
22% ee



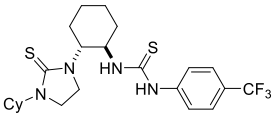
87% (2 h)
55% ee



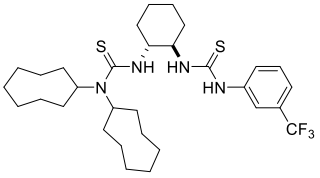
32% (4 h)
0% ee



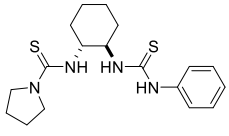
55% (4 h)
53% ee



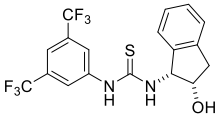
89% (2 h)
5% ee



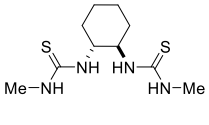
84% (2 h)
76% ee



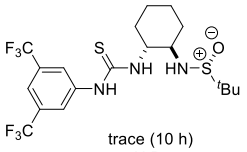
86% (2 h)
68% ee



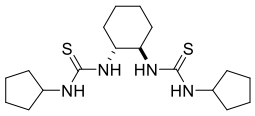
89% (3 h)
20% ee



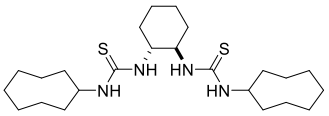
80% (2 h)
43% ee



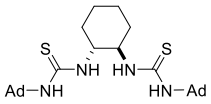
trace (10 h)
N.D.



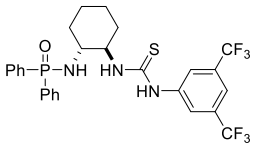
83% (4 h)
61% ee



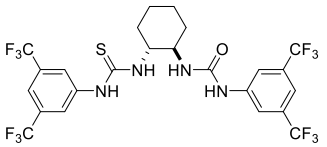
87% (4 h)
59% ee



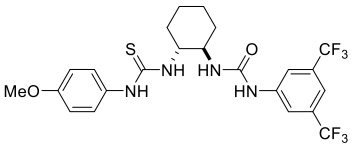
88% (4 h)
58% ee



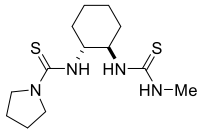
trace (10 h)
N.D.



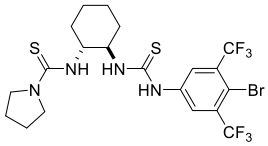
53% (4 h)
21% ee



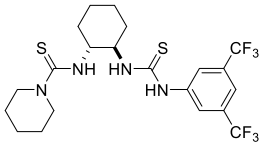
88% (3 h)
39% ee



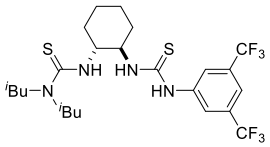
78% (4 h)
59% ee



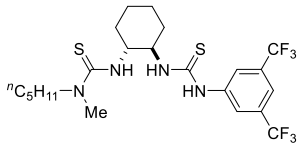
87% (2 h)
62% ee



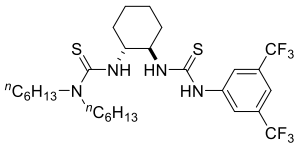
90% (2 h)
66% ee



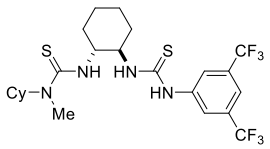
93% (2 h)
68% ee



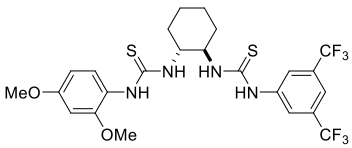
90% (2 h)
66% ee



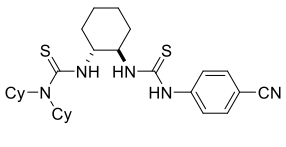
88% (2 h)
68% ee



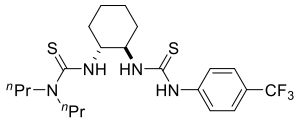
90% (2 h)
67% ee



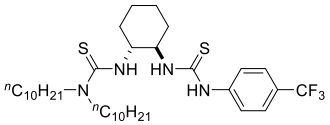
85% (3 h)
46% ee



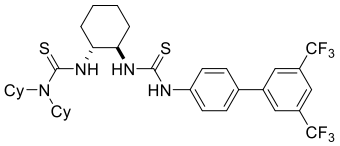
72% (13 h)
75% ee



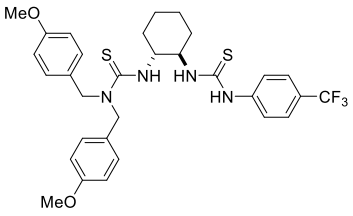
87% (2 h)
69% ee



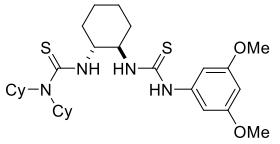
90% (2 h)
71% ee



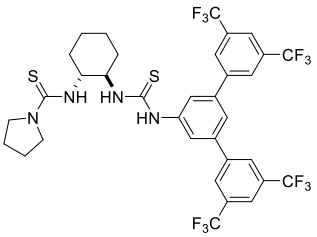
58% (8 h)
77% ee



42% (5 h)
62% ee

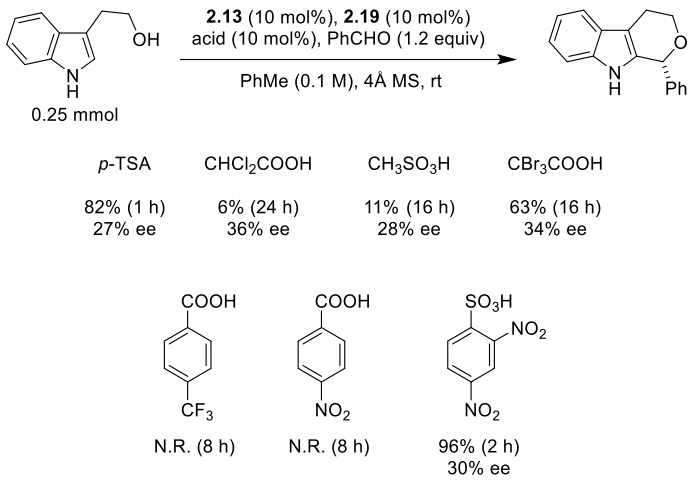


trace (6 h)
N.D.

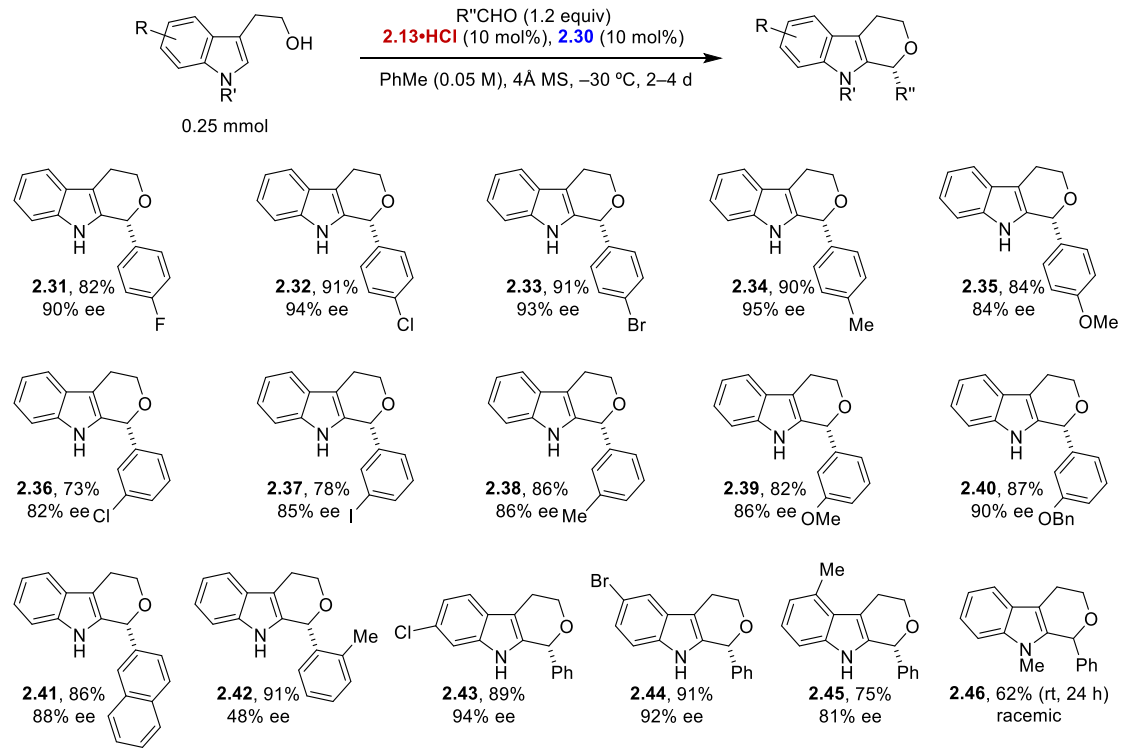


94% (2 h)
60% ee

Scheme 2.11 Evaluation of other amine salts.



Scheme 2.12 Substrate scope.



2.3.3 Substrate Scope

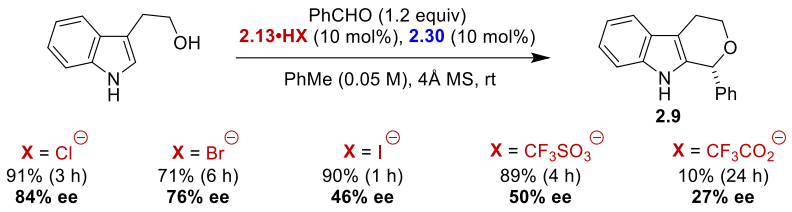
A range of aromatic aldehydes readily participated in oxa-Pictet–Spengler reactions (Scheme 2.12). Electronically diverse substituents were readily accommodated in the *para*-

and *meta*-positions. Introduction of an *ortho*-substituent led to a drop in enantioselectivity (product **2.42**). A number of substituted tryptophols also provided products in good yields and enantioselectivities. Interestingly, the presence of an indole *N*-H proton was found to be a strict requirement. Product **2.46**, derived from *N*-Me tryptophol, was formed more sluggishly and was obtained in racemic form.

2.3.4 Further Mechanistic Studies

To firmly establish the role of catalyst **2.30** as an anion receptor, a number amine salts were evaluated (Scheme 2.13). While chloride, bromide, iodide and triflate all provided reactive systems, chloride furnished the highest ee. On the other hand, iodide exhibited the fastest reaction rate. The use of trifluoroacetate dramatically retarded the reaction rate.

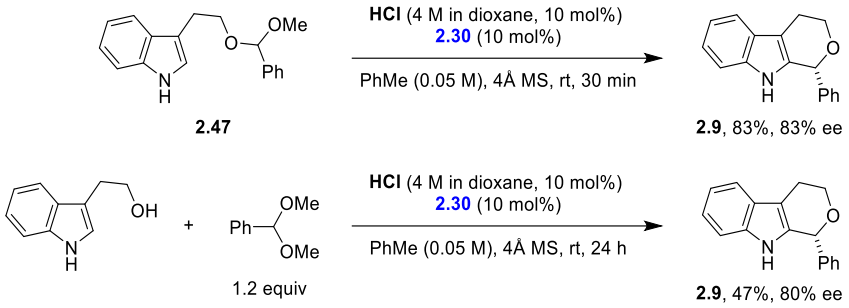
Scheme 2.13 Evidence for the intermediacy of oxocarbenium ions.



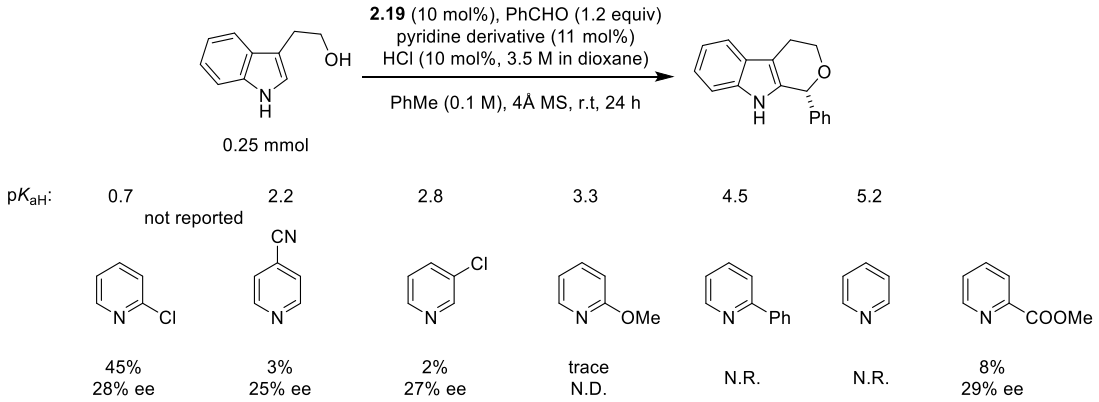
Experiments designed to provide evidence for the involvement of oxocarbenium ion intermediates are summarized in Scheme 2.14. Exposure of mixed acetal **2.47** to 10 mol % of each, HCl (added as a 4 M solution in dioxane) and catalyst **2.30**, provided product **2.9** in rapid fashion and nearly identical selectivity as observed before (cf. Table 2.1, entry 25). The same catalyst combination also facilitated the reaction between tryptophol and benzaldehyde dimethylacetal. In this instance, a reduction in reaction rate was noted and product **2.9** was recovered with slightly diminished ee.

The high levels of enantioselectivity observed for a range of substrates are consistent with the existence of a tight ion pair between the bisthiourea−anion complex and the oxocarbenium ion. Multiple non-covalent interactions likely exist between the ions. While the chloride anion is almost certainly engaged in hydrogen-bonding interactions with the electron-deficient thiourea, the electron-rich thiourea may be involved in interactions with the substrate. For instance, the thiourea sulfur atom could act as a hydrogen-bond acceptor, increasing the nucleophilicity of the indole moiety via a S···H−N interaction.

Scheme 2.14 Evidence for the intermediacy of oxocarbenium ions.



Scheme 2.15 Evaluation of pyridine derivatives as cocatalyst.

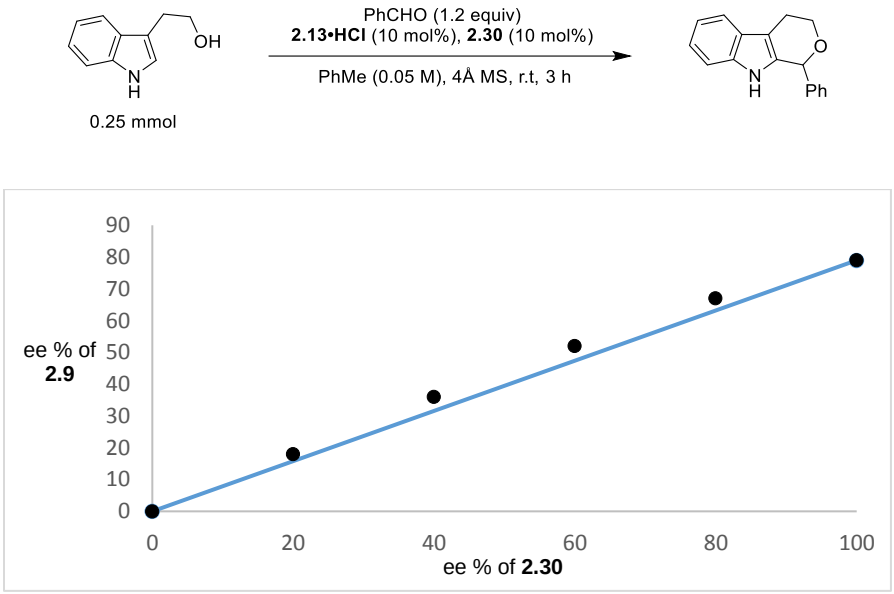


To further evaluate the possibility of the amine salt simply acting as a buffered source of HCl, we prepared pyridine derivatives with pK_{aH} ranging from 0.7 to 5.2, which indoline-2-carboxylic acid ester **2.13** most likely lies between (Scheme 2.15). None of these pyridine

derivatives demonstrates comparable reactivity compared to **2.13**, further corroborating the importance of the nucleophilicity of **2.13** in catalyzing the reaction.

To gain insight into potential aggregation behavior of the catalytic system, a non-linear effect study was performed. The reaction was set up using catalyst **2.30** with 0%, 20%, 40%, 60%, 80%, > 99% ee at room temperature, the results suggest the absence of a strong non-linear effect.

Figure 2.2 Non-linear effect study.

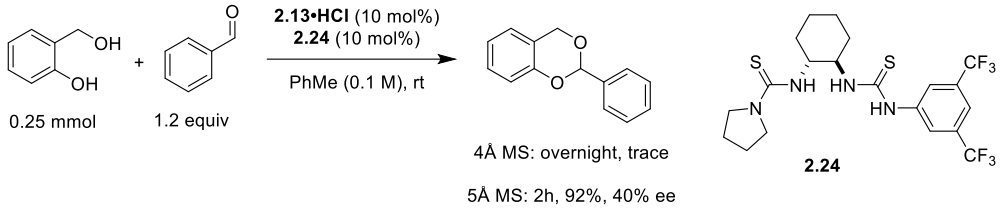


2.4 Catalytic Enantioselective Acetalization Reactions

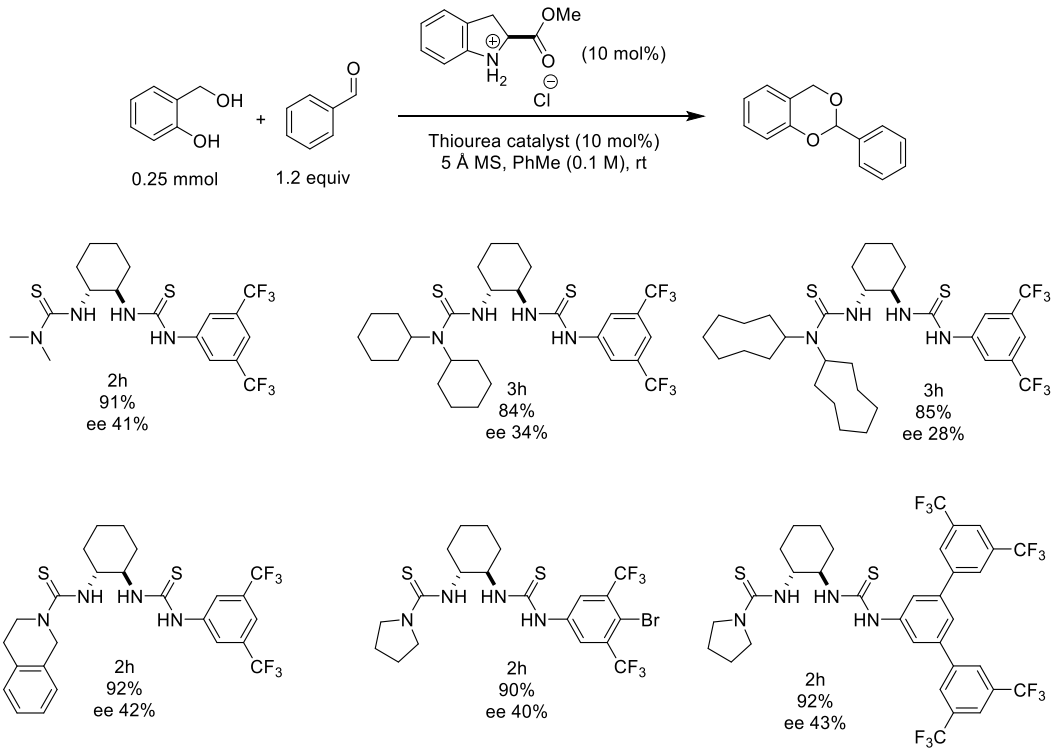
We wished to extend our methodology to other systems. Catalytic enantioselective acetalization reactions were previously realized by List using a chiral imidophophoric acid catalyst (Scheme 2.5).[30] Given the nontrivial synthesis as well as potentially high acidity of the catalyst, a complementary method, using readily available catalysts under weakly acidic conditions is highly desirable. We selected 2-hydroxybenzyl alcohol and benzaldehyde as reacting partners with a catalyst system that is highly reactive in the oxa-Pictet–Spengler

reactions, only trace amount of desired product was observed with mostly unreacted starting materials (Scheme 2.16). The poor reactivity can be partly attributed to the weak nucleophilicity of benzyl alcohol, as the ensued oxocarbenium ion is presumably highly reactive. Surprisingly, switching to 5 Å molecular sieves vastly increased the reaction rate, affording the desired product with 92% yield and 40% ee in 2 hours.

Scheme 2.16 Initial Evaluation of the Enantioselective Acetalization reaction.



Scheme 2.17 Evaluation of thiourea catalysts for the Enantioselective Acetalization reaction.

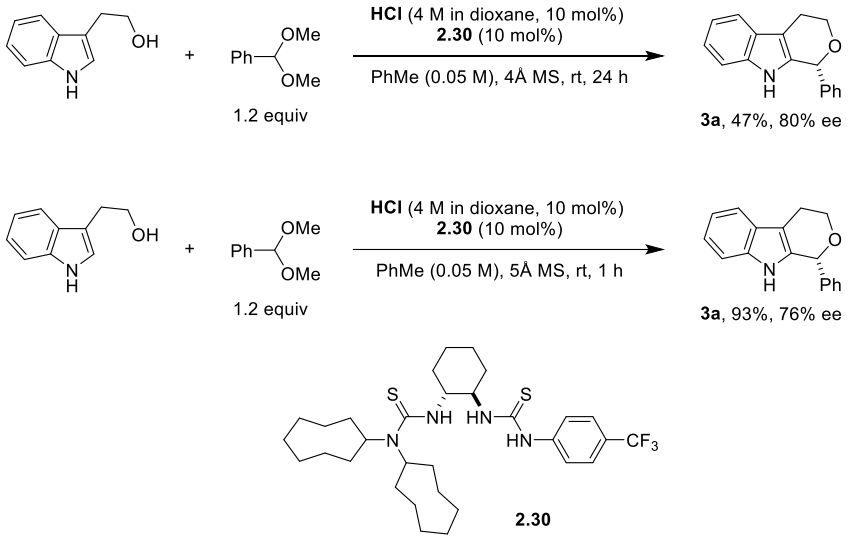


Evaluation of different thiourea catalysts was performed for the acetalization reaction (Scheme 2.17). The ring size of the electron rich thiourea has a different impact on ee

compared to the oxa-Pictet–Spengler reactions, as dicyclooctyl and dicyclohexyl thioureas are inferior to those of smaller size. On the other hand, variation on the electron poor thiourea has very minor influence on the ee. Satisfactory yields are observed for all cases in 2 to 3 hours. It seems a fundamental change in addressing the enantioselectivity issue is needed.

2.5 Related Systems Using Acetal/Ketal as Carbonyl Surrogate

Scheme 2.18 Effect of molecular sieves.

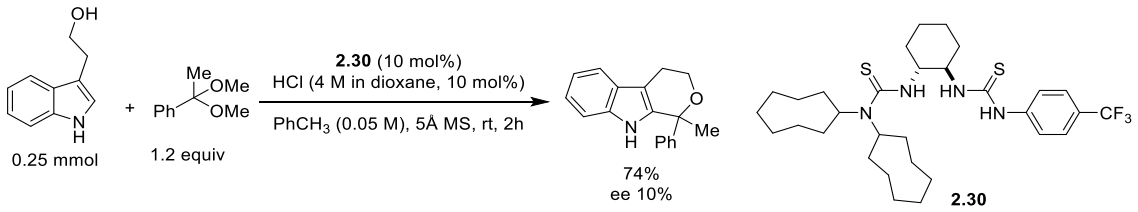


As described in the previous section, when benzaldehyde dimethyl acetal is used in the oxa-Pictet–Spengler reaction, the thiourea/HCl combination gives the desired product with comparable ee but moderate yield. Surprisingly, switching to 5 Å molecular sieves drastically improved the reactivity, presumably because the large pore size facilitates the adsorption of the side product methanol (Scheme 2.18). The reaction finishes in 1 hour with excellent yield but slightly diminished ee. Nevertheless, we questioned the possibility of applying this strategy to other systems with presumably more challenging substrates.

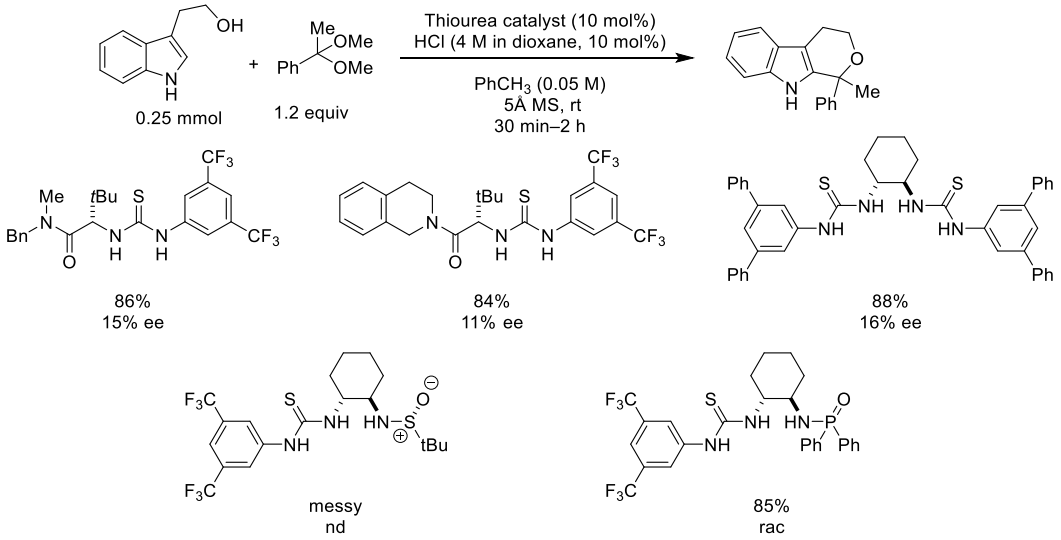
2.5.1 Catalytic Enantioselective Oxa-Pictet–Spengler Reactions towards Tetra-substituted Stereogenic Centers

The use of acetals in combination with 5 Å molecular sieves results in a highly reactive system for the oxa-Pictet–Spengler reactions (Scheme 2.18). If similar ketals can also be accommodated, then products bearing fully substituted stereogenic centers will be obtained. Simple ketals are readily available from corresponding ketones via a one-step reaction.[56] Indeed, a test reaction using benzophenone dimethyl ketal affords the desired product in satisfactory yield but with low levels of enantioselectivity (Scheme 2.19).

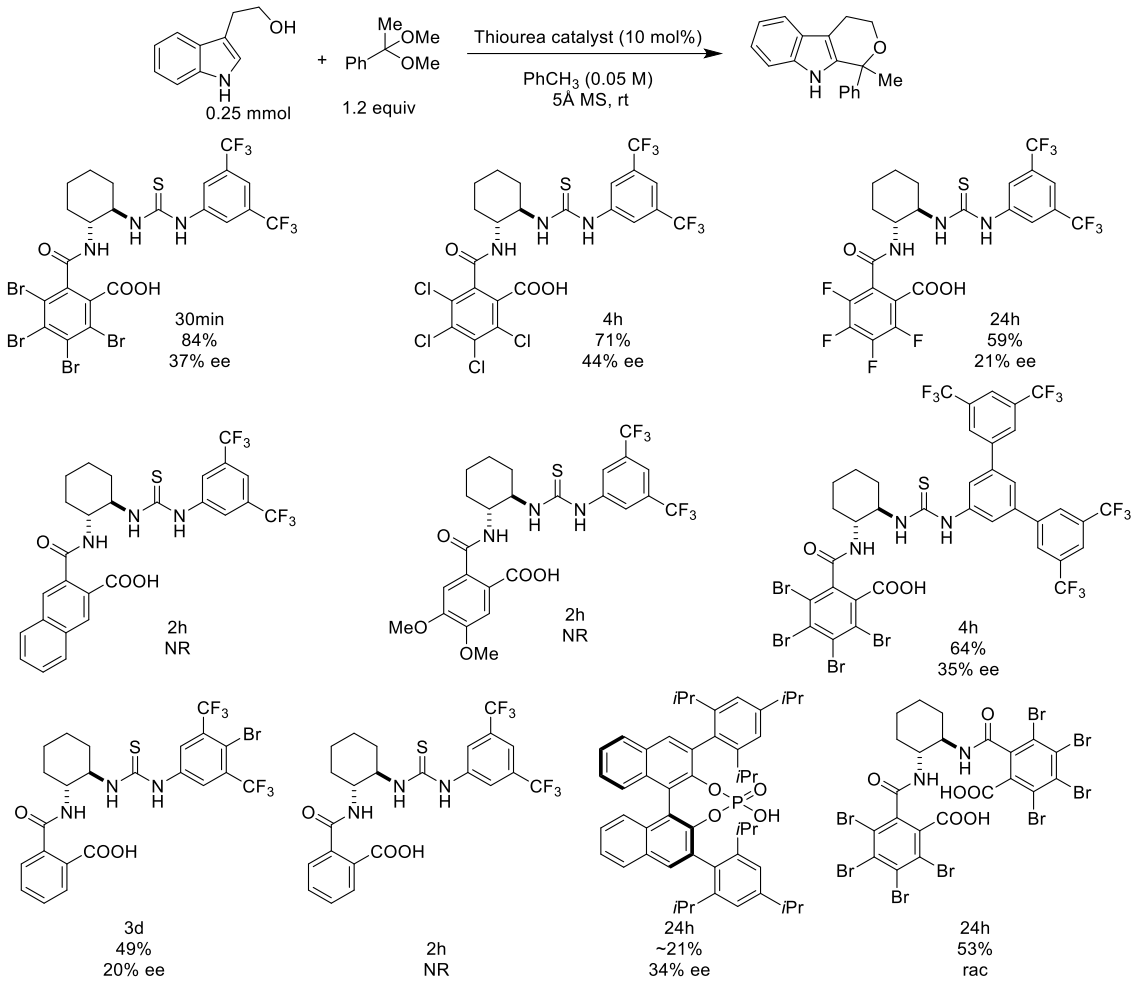
Scheme 2.19 Initial evaluation of the oxa-Pictet–Spengler reaction using ketal.



Scheme 2.20 Evaluation of thiourea catalysts for the oxa-Pictet–Spengler reaction using a ketal.



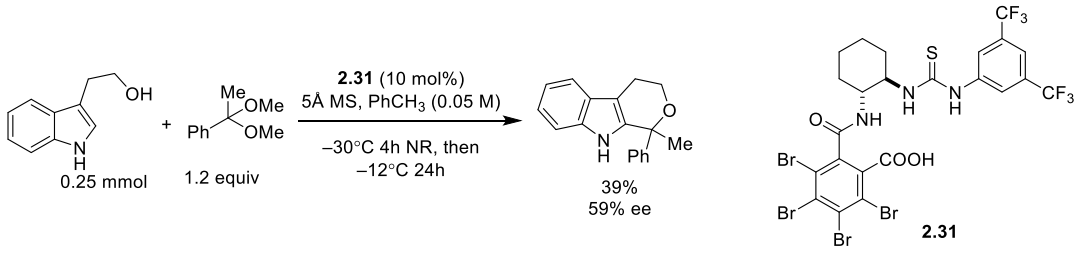
Scheme 2.21 Evaluation of chiral Brønsted acids for the oxa-Pictet–Spengler reaction using a ketal.



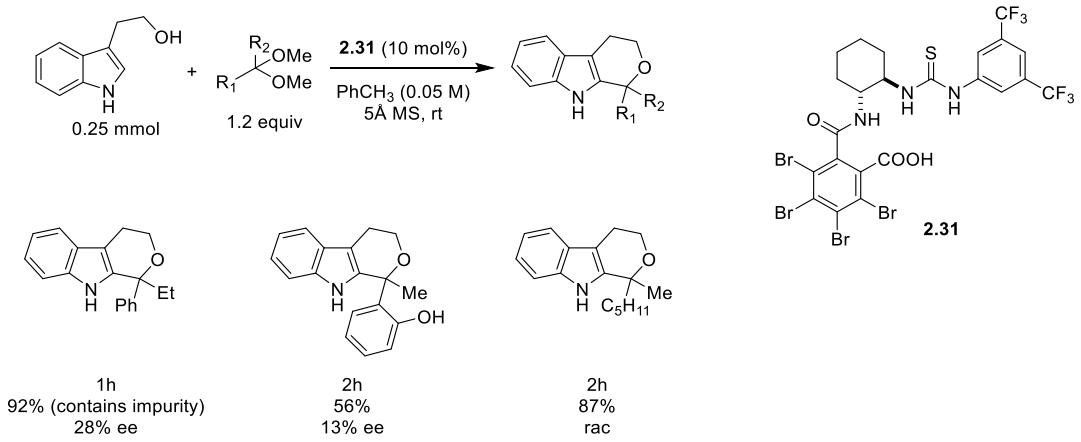
Thiourea catalysts of other types were tested for this reaction (Scheme 2.20).[4,57] Good reactivity was generally observed except in one case where a complex reaction mixture was observed. However, a low level of enantioselectivity was revealed in all cases. Surprisingly, the conjugate-base-stabilized Brønsted acid developed by our group resulted in a fast reaction with a slight boost of the ee (Scheme 2.21). The acidity of the catalyst has a profound influence in reactivity, as reflected by the necessity of electron-withdrawing bromo groups. Interestingly, when the bromo groups are replaced with chloro, slightly higher ee was observed, albeit with prolonged reaction time. The enantioselectivity seems not affected by variation on the thiourea phenyl ring. Significantly lower yield was observed with chiral phosphoric acids as catalyst, although the same level of ee was observed.

A study was performed to explore the possibility of enhancing the ee by lowering the reaction temperature (Scheme 2.22). No reaction was observed with a reaction temperature of -30 °C. Reactions proceeded at –12 °C at a relatively slow rate, affording 39% of the desired product in 24 hours with appreciable increase of the ee. Lowering the temperature indeed served as a strategy to increase the stereoselectivity of the reaction, but a more reactive and/or selective catalytic system is needed.

Scheme 2.22 Evaluation of the reaction at lower temperature.



Scheme 2.23 Evaluation of other substrates.

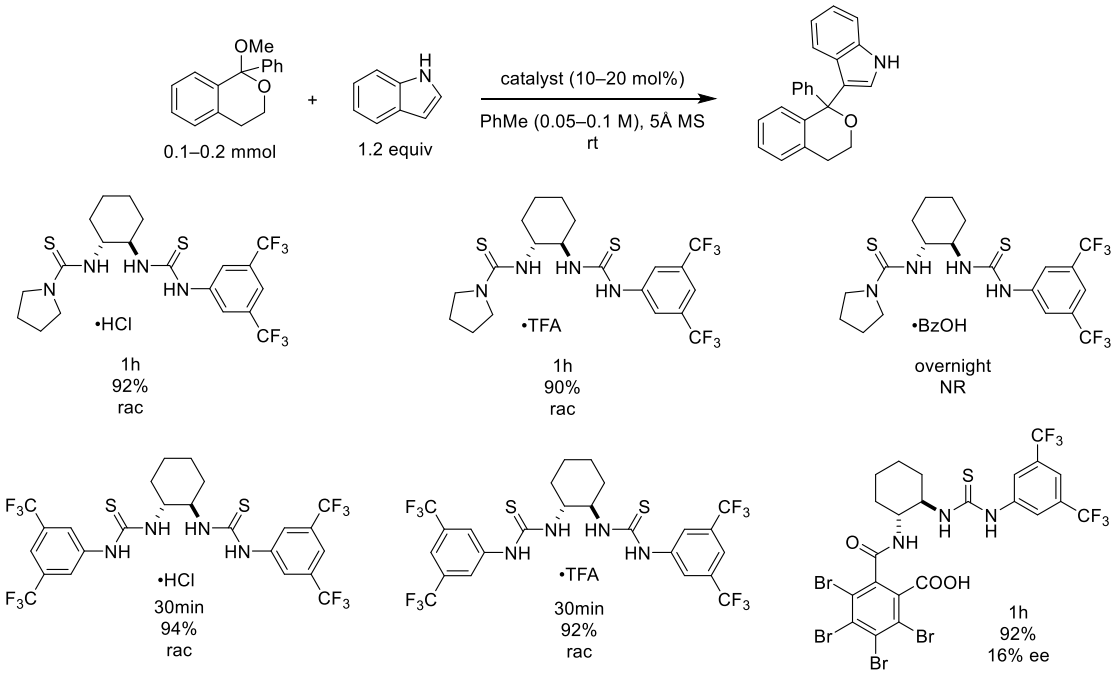


Other substrates were also tested (Scheme 2.23). Propiophenone dimethyl ketal behaves very similarly to benzophenone dimethyl ketal. An attempt to provide an additional interacting site with the catalyst by using 2-hydroxybenzophenone dimethyl ketal proved to be ineffective. Aliphatic ketal resulted in complete loss of enantioselectivity.

2.5.2 Catalytic Enantioselective Indole Additions to Oxocarbenium Ions

Isochroman ketals are useful starting materials towards isochromans bearing tetra-substituted stereogenic centers via dynamic kinetic resolution (Scheme 2.24).[15] We wished to apply our methodology to the indole addition reactions to isochroman ketals. However, various thiourea-acid combinations resulted in racemic products. Weaker acids such as TFA were also effective in terms of reactivity, while no product was detected when benzoic acid is used. On the other hand, the tetrabromo chiral Brønsted acid catalyst affords the desired product in 16% ee.

Scheme 2.24 Indole addition reaction to isochroman ketal.

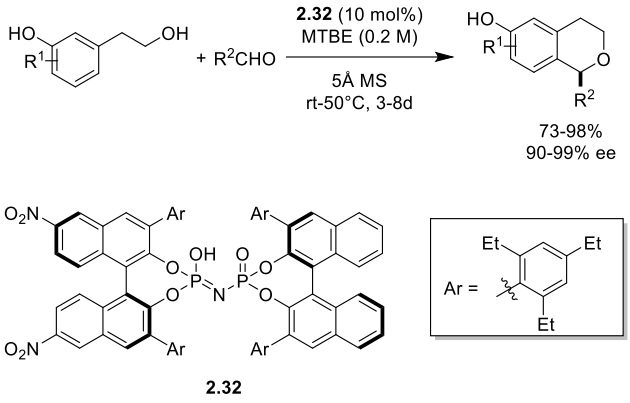


2.5.3 Catalytic Enantioselective Reduction of Isochroman Ketals.

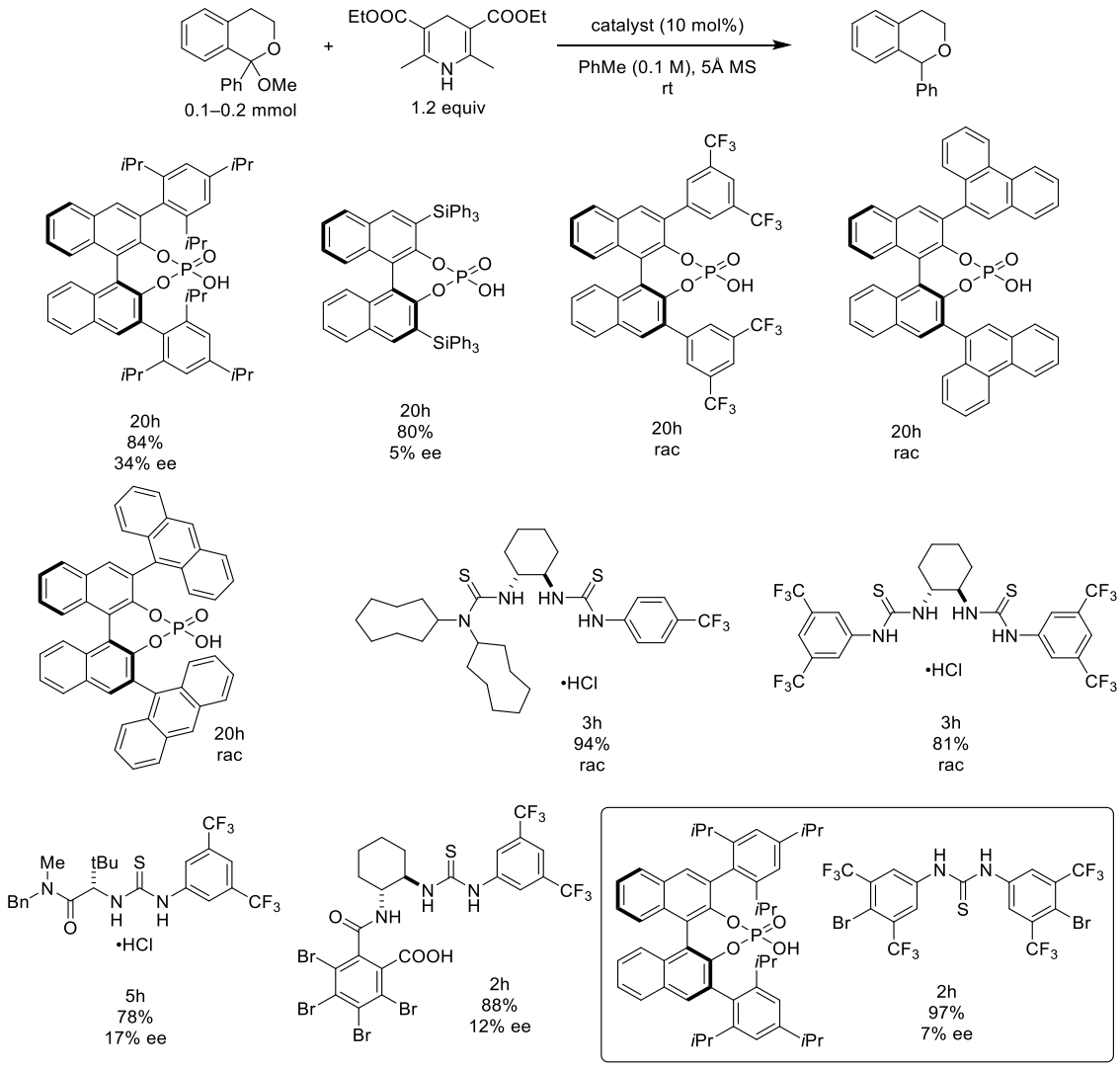
List reported enantioselective oxa-Pictet–Spengler reactions between benzaldehyde and 3-(2-hydroxyethyl)phenols (Scheme 2.25).[58] The phenol group serves as a necessary directing group to interact with the catalyst. Under this prerequisite, both aliphatic and aromatic aldehydes can be tolerated. Given the challenge of this reaction, the catalyst is powerful, yet its synthesis is nontrivial. We expect the same class of products can be obtain via

enantioselective reduction of isochroman ketals. Moreover, the required directing group may not be needed. Our preliminary studies indicate Hantzsch ester[59] to be a suitable reductant for the enantioselective reduction of isochroman ketals (Scheme 2.26). Various chiral phosphoric acids were tested, with TRIP giving the best ee of 34%. Thiourea–HCl combinations provided faster reactions, albeit with very low or no enantioselectivity. The tetrabromo chiral carboxylic acid also readily facilitated the reaction with only 12% ee. Interestingly, when TRIP was used in combination with an achiral thiourea catalyst, appreciable acceleration was observed, but with jeopardized ee compared to that in the absence of thiourea catalyst. Attempts to use various silanes resulted in no enantioselectivity in all cases (Scheme 2.27).

Scheme 2.25 Enantioselective oxa-Pictet–Spengler reactions with 3-(2-hydroxyethyl)phenols.

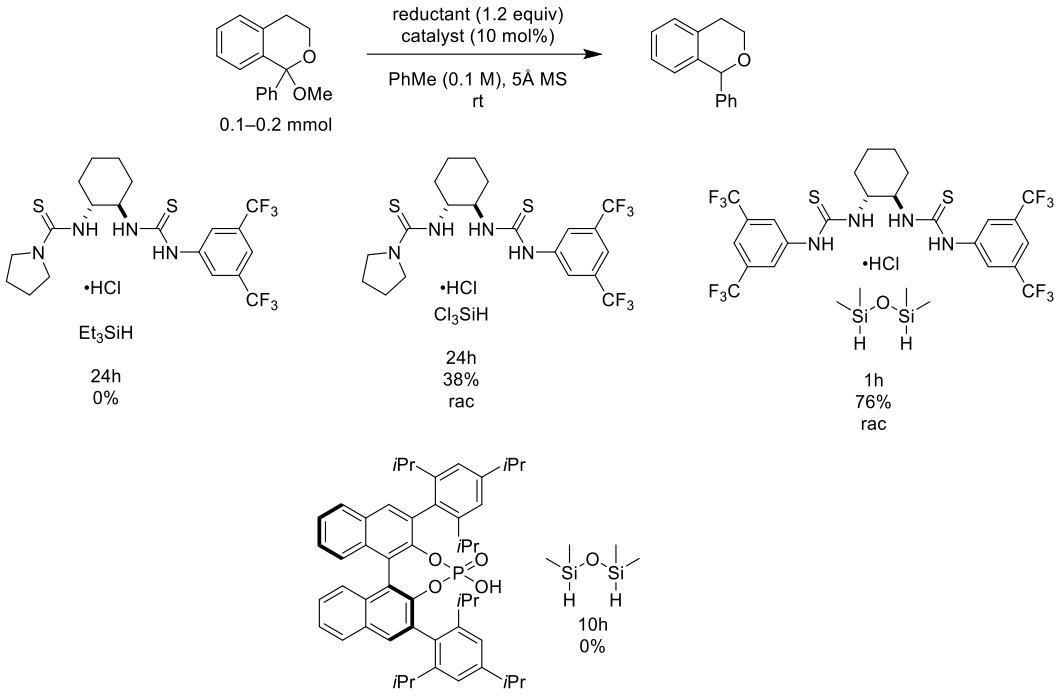


Scheme 2.26 Enantioselective reduction of an isochroman ketal using Hantzsch ester.

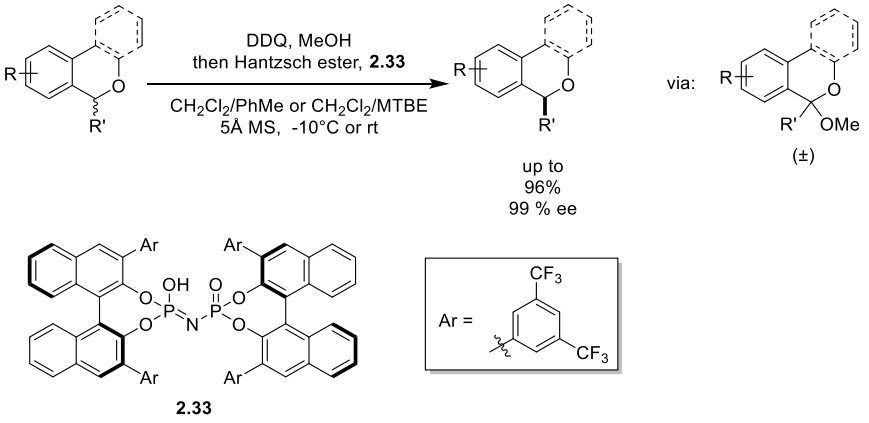


A highly related work appeared during our optimization of reaction conditions. Liu reported the deracemization reactions of benzylic ethers (Scheme 2.28).[60] The reaction conditions resemble a one-pot procedure combining generation and the enantioselective reduction of isochroman ketals.[15] The key to success is the utilization of a chiral imidophosphoric acid developed by List.[21]

Scheme 2.27 Attempted reduction of isochroman ketal with silanes.



Scheme 2.28 One-pot generation and enantioselective reduction of isochroman ketals by Liu.



2.6 Summary

In summary, we have outlined a new dual catalysis concept for the direct generation of oxocarbenium ions from aldehydes and alcohols, enabling catalytic enantioselective oxa-Pictet Spengler reactions under weakly acidic conditions. A new amine catalyst and a novel bis-thiourea catalyst were identified in the course of this study. The two catalysts work in

concert and fulfil crucial roles in the efficient generation of the oxa-Pictet Spengler products. When acetals and ketals are used, high reactivity is obtained with chiral Brønsted acid catalysts of sufficient acidity for various reactions of the oxocarbenium intermediacy. For future development, better stereochemical control is highly in need for these transformations.

Experimental Section

General Information: Reagents and solvents were purchased from commercial sources and were purified by distillation or recrystallization prior to use. Toluene was freshly distilled from sodium under nitrogen prior to use. Reactions were run under a nitrogen atmosphere. Purification of reaction products was carried out by flash column chromatography using EM Reagent silica gel 60 (230–400 mesh). Analytical thin layer chromatography was performed on EM Reagent 0.25 mm silica gel 60 F_{254} plates. Visualization was accomplished with UV light, and potassium permanganate, Dragendorff-Munier stains, followed by heating. Melting points were recorded on a Thomas Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on an ATI Mattson Genesis Series FT-Infrared spectrophotometer. Proton nuclear magnetic resonance spectra (^{1}H-NMR) were recorded on a Varian VNMRS-500 MHz instrument and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 7.26 ppm, $(CD_3)_2SO$ at 2.50 ppm, CD_3OD at 3.31 ppm). Data are reported as app = apparent, s = singlet, d = doublet, t = triplet, dd = doublet of doublets, ddd = doublet of doublet of doublets, dddd = doublet of doublet of doublet of doublets, m = multiplet, comp = complex; integration; coupling constant(s) in Hz. Proton-decoupled carbon nuclear magnetic resonance spectra (^{13}C-NMR) were recorded on a Varian VNMRS-500 MHz instrument and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 77.16 ppm, $(CD_3)_2SO$ at 39.52 ppm, CD_3OD at 49.00 ppm). Mass spectra were recorded on a Finnigan LCQ-DUO mass spectrometer. HPLC analysis was carried out on an Agilent 1100 series instrument with auto sampler and multiple wavelength detectors. Optical rotations were measured using a 1 mL cell with a 1 dm path length on a Jasco P–2000 polarimeter at 589 nm and at 20 °C. **2.12**,[61] **2.13**,[62] **2.18**,[63] **2.19**,[64] **2.20**,[65] **2.21**,[66] **2.22**,[67] **2.23**[68] were prepared according to reported procedures.

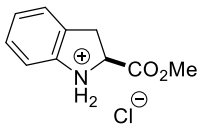
Evaluation of Pyridinium Salts with Different $pK_{a(H)}$ values:[69–72]

To a flame dried vial was added pyridine derivatives (0.0275 mmol, 11 mol %), thiourea catalyst **2.19** (16 mg, 0.025 mmol, 10 mol %), tryptophol (40 mg, 0.25 mmol, 1.0 equiv), 4Å MS (100 mg) and dry toluene (2.5 mL, 0.1 M). The resulting mixture was stirred under nitrogen and HCl (3.5 M in dioxane) was added followed by benzaldehyde (30 μL, 0.3 mmol, 1.2 equiv). The reaction was stirred for 24 hours before being quenched with triethylamine (40 μL). The resulting mixture was directly purified by flash chromatography on silica gel topped with Celite.

General Procedure A for Co-catalyst Synthesis:

To a solution of the corresponding amine (5.33 mmol, 1 equiv) in diethyl ether(10.7 mL, 0.5 M) was added HCl (4.0 M in dioxane, 1.33 mL, 5.33 mmol, 1 equiv) and the resulting mixture was vigorously stirred for 10 min before filtration. The solid was washed with cold diethyl ether (3 × 5 mL) and dried under vacuum to afford the desired product.

(*S*)-2-(methoxycarbonyl)indolin-1-ium chloride (2.13·HCl): Following general procedure



A, **2.13** was obtained as a white solid in 95% yield; mp = 161–163 ºC; $[\alpha]_D^{20}$ –73.2 (c 0.5, $CHCl_3$); IR (KBr) 3119, 3054, 2957, 2359, 1741, 1506, 1391, 1236, 1143, 1021, 860, 758, 420 cm^{-1}; ^1H NMR (500 MHz, $(CD_3)_2SO$) δ 10.61 (br s, 3H, contains water), 7.28 (app d, *J* = 7.4 Hz, 1H), 7.22 (app td, *J* = 7.8, 1.2 Hz, 1H), 7.17–7.05 (comp, 2H), 4.78 (dd, *J* = 9.8, 6.9 Hz, 1H), 3.73 (s, 3H), 3.44 (dd, *J* = 16.2, 9.8 Hz, 1H), 3.28 (dd, *J* = 16.2, 6.9 Hz, 1H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ 170.56, 141.63, 131.11, 127.96, 125.25, 125.02, 115.68, 58.98, 52.78, 32.73; *m/z* (ESI-MS) 178.1 $[M - Cl]^+$.

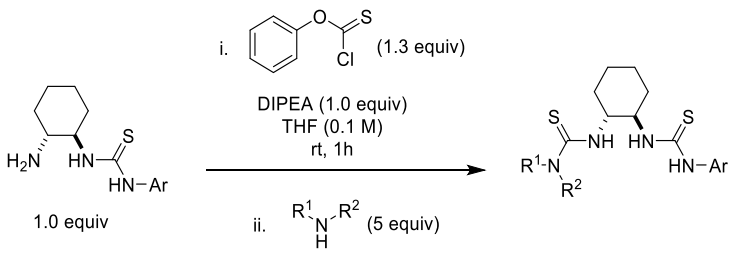
(2*S*)-2-(methoxycarbonyl)-1-methylindolin-1-ium chloride (2.18·HCl): Following general procedure **A**, **2.18·HCl** was obtained as a white solid in 70% yield; mp = 101–103 ºC; $[\alpha]_D^{20}$ –58.3 (c 0.5, MeOH); IR (KBr) 3400, 2904, 1738, 1486, 1428, 1368, 1343, 1251, 1128, 995, 825, 803, 763, 605, 513, 428 cm^{-1}; ^1H NMR (500 MHz, $(CD_3)_2SO$) δ 9.83 (br s, 3H, contains water), 7.07–6.93 (comp, 2H), 6.60 (app td, *J* = 7.4, 1.0 Hz, 1H), 6.49 (app d, *J* = 7.8 Hz, 1H), 4.14 (dd, *J* = 10.1, 8.4 Hz, 1H), 3.69 (s, 3H), 3.30 (dd, *J* = 16.0, 10.2 Hz, 1H), 2.98 (dd, *J* = 15.9, 8.4 Hz, 1H), 2.75 (s, 3H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ 172.52, 151.98, 127.57, 126.89, 123.89, 117.67, 106.67, 66.72, 51.90, 34.39, 32.75; *m/z* (ESI-MS) 192.1 $[M - Cl]^+$.

(*S*)-2-(methoxycarbonyl)indolin-1-ium bromide: Following general procedure **A**, HBr (48% in water) was used and the desired product was obtained as a white solid in 77% yield; mp = 172–174 ºC; $[\alpha]_D^{20}$ –50.7 (c 0.5, MeOH); IR (KBr) 3092, 3054, 2997, 2954, 2587, 2514, 1738, 1503, 1378, 1348, 1231, 1020, 860, 753 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) 7.54–7.49 (comp, 3H), 7.49–7.44 (m, 1H), 5.13 (dd, *J* = 9.5, 7.3 Hz, 1H), 3.91 (s, 3H), 3.73 (dd, *J* = 16.5, 9.5 Hz, 1H), 3.54 (dd, *J* = 16.3, 7.3 Hz, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 169.91, 136.81, 134.85, 131.27, 130.04, 127.32, 120.19, 61.28, 54.18, 33.93; *m/z* (ESI-MS) 178.2 $[M - Br]^+$.

(*S*)-2-(methoxycarbonyl)indolin-1-ium iodide: Following general procedure **A**, HI (57% in water) was used and the desired product was obtained as a yellow solid in 87% yield; mp = 145–147 ºC; $[\alpha]_D^{20}$ –39.8 (c 0.5, MeOH); IR (KBr) 3417, 3379, 2942, 2914, 2464, 1756, 1428, 1351, 1283, 1246, 1208, 1161, 1001, 763 cm^{-1}; ^1H NMR (500 MHz, $(CD_3)_2SO$) δ 7.14 (app d, *J* = 7.2 Hz, 1H), 7.07 (app td, *J* = 7.8, 1.1 Hz, 1H), 6.86–6.78 (comp, 2H), 6.50 (br s, 4H, contains water), 4.60 (dd, *J* = 10.2, 6.4 Hz, 1H), 3.70 (s, 3H), 3.37 (dd, *J* = 16.2, 10.2 Hz, 1H), 3.17 (dd, *J* = 16.2, 6.2 Hz, 1H); ^{13}C NMR

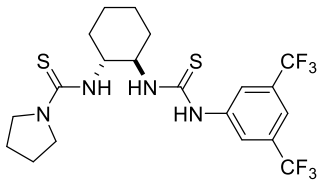
(125 MHz, $(CD_3)_2SO$) δ 172.51, 146.54, 128.44, 127.62, 124.66, 121.03, 111.73, 59.18, 52.34, 32.99; *m/z* (ESI-MS) 178.4 $[M - I]^+$.

General Procedure B for Catalyst Synthesis:



To a solution of amino(thio)urea[73,74] (0.39 mmol, 1.0 equiv) in dry THF (3.9 mL, 0.1 M) was added *o*-Phenyl chlorothionoformate (70 µL, 0.51 mmol, 1.3 equiv) and *N*,*N*-Diisopropylethylamine (68 µL, 0.39 mmol, 1.0 equiv). The resulting solution was stirred at room temperature for 1 hour before amine nucleophile (1.95 mmol, 5.0 equiv) was added. The resulting mixture was stirred at room temperature for indicated time. Then, saturated aqueous $NaHCO_3$ (10 mL) was added and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic layer was washed with brine (10 mL), dried over Na_2SO_4 and filtered. The resulting solution was then concentrated under reduced pressure and purified by flash chromatography on silica gel.

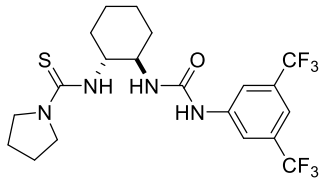
***N*-((1*R*,2*R*)-2-(3-(3,5-bis(trifluoromethyl)phenyl)thioureido)cyclohexyl)pyrrolidine-1-carbothioamide (2.24):**



Following general procedure **B**, reaction was stirred at room temperature for 2 hours and **2.24** was isolated as a white solid in 88% yield; mp = 171–173 ºC; R_f = 0.30 (Hexanes/EtOAc 70:30 v/v); $[\alpha]_D^{20}$ +68.2 (c 0.5, $CHCl_3$); IR (KBr) 3246, 3048, 2938, 2861, 1545, 1385, 1277, 1178, 1132, 971, 885, 681 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.56 (s, 1H), 8.37 (d, *J* = 8.3 Hz, 1H), 8.25 (s, 2H), 7.57 (s, 1H), 7.09 (d, *J* = 5.9 Hz, 1H),

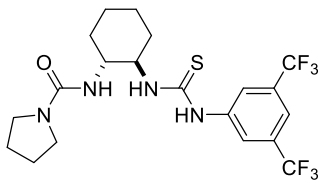
4.73–4.60 (m, 1H), 4.07–3.82 (comp, 2H), 3.65–3.42 (comp, 2H), 3.42–3.25 (m, 1H), 2.72–2.58 (m, 1H), 2.28–2.16 (m, 1H), 2.13–1.72 (comp, 6H), 1.73–1.61 (m, 1H), 1.51–1.37 (m, 1H), 1.37–1.17 (comp, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 181.42, 175.90, 140.77, 131.79 (q, $J_{C\text{-}F}$ = 33.5 Hz), 123.23 (q, $J_{C\text{-}F}$ = 272.8 Hz), 122.25, 117.62, 62.38, 56.43, 52.58, 48.57, 32.77, 32.74, 26.03, 25.07, 24.77, 24.54; *m/z* (ESI-MS) 497.1 $[M - H]^-$.

***N*-((1*R*,2*R*)-2-(3-(3,5-bis(trifluoromethyl)phenyl)ureido)cyclohexyl)pyrrolidine-1-carbothioamide (2.25):**



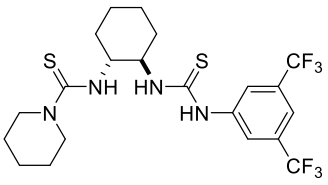
Following general procedure **B**, reaction was stirred at room temperature for 2 hours and **2.25** was isolated as a white solid in 66% yield; mp > 200 ºC; R_f = 0.28 (Hexanes/EtOAc 70:30 v/v); $[\alpha]_D^{20}$ +31.9 (c 0.5, $CHCl_3$); IR (KBr) 3349, 3307, 3282, 3207, 3087, 2938, 1697, 1571, 1474, 1391, 1275, 1186, 1130, 1023, 895, 870, 703, 673 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.56 (s, 1H), 8.00 (s, 2H), 7.41 (s, 1H), 6.95 (d, *J* = 5.5 Hz, 1H), 6.90 (d, *J* = 7.3 Hz, 1H), 4.14–3.92 (m, 1H), 3.91–3.71 (comp, 2H), 3.66–3.50 (m, 1H), 3.49–3.28 (comp, 2H), 2.69–2.58 (m, 1H), 2.21–2.14 (m, 1H), 2.14–1.96 (m, 1H), 1.95–1.75 (comp, 5H), 1.64–1.52 (m, 1H), 1.47–1.37 (m, 1H), 1.37–1.24 (m, 1H), 1.23–1.10 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.22, 156.72, 141.52, 132.25 (q, $J_{C\text{-}F}$ = 33.2 Hz), 123.39 (q, $J_{C\text{-}F}$ = 272.7 Hz), 117.48, 115.03, 62.88, 53.01, 52.36, 47.42, 32.74, 32.63, 25.77, 25.31, 24.79, 24.58; *m/z* (ESI-MS) 481.2 $[M - H]^-$.

***N*-((1*R*,2*R*)-2-(3-(3,5-bis(trifluoromethyl)phenyl)thioureido)cyclohexyl)pyrrolidine-1-carboxamide (2.26):**

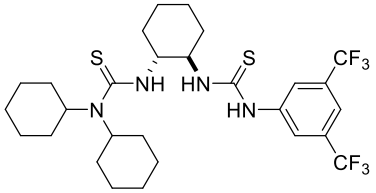


Following general procedure **B**, reaction was stirred at room temperature for 2 days and **2.26** was isolated as a white solid in 44% yield; mp = 188–190 ºC; R_f = 0.18 (Hexanes/EtOAc 40:60 v/v); $[\alpha]_D^{20}$ +41.7 (c 0.5, $CHCl_3$); IR (KBr) 3300, 3097, 2938, 2859, 1618, 1535, 1474, 1396, 1278, 1181, 1131, 968, 880, 678 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$)

δ 9.74 (s, 1H), 8.21 (d, *J* = 9.1 Hz, 1H), 7.97 (s, 2H), 7.56 (s, 1H), 5.00 (d, *J* = 8.8 Hz, 1H), 4.69–4.54 (m, 1H), 3.68–3.58 (m, 1H), 3.46–3.30 (comp, 2H), 3.21–3.02 (comp, 2H), 2.28–2.18 (m, 1H), 2.14–2.05 (m, 1H), 1.98–1.67 (comp, 6H), 1.55–1.28 (comp, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.08, 157.40, 141.11, 131.53 (q, $J_{C\text{-}F}$ = 33.4 Hz), 124.27, 123.26 (q, $J_{C\text{-}F}$ = 271.3 Hz), 117.87, 57.39, 56.25, 46.33, 33.77, 32.65, 25.34, 24.94; *m/z* (ESI-MS) 481.2 $[M - H]^-$.

***N*-((1*R*,2*R*)-2-(3-(3,5-bis(trifluoromethyl)phenyl)thioureido)cyclohexyl)piperidine-1-carbothioamide (2.27):** 

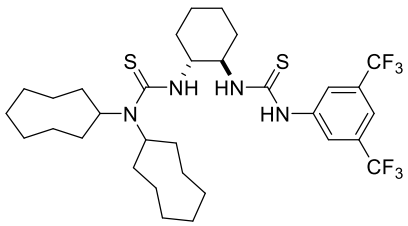
Following general procedure **B**, reaction was stirred at room temperature for 5 hours and **2.27** was isolated as a white solid in 69% yield; mp = 96–98 ºC; R_f = 0.21 (Hexanes/EtOAc 80:20 v/v); $[\alpha]_D^{20}$ +93.1 (c 0.5, $CHCl_3$); IR (KBr) 3266, 3042, 2939, 2859, 1541, 1474, 1385, 1333, 1277, 1178, 1132, 968, 885, 681 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.42 (s, 1H), 8.31 (d, *J* = 8.3 Hz, 1H), 8.18 (s, 2H), 7.57 (s, 1H), 7.33 (d, *J* = 5.8 Hz, 1H), 4.71–4.59 (m, 1H), 4.18–4.06 (m, 1H), 3.94–3.78 (comp, 2H), 3.78–3.66 (comp, 2H), 2.69–2.57 (m, 1H), 2.27–2.17 (m, 1H), 1.97–1.79 (comp, 2H), 1.76–1.38 (comp, 8H), 1.38–1.18 (comp, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 181.49, 177.86, 140.65, 131.82 (q, $J_{C\text{-}F}$ = 33.5 Hz), 123.22 (q, $J_{C\text{-}F}$ = 272.9 Hz), 122.53, 117.81, 62.76, 56.63, 49.61, 32.63, 32.51, 25.54, 25.07, 24.76, 24.17; *m/z* (ESI-MS) 511.1 $[M - H]^-$.

3-((1*R*,2*R*)-2-(3-(3,5-bis(trifluoromethyl)phenyl)thioureido)cyclohexyl)-1,1-dicyclohexylthiourea (2.28): 

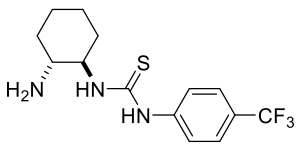
Following general procedure **B**, reaction was stirred at room temperature for 24 hours and **2j** was isolated as a white solid in 66% yield; mp = 98–100 ºC; R_f = 0.36 (Hexanes/EtOAc 90:10 v/v); $[\alpha]_D^{20}$ –27.1 (c 0.5, $CHCl_3$); IR (KBr) 3442, 3247, 2935, 2857, 1534, 1473, 1383, 1323, 1278, 1178, 1135, 968, 885, 675 cm^{-1}; ^{1}H NMR

(500 MHz, $CDCl_3$) δ 8.40–8.17 (comp, 2H), 7.91 (s, 2H), 7.60 (s, 1H), 5.61 (d, *J* = 8.4 Hz, 1H), 4.72–4.58 (m, 1H), 4.49–3.94 (comp, 3H), 2.43–2.28 (m, 1H), 2.25–2.13 (m, 1H), 1.95–1.46 (comp, 16H), 1.46–1.15 (comp, 8H), 1.12–1.00 (comp, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.72, 180.50, 140.24, 132.05 (q, J_{C-F} = 36.6 Hz), 123.58, 123.18 (q, J_{C-F} = 272.7 Hz), 118.33, 61.17, 59.75, 57.86, 32.76, 32.05, 31.55, 30.94, 26.16, 25.50, 25.05, 24.48; *m/z* (ESI-MS) 607.1 $[M - H]^-$.

3-((1*R*,2*R*)-2-(3-(3,5-bis(trifluoromethyl)phenyl)thioureido)cyclohexyl)-1,1-dicyclooctylthiourea (2.29): Following general procedure **B**, 2.5 equivalent of dicyclooctylamine[75] was used and reaction was stirred at room temperature for 2 days to afford **2.29** as a white solid in 61% yield; mp = 105–108 ºC; R_f = 0.33 (Hexanes/EtOAc 85:15 v/v); $[\alpha]_D^{20}$ –31.4 (c 0.5, $CHCl_3$); IR (KBr) 3437, 3247, 2926, 2855, 1534, 1473, 1384, 1323, 1277, 1178, 1135, 973, 880, 680 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.44 (s, 1H), 8.18 (s, 1H), 7.93 (s, 2H), 7.58 (s, 1H), 5.61 (s, 1H), 5.20–5.06 (m, 1H), 4.70–4.56 (m, 1H), 4.33–4.19 (m, 1H), 3.66–3.50 (m, 1H), 2.44–2.28 (m, 1H), 2.16–2.07 (m, 1H), 2.05–1.05 (comp, 34H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.38, 178.22, 140.41, 131.99 (q, J_{C-F} = 33.4 Hz), 123.33, 123.20 (q, J_{C-F} = 272.9 Hz), 118.09, 62.07, 61.65, 57.59, 56.82, 34.42, 33.79, 32.83, 32.69, 32.28, 32.02, 26.48, 26.23, 26.04, 25.05, 24.80, 24.45; *m/z* (ESI-MS) 663.2 $[M - H]^-$.

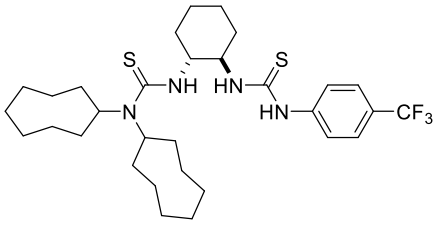


1-((1*R*,2*R*)-2-thioureidocyclohexyl)-3-(4-(trifluoromethyl)phenyl)thiourea: Following a similar procedure,[76] (1*R*,2*R*)-cyclohexane-1,2-diamine (2.24 g, 19.6 mmol, 1.5 equiv) dissolved in a minimum amount of CH_2Cl_2 (ca. 1.0 mL) was cooled to 0 ºC. 1-isothiocyanato-4-(trifluoromethyl)benzene (2.66g, 13.1 mmol, 1.0 equiv), dissolved in 262 mL CH_2Cl_2, was



added dropwise over 1 hour. The mixture was then allowed to warm to room temperature and concentrated under reduced pressure. Purification by flash chromatography on silica gel afforded the desired product as a white solid in 87% yield; mp = 144–146 ºC; R_f = 0.10 (MeOH/CH_2Cl_2/Et_3N 10:89:1 v/v/v); $[\alpha]_D^{20}$ +125.5 (c 0.5, $CHCl_3$); IR (KBr) 3259, 2937, 2854, 1613, 1523, 1341, 1161, 1111, 1068, 1008, 825, 708 cm^{-1}; ^1H NMR (500 MHz, $(CD_3)_2SO$) δ 7.79 (app d, J = 8.2 Hz, 2H), 7.60 (app d, J = 8.4 Hz, 2H), 4.08–3.75 (m, 1H), 2.62–2.52 (m, 1H), 2.23–1.99 (m, 1H), 1.92–1.78 (m, 1H), 1.73–1.50 (comp, 2H), 1.34–0.98 (comp, 4H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ 180.31, 143.76, 125.36, 124.46 (q, $J_{C\text{-}F}$ = 271.3 Hz), 123.25 (q, $J_{C\text{-}F}$ = 31.9 Hz), 121.57, 60.08, 54.02, 35.05, 31.05, 24.62.; *m/z* (ESI-MS) 318.1 $[M + H]^-$.

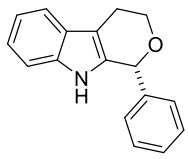
1,1-dicyclooctyl-3-((1*R*,2*R*)-2-(3-(4-(trifluoromethyl)phenyl)thioureido)cyclohexyl) thiourea (2.30): Following general procedure **B**, 2.5 equivalent of dicyclooctylamine[75] was used and the reaction was stirred at 50 ºC for 24 hours to afford **2.30** as a white solid in 65% yield; mp = 110–112 ºC; R_f = 0.31 (Hexanes/EtOAc 85:15 v/v); $[\alpha]_D^{20}$ –25.1 (c 0.5, $CHCl_3$); IR (KBr) 3432, 3222, 2924, 2847, 1614, 1522, 1441, 1324, 1124, 1067, 1011, 948, 828 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.71 (s, 1H), 7.59 (app d, *J* = 8.3 Hz, 2H), 7.44 (app d, *J* = 8.3 Hz, 2H), 5.65 (s, 1H), 5.18–5.05 (m, 1H), 4.81–4.68 (m, 1H), 4.35–4.22 (m, 1H), 3.67–3.50 (m, 1H), 2.44–2.31 (m, 1H), 2.15–2.06 (m, 1H), 2.05–1.23 (m, 34H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.85, 178.51, 140.74, 127.17 (q, $J_{C\text{-}F}$ = 33.3 Hz), 126.56, 124.06 (q, $J_{C\text{-}F}$ = 270 Hz), 123.36, 61.71, 61.48, 57.33, 56.60, 34.33, 33.82, 32.94, 32.66, 32.36, 32.07, 26.59, 26.27, 25.05, 24.90, 24.52; *m/z* (ESI-MS) 595.3 $[M – H]^-$.



General Procedure C for the Enantioselective Oxa-Pictet-Spengler Reactions:

To a flame dried vial was added amine salt **2.13·HCl** (5.3 mg, 0.025 mmol, 10 mol %), thiourea catalyst **2.30** (15 mg, 0.025 mmol, 10 mol %), tryptophol (40 mg, 0.25 mmol, 1 equiv), 4Å MS (100 mg) and dry toluene (5 mL, 0.05 M). The resulting mixture was stirred under nitrogen and cooled to –30 ºC over 15 minutes. Aldehyde (0.3 mmol, 1.2 equiv) was then added and the reaction was stirred for the indicated time before being quenched with triethylamine (40 μL). The resulting mixture was directly purified by flash chromatography on silica gel topped with Celite.

(*R*)-1-(4-chlorophenyl)-1,3,4,9-tetrahydropyrano[3,4-b]indole (2.9): Following general procedure **C**, the reaction was run for 2 days and **2.9** was obtained as a white solid in 90% yield; mp = 153–155 ºC; R_f = 0.32 (Hexanes/EtOAc 90:10 v/v); $[\alpha]^{D}_{20}$ –15.7 (c 0.5, $CHCl_3$, 91% ee); IR (KBr) 3397, 3032, 2909, 2837, 1446, 1311, 1273, 1251, 1136, 1083, 1048, 978, 738, 693, 470 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.57 (app dd, *J* = 7.0, 2.1 Hz, 1H), 7.46 (br s, 1H), 7.42–7.36 (comp, 5H), 7.25–7.19 (m, 1H), 7.19–7.11 (comp, 2H), 5.80 (app t, *J* = 1.9 Hz, 1H), 4.34 (ddd, *J* = 11.2, 5.4, 2.9 Hz, 1H), 4.00 (ddd, *J* = 11.3, 9.6, 4.0 Hz, 1H), 3.12 (dddd, *J* = 15.2, 9.7, 5.4, 2.1 Hz, 1H), 2.84 (dddd, *J* = 15.4, 4.1, 3.0, 1.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.59, 136.16, 133.74, 129.06, 128.94, 128.57, 127.14, 122.08, 119.78, 118.47, 111.13, 108.91, 76.28, 65.00, 22.44; *m/z* (ESI-MS) 250.2 $[M + H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 280.16 nm, t_R = 14.7 min (minor) and t_R = 19.6 min (major).



The absolute configuration was assigned by analogy.

(*R*)-1-(4-fluorophenyl)-1,3,4,9-tetrahydropyrano[3,4-b]indole (2.31): Following general procedure **C**, the reaction was run for 2 days and **2.31** was obtained as a white solid in 82% yield; mp = 116–118 ºC; R_f = 0.21 (Hexanes/EtOAc 90:10 v/v); $[\alpha]^{D}_{20}$ –8.1 (c 0.5, $CHCl_3$, 90% ee); IR (KBr) 3389, 3292, 3047, 2957, 2914, 2847, 1713, 1606, 1509, 1446, 1224, 1153, 1071, 1043, 830, 743 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.59–7.55 (m, 1H), 7.44 (br s, 1H), 7.38–7.32 (comp, 2H), 7.27–7.23 (m, 1H), 7.21–7.12 (comp, 2H), 7.11–7.04 (comp, 2H), 5.78 (t, *J* = 1.9 Hz, 1H), 4.31 (ddd, *J* = 11.3, 5.4, 3.0 Hz, 1H), 3.99 (ddd, *J* = 11.3, 9.6, 4.0 Hz, 1H), 3.10 (dddd, *J* = 15.2, 9.6, 5.4, 2.1 Hz, 1H), 2.84 (dddd, *J* = 15.4, 4.0, 3.0, 1.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.03 (d, J_{C-F} = 247.7 Hz), 136.05, 135.37 (d, J_{C-F} = 3.2 Hz), 133.28, 130.28 (d, J_{C-F} = 8.3 Hz), 126.96, 122.11, 119.76, 118.39, 115.71 (d, J_{C-F} = 21.6 Hz), 111.01, 109.01, 75.37, 64.82, 22.26; *m/z* (ESI-MS) 268.2 $[M + H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 280.16 nm, t_R = 15.7 min (major) and t_R = 18.2 min (minor).

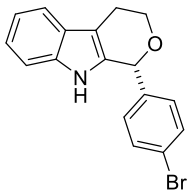
The absolute configuration was assigned by analogy.

(*R*)-1-(4-chlorophenyl)-1,3,4,9-tetrahydropyrano[3,4-b]indole (2.32): Following general procedure **C**, the reaction was run for 2 days and **2.32** was obtained as a white solid in 91% yield; mp = 101–103 ºC; R_f = 0.28 (Hexanes/EtOAc 90:10 v/v); $[\alpha]^{D}_{20}$ –9.3 (c 0.5, $CHCl_3$, 94% ee); IR (KBr) 3393, 3307, 3052, 2919, 2834, 1713, 1611, 1490, 1451, 1246, 1087, 1015, 815, 743, 510 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.57 (app dd, *J* = 7.6, 1.2 Hz, 1H), 7.45 (br s, 1H), 7.38–7.34 (comp, 2H), 7.33–7.29 (comp, 2H), 7.26–7.22 (m, 1H), 7.20–7.13 (comp, 2H), 5.76 (app t, *J* = 1.9 Hz, 1H), 4.30 (ddd, *J* = 11.3, 5.4, 3.1 Hz, 1H), 3.98 (ddd, *J* = 11.4, 9.5, 4.1 Hz, 1H), 3.09 (dddd, *J* = 15.0, 9.5, 5.3, 2.0 Hz, 1H), 2.90–2.79 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ

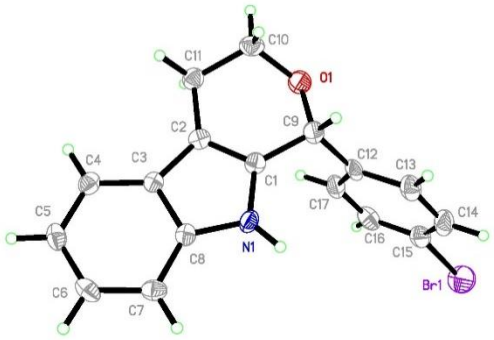
138.14, 136.20, 134.91, 133.14, 129.93, 129.11, 127.06, 122.29, 119.92, 118.54, 111.16, 109.13, 75.47, 64.90, 22.37; *m/z* (ESI-MS) 284.2 $[M + H]^+$; HPLC: Daicel Chiralpak AS-H, *n*-hexane/*i*-PrOH = 93/7, Flow rate = 0.2 mL/min, UV = 280.16 nm, t_R = 66.4 min (minor) and t_R = 69.8 min (major).

The absolute configuration was assigned by analogy.

(*R*)-1-(4-bromophenyl)-1,3,4,9-tetrahydropyrano[3,4-b]indole (2.33): Following general procedure **C**, the reaction was run for 2 days and **2.33** was obtained as a white solid in 91% yield; mp = 116–118 ºC; R_f = 0.25 (Hexanes/EtOAc 90:10 v/v); $[\alpha]^D_{20}$ –7.2 (c 0.5, $CHCl_3$, 93% ee); IR (KBr) 3394, 3312, 3062, 2962, 2914, 2852, 2369, 2341, 1716, 1506, 1481, 1451, 1253, 1073, 1043, 1011, 810, 735, 508 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.59–7.55 (m, 1H), 7.53–7.49 (comp, 2H), 7.44 (br s, 1H), 7.26–7.23 (comp, 3H), 7.20–7.12 (comp, 2H), 5.75 (app t, *J* = 1.9 Hz, 1H), 4.30 (ddd, *J* = 11.3, 5.4, 3.0 Hz, 1H), 3.98 (ddd, *J* = 11.3, 9.5, 4.1 Hz, 1H), 3.09 (dddd, *J* = 15.4, 9.5, 5.4, 2.0 Hz, 1H), 2.84 (dddd, *J* = 15.5, 4.1, 3.1, 1.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.65, 136.20, 133.07, 132.08, 130.23, 127.05, 123.11, 122.31, 119.92, 118.55, 111.16, 109.13, 75.53, 64.91, 22.37; *m/z* (ESI-MS) 328.3 (^{79}Br) $[M + H]^+$, 330.3 (^{81}Br) $[M + H]^+$; HPLC: Daicel Chiralpak AS-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 0.2 mL/min, UV = 280.16 nm, t_R = 55.0 min (minor) and t_R = 59.5 min (major).

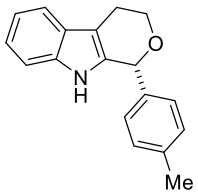


The absolute configuration of **2.33** was assigned by X-ray crystallography:



Compound **2.33** was crystallized from MeOH through slow evaporation at room temperature. The requisite CIF has been submitted to the journal.

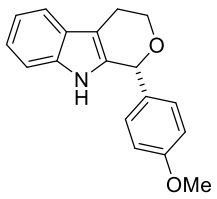
(*R*)-1-(*p*-tolyl)-1,3,4,9-tetrahydropyrano[3,4-b]indole (2.34): Following general procedure



C, the reaction was run for 2 days and **2.34** was obtained as a white solid in 90% yield; mp = 179–180 ºC; R_f = 0.24 (Hexanes/EtOAc 90:10 v/v); $[\alpha]^{D}_{20}$ –2.4 (c 0.5, $CHCl_3$, 95% ee); IR (KBr) 3394, 2947, 2909, 2859, 2819, 1446, 1298, 1081, 1041, 808, 740, 455 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.59 (app d, *J* = 6.5 Hz, 1H), 7.49 (br s, 1H), 7.33–7.24 (comp, 2H), 7.24–7.19 (comp, 3H), 7.19–7.13 (comp, 2H), 5.76 (s, 1H), 4.32 (ddd, *J* = 11.4, 5.5, 3.2 Hz, 1H), 3.99 (ddd, *J* = 11.3, 9.6, 4.1 Hz, 1H), 3.16–3.06 (m, 1H), 2.89–2.81 (m, 1H), 2.40 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.86, 136.61, 136.11, 133.90, 129.53, 128.55, 127.13, 121.96, 119.69, 118.40, 111.10, 108.82, 75.98, 64.78, 22.42, 21.35; *m/z* (ESI-MS) 264.1 $[M + H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 280.16 nm, t_R = 11.9 min (minor) and t_R = 18.3 min (major).

The absolute configuration was assigned by analogy.

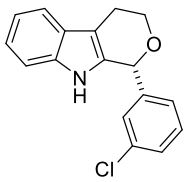
(*R*)-1-(4-methoxyphenyl)-1,3,4,9-tetrahydropyrano[3,4-b]indole (2.35): Following



general procedure **C**, the reaction was run for 3 days and **2.35** was obtained as a white solid in 84% yield; mp = 115–117 ºC; R_f = 0.26 (Hexanes/EtOAc 80:20 v/v); $[\alpha]^{D}_{20}$ +0.6 (c 0.5, $CHCl_3$, 84% ee); IR (KBr) 3392, 2949, 2907, 2837, 1611, 1448, 1301, 1243, 1173, 1078, 1033, 968, 830, 735, 465, 508, 473 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.59–7.54 (m, 1H), 7.46 (br s, 1H), 7.32–7.27 (comp, 2H), 7.25–7.22 (m, 1H), 7.19–7.11 (comp, 2H), 6.92–6.88 (comp, 2H), 5.76 (app t, *J* = 1.9 Hz, 1H), 4.31 (ddd, *J* = 11.2, 5.3, 3.1 Hz, 1H), 3.98 (ddd, *J* = 11.2, 9.4, 4.1 Hz, 1H), 3.82 (s, 3H), 3.09 (dddd, *J* = 15.0, 9.5, 5.4, 2.1 Hz, 1H), 2.842 (dddd, *J* = 15.4, 4.0, 3.1, 1.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.17, 136.11, 133.98, 131.75, 129.99, 127.14, 121.99, 119.71, 118.41, 114.22, 111.10, 108.94, 75.73, 64.79, 55.45, 22.44; *m/z* (ESI-MS) 280.1 $[M + H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 280.16 nm, t_R = 20.8 min (minor) and t_R = 31.3 min (major).

The absolute configuration was assigned by analogy.

(*R*)-1-(3-chlorophenyl)-1,3,4,9-tetrahydropyrano[3,4-b]indole (2.36): Following general

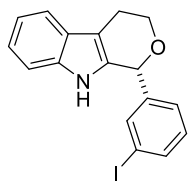


procedure **C**, the reaction was run for 2 days and **2.36** was obtained as a white solid in 73% yield; mp = 157–160 ºC; R_f = 0.18 (Hexanes/EtOAc 90:10 v/v); $[\alpha]^{D}_{20}$ –3.6 (c 0.5, $CHCl_3$, 82% ee); IR (KBr) 3394, 3052, 2957, 2922, 2837, 1718, 1621, 1596, 1571, 1461, 1433, 1296, 1253, 1078, 1041, 855, 790, 740, 705, 690 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.57 (ddd, *J* = 7.4, 1.5, 0.8 Hz, 1H), 7.45 (br s, 1H), 7.39–7.34 (comp, 2H), 7.34–7.30 (m, 1H), 7.29–7.23 (comp, 2H), 7.21–7.11 (comp, 2H), 5.77 (app t, *J* = 2.0 Hz, 1H), 4.32 (ddd, *J* = 11.3, 5.4, 3.0 Hz, 1H), 3.99 (ddd, *J* = 11.3, 9.5, 4.1 Hz, 1H), 3.10 (dddd, *J* = 15.1, 9.5, 5.4, 2.0 Hz, 1H), 2.89–2.78 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.75, 136.29, 134.95, 132.94, 130.22, 129.23, 128.59, 127.10,

126.62, 122.36, 119.96, 118.58, 111.21, 109.19, 75.61, 65.00, 22.38; *m/z* (ESI-MS) 284.1 $[M + H]^+$; HPLC: Daicel Chiralpak AS-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 280.16 nm, t_R = 8.3 min (minor) and t_R = 10.6 min (major).

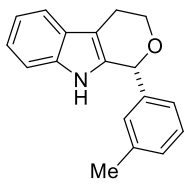
The absolute configuration was assigned by analogy.

(*R*)-1-(3-iodophenyl)-1,3,4,9-tetrahydropyrano[3,4-b]indole (2.37): Following general procedure **C**, the reaction was run for 3 days and **2.37** was obtained as a white solid in 78% yield; mp = 158–160 ºC; R_f = 0.17 (Hexanes/EtOAc 90:10 v/v); $[\alpha]^D_{20}$ +3.1 (c 0.5, $CHCl_3$, 85% ee); IR (KBr) 3399, 2957, 2914, 2864, 2822, 1568, 1468, 1296, 1076, 1056, 800, 745, 675, 465 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.78–7.67 (comp, 2H), 7.58 (app d, *J* = 7.2 Hz, 1H), 7.48 (br s, 1H), 7.34 (app d, *J* = 7.8 Hz, 1H), 7.25 (app d, *J* = 8.2 Hz, 1H), 7.22–7.14 (comp, 2H), 7.12 (app t, *J* = 7.7 Hz, 1H), 5.71 (app t, *J* = 1.9 Hz, 1H), 4.31 (ddd, *J* = 11.3, 5.3, 2.9 Hz, 1H), 3.98 (ddd, *J* = 11.3, 9.6, 4.1 Hz, 1H), 3.11 (dddd, *J* = 15.2, 9.7, 5.4, 2.1 Hz, 1H), 2.89–2.79 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.94, 138.11, 137.32, 136.22, 132.87, 130.62, 127.77, 127.01, 122.30, 119.90, 118.54, 111.21, 109.10, 94.86, 75.46, 64.99, 22.33; *m/z* (ESI-MS) 376.0 $[M + H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 280.16 nm, t_R = 14.2 min (minor) and t_R = 17.1 min (major).



The absolute configuration was assigned by analogy.

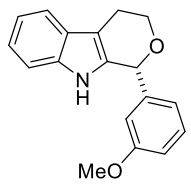
(*R*)-1-(m-tolyl)-1,3,4,9-tetrahydropyrano[3,4-b]indole (2.38): Following general procedure **C**, the reaction was run for 2 days and **2.38** was obtained as a white solid in 86% yield; mp = 126–128 ºC; R_f = 0.17 (Hexanes/EtOAc 90:10 v/v); $[\alpha]^D_{20}$ –4.9 (c 0.5, $CHCl_3$, 86% ee); IR (KBr) 3399, 3024, 2962, 2917, 2832, 1611, 1466, 1443, 1368, 1291, 1276, 1138, 1076, 1043, 748, 690 cm^{-1}; ^1H



NMR (500 MHz, $CDCl_3$) δ 7.61–7.55 (m, 1H), 7.47 (br s, 1H), 7.32–7.27 (m, 1H), 7.27–7.22 (m, 1H), 7.22–7.12 (comp, 5H), 5.76 (app t, *J* = 2.0 Hz, 1H), 4.35 (ddd, *J* = 11.5, 5.5, 2.8 Hz, 1H), 4.05–3.93 (m, 1H), 3.19–3.05 (m, 1H), 2.84 (dddd, *J* = 15.5, 3.9, 2.7, 1.4 Hz, 1H), 2.35 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.48, 138.76, 136.14, 133.91, 129.84, 129.10, 128.78, 127.17, 125.67, 122.02, 119.75, 118.45, 111.14, 108.79, 76.37, 65.10, 22.44, 21.51; *m/z* (ESI-MS) 264.2 $[M + H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 254.16 nm, t_R = 11.4 min (minor) and t_R = 19.7 min (major).

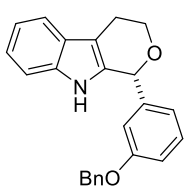
The absolute configuration was assigned by analogy.

(*R*)-1-(3-methoxyphenyl)-1,3,4,9-tetrahydropyrano[3,4-b]indole (2.39): Following general procedure **C**, the reaction was run for 2 days and **2.39** was obtained as a white solid in 82% yield; mp = 107–109 ºC; R_f = 0.14 (Hexanes/EtOAc 90:10 v/v); $[\alpha]^D_{20}$ –2.6 (c 0.5, $CHCl_3$, 86% ee); IR (KBr) 3284, 3049, 2939, 2894, 2844, 1606, 1581, 1491, 1448, 1276, 1228, 1151, 1041, 875, 805, 763, 690 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.56 (app dd, *J* = 7.5, 1.5 Hz, 1H), 7.47 (br s, 1H), 7.34–7.27 (m, 1H), 7.24 (app dd, *J* = 6.9, 1.4 Hz, 1H), 7.19–7.11 (comp, 2H), 6.98 (app dt, *J* = 7.5, 1.2 Hz, 1H), 6.95–6.89 (comp, 2H), 5.77 (app t, *J* = 1.9 Hz, 1H), 4.36 (ddd, *J* = 11.3, 5.5, 2.8 Hz, 1H), 4.00 (ddd, *J* = 11.3, 9.8, 4.0 Hz, 1H), 3.78 (s, 3H), 3.12 (dddd, *J* = 15.3, 9.8, 5.5, 2.1 Hz, 1H), 2.83 (dddd, *J* = 15.4, 4.3, 2.7, 1.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.19, 141.19, 136.20, 133.72, 129.95, 127.22, 122.09, 120.70, 119.78, 118.46, 114.78, 113.67, 111.16, 108.76, 76.27, 65.12, 55.44, 22.43; *m/z* (ESI-MS) 280.3 $[M + H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 280.16 nm, t_R = 15.8 min (minor) and t_R = 30.7 min (major).



The absolute configuration was assigned by analogy.

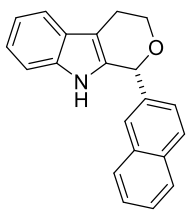
(*R*)-1-(3-(benzyloxy)phenyl)-1,3,4,9-tetrahydropyrano[3,4-b]indole (2.40): Following



general procedure **C**, the reaction was run for 3 days and **2.40** was obtained as a white solid in 87% yield; mp = 154–156 ºC; R_f = 0.15 (Hexanes/EtOAc 90:10 v/v); $[\alpha]^{D}_{20}$ –9.0 (c 0.5, $CHCl_3$, 90% ee); IR (KBr) 3439, 3059, 3032, 2959, 2917, 2857, 1586, 1491, 1446, 1256, 1153, 1071, 1038, 735, 693 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.57–7.54 (m, 1H), 7.44–7.37 (comp, 3H), 7.37–7.33 (comp, 2H), 7.33–7.28 (comp, 2H), 7.25–7.22 (m, 1H), 7.19–7.11 (comp, 2H), 7.03–6.94 (comp, 3H), 5.77 (app t, *J* = 1.8 Hz, 1H), 5.05 (d, *J* = 11.6 Hz, 1H), 5.02 (d, *J* = 11.5 Hz, 1H), 4.34 (ddd, *J* = 11.4, 5.4, 2.8 Hz, 1H), 4.02–3.95 (m, 1H), 3.15–3.04 (m, 1H), 2.87–2.76 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.31, 141.19, 136.90, 136.17, 133.65, 130.04, 128.70, 128.14, 127.70, 127.19, 122.10, 120.95, 119.80, 118.48, 115.61, 114.61, 111.19, 108.78, 76.21, 70.15, 65.13, 22.43; *m/z* (ESI-MS) 356.3 $[M + H]^+$; HPLC: Daicel Chiralpak AS-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 254.16 nm, t_R = 12.0 min (minor) and t_R = 15.8 min (major).

The absolute configuration was assigned by analogy.

(*R*)-1-(naphthalen-2-yl)-1,3,4,9-tetrahydropyrano[3,4-b]indole (2.41): Following general

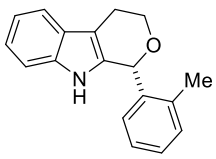


procedure **C**, the reaction was run for 2 days and **2.41** was obtained as a white solid in 86% yield; mp = 185–187 ºC; R_f = 0.21 (Hexanes/EtOAc 90:10 v/v); $[\alpha]^{D}_{20}$ –104.6 (c 0.5, $CHCl_3$, 88% ee); IR (KBr) 3378, 3042, 2961, 2889, 2839, 1506, 1466, 1449, 1370, 1293, 1253, 1141, 1073, 1048, 863, 824, 739, 484 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.90–7.81 (comp, 4H), 7.64–7.58 (m, 1H), 7.56–7.50 (comp, 2H), 7.49–7.44 (comp, 2H), 7.23–7.14 (comp, 3H), 5.94 (app t, *J* = 1.9 Hz, 1H), 4.37 (ddd, *J* = 11.3, 5.4, 3.0 Hz, 1H), 4.04 (ddd, *J* = 11.2, 9.5, 4.1 Hz, 1H), 3.16 (dddd, *J* = 15.2, 9.5, 5.4, 2.1 Hz, 1H), 2.95–2.79 (m, 1H); ^{13}C NMR (125 MHz,

$CDCl_3$) δ 137.02, 136.21, 133.73, 133.28, 128.94, 128.22, 127.89, 127.72, 127.18, 126.61, 126.50, 125.99, 122.11, 119.80, 118.50, 111.18, 108.94, 76.36, 64.95, 22.47; *m/z* (ESI-MS) 300.1 $[M + H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 280.16 nm, t_R = 20.0 min (minor) and t_R = 25.0 min (major).

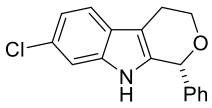
The absolute configuration was assigned by analogy.

(*R*)-1-(o-tolyl)-1,3,4,9-tetrahydropyrano[3,4-b]indole (2.42): Following general procedure **C**, the reaction was run for 2 days and **2.42** was obtained as a white solid in 91% yield; mp = 98–100 ºC; R_f = 0.26 (Hexanes/EtOAc 90:10 v/v); $[\alpha]^D_{20}$ –4.5 (c 0.5, $CHCl_3$, 48% ee); IR (KBr) 3397, 3289, 3052, 2954, 2909, 2847, 1453, 1303, 1256, 1076, 1041, 740 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.60–7.54 (m, 1H), 7.47 (br s, 1H), 7.30–7.22 (comp, 3H), 7.20–7.10 (comp, 4H), 6.02 (app t, *J* = 2.1 Hz, 1H), 4.29 (ddd, *J* = 11.3, 5.2, 3.5 Hz, 1H), 3.99 (ddd, *J* = 11.4, 9.0, 4.1 Hz, 1H), 3.08 (dddd, *J* = 16.1, 9.0, 5.3, 1.9 Hz, 1H), 2.87 (app dtd, *J* = 15.4, 4.0, 1.8 Hz, 1H), 2.42 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.83, 137.15, 136.09, 133.58, 131.26, 129.49, 128.95, 127.15, 126.17, 121.99, 119.77, 118.39, 111.11, 109.21, 73.98, 64.70, 22.47, 19.14; *m/z* (ESI-MS) 264.2 $[M + H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 280.16 nm, t_R = 10.5 min (minor) and t_R = 16.6 min (major).



The absolute configuration was assigned by analogy.

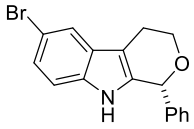
(*R*)-7-chloro-1-phenyl-1,3,4,9-tetrahydropyrano[3,4-b]indole (2.43): Following general procedure **C**, the reaction was run for 4 days and **2.43** was obtained as a white solid in 89% yield; mp = 106–108 ºC; R_f = 0.18 (Hexanes/EtOAc 90:10 v/v); $[\alpha]^D_{20}$ +25.2 (c 0.5, $CHCl_3$, 94% ee); IR (KBr) 3414, 3279, 2964, 2917, 2837, 1451, 1301, 1241, 1146, 1051, 903, 850, 803, 755, 690 cm^{-1}; ^1H NMR (500 MHz) δ 7.45 (s,



1H), 7.44 (br s, 1H), 7.41–7.33 (comp, 5H), 7.22–7.19 (m, 1H), 7.11–7.08 (m, 1H), 5.76 (app t, *J* = 1.9 Hz, 1H), 4.32 (ddd, *J* = 11.4, 5.5, 2.9 Hz, 1H), 3.98 (ddd, *J* = 11.3, 9.8, 4.0 Hz, 1H), 3.15–3.00 (m, 1H), 2.85–2.72 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 139.27, 136.48, 134.47, 129.20, 129.03, 128.51, 127.82, 125.79, 120.46, 119.28, 111.14, 109.02, 76.14, 64.89, 22.30; *m/z* (ESI-MS) 284.2 $[M + H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 254.16 nm, t_R = 9.9 min (minor) and t_R = 14.1 min (major).

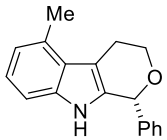
The absolute configuration was assigned by analogy.

(*R*)-6-bromo-1-phenyl-1,3,4,9-tetrahydropyrano[3,4-b]indole (2.44): Following general procedure **C**, the reaction was run for 4 days and **2.44** was obtained as a white solid in 91% yield; mp = 100–102 ºC; R_f = 0.21 (Hexanes/EtOAc 90:10 v/v); $[\alpha]^D_{20}$ –62.5 (c 0.5, $CHCl_3$, 92% ee); IR (KBr) 3414, 3282, 2954, 2917, 2842, 1451, 1296, 1078, 1043, 986, 793 ,698 cm^{-1}; ^{1}H NMR (500 MHz) δ 7.67 (s, 1H), 7.46 (br s, 1H), 7.43–7.33 (comp, 5H), 7.25–7.21 (m, 1H), 7.12–7.08 (m, 1H), 5.78 (app t, *J* = 2.0 Hz, 1H), 4.33 (ddd, *J* = 11.5, 5.5, 2.8 Hz, 1H), 4.02–3.94 (m, 1H), 3.06 (dddd, *J* = 15.5, 9.6, 5.6, 2.0 Hz, 1H), 2.81–2.74 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.25, 135.24, 134.78, 129.21, 129.06, 128.98, 128.47, 124.88, 121.22, 113.04, 112.52, 108.66, 76.20, 65.00, 22.29; *m/z* (ESI-MS) 328.1 (^{79}Br) $[M + H]^+$, 330.1 (^{81}Br) $[M + H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 280.16 nm, t_R = 13.9 min (minor) and t_R = 21.1 min (major).



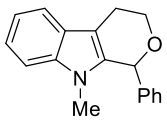
The absolute configuration was assigned by analogy.

(*R*)-5-methyl-1-phenyl-1,3,4,9-tetrahydropyrano[3,4-b]indole (2.45): Following general procedure **C**, the reaction was run for 4 days and **2.45** was obtained as a white solid in 75% yield; mp = 155–158 ºC; R_f = 0.20 (Hexanes/EtOAc 90:10 v/v); $[\alpha]^{D}_{20}$ –45.9 (c 0.5, $CHCl_3$, 81% ee); IR (KBr) 3294, 2979, 2937, 2849, 1443, 1373, 1333, 1141, 1073, 1041, 976, 750, 698 cm^{-1}; ^1H NMR (500 MHz) δ 7.47–7.32 (comp, 6H), 7.08–6.98 (comp, 2H), 6.87–6.82 (m, 1H), 5.80 (app t, *J* = 1.9 Hz, 1H), 4.31 (ddd, *J* = 11.4, 5.5, 2.9 Hz, 1H), 3.98 (ddd, *J* = 11.3, 9.7, 4.0 Hz, 1H), 3.35 (dddd, *J* = 15.3, 9.8, 5.5, 2.2 Hz, 1H), 3.14–3.06 (m, 1H), 2.69 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.69, 136.10, 133.29, 130.74, 129.06, 128.96, 128.58, 126.21, 122.09, 120.93, 109.15, 108.86, 76.44, 65.24, 24.95, 19.71; *m/z* (ESI-MS) 264.1 $[M + H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 280.16 nm, t_R = 19.1 min (major) and t_R = 26.7 min (minor).



The absolute configuration was assigned by analogy.

9-methyl-1-phenyl-1,3,4,9-tetrahydropyrano[3,4-b]indole (2.46): Following general procedure **C**, the reaction was run at room temperature for 24 hours and **2.46** was obtained as a white solid in 62 % yield; mp = 103–105 ºC; R_f = 0.36 (Hexanes/EtOAc 90:10 v/v); IR (KBr) 3029, 2977, 2917, 2854, 1466, 1378, 1258, 1183, 1056, 898, 735, 698, 615, 503 cm^{-1}; ^1H NMR (500 MHz) δ 7.63–7.60 (m, 1H), 7.41–7.35 (comp, 3H), 7.34–7.29 (comp, 2H), 7.29–7.28 (m, 1H), 7.28–7.23 (m, 1H), 7.20–7.15 (m, 1H), 5.92 (app t, *J* = 1.3 Hz, 1H), 4.04 (app dt, *J* = 11.4, 5.6 Hz, 1H), 3.94 (app dt, *J* = 11.3, 5.2 Hz, 1H), 3.28 (s, 3H), 2.99–2.95 (comp, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.65, 137.30, 134.09, 129.09, 128.85, 128.78, 126.60, 121.61, 119.26, 118.43, 109.00, 108.59, 74.66, 62.13, 30.29, 22.50; *m/z* (ESI-MS) 264.2 $[M + H]^+$; HPLC: Daicel



Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 280.16 nm, t_R = 9.8 min and 13.3 min.

3-(2-(methoxy(phenyl)methoxy)ethyl)-1H-indole (2.47): To a solution of tryptophol (0.5 g, 3.1 mmol, 1 equiv) in CH_2Cl_2 (62 mL, 0.05 M) was added benzaldehyde dimethyl acetal (0.70 mL, 4.65 mmol, 1.5 equiv) and pyridinium *p*-toluenesulfonate (39 mg, 0.16 mmol, 5 mol%). The reaction mixture was stirred at room temperature for 1 hour before being quenched with trimethylamine (0.1 mL). The resulting mixture was then concentrated under reduced pressure and purified by flash chromatography on silica gel to afford **2.47** as a colorless oil in 16% yield. R_f = 0.31 (Hexanes/EtOAc 85:15 v/v); IR (film) 3409, 3054, 2927, 2872, 2361, 1453, 1418, 1353, 1203, 1098, 1043, 740, 703 cm^{-1}; ^1H NMR (500 MHz) δ 7.97 (br s, 1H), 7.63–7.60 (m, 1H), 7.51–7.46 (comp, 2H), 7.41–7.30 (comp, 4H), 7.20 (ddd, *J* = 8.1, 7.0, 1.2 Hz, 1H), 7.13 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 7.05–7.03 (m, 1H), 5.52 (s, 1H), 3.90 (app dt, *J* = 9.4, 7.2 Hz, 1H), 3.81 (app dt, *J* = 9.5, 7.2 Hz, 1H), 3.32 (s, 3H), 3.15–3.10 (comp, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.55, 136.24, 128.51, 128.30, 127.65, 126.82, 122.14, 122.00, 119.33, 118.92, 113.01, 111.17, 102.69, 66.08, 52.80, 25.93; *m/z* (ESI-MS) 250.1 $[M - OMe]^+$.

References

(1) Braun, M.; Kotter, W. *Angew. Chem. Int. Ed.* **2004**, *43*, 514.
(2) Evans, D. A.; Thomson, R. J. *J. Am. Chem. Soc.* **2005**, *127*, 10506.
(3) Umebayashi, N.; Hamashima, Y.; Hashizume, D.; Sodeoka, M. *Angew. Chem. Int. Ed.* **2008**, *47*, 4196.
(4) Reisman, S. E.; Doyle, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2008**, *130*, 7198.
(5) Moquist, P. N.; Kodama, T.; Schaus, S. E. *Angew. Chem. Int. Ed.* **2010**, *49*, 7096.
(6) Čorić, I.; Vellalath, S.; List, B. *J. Am. Chem. Soc.* **2010**, *132*, 8536.
(7) Čorić, I.; Müller, S.; List, B. *J. Am. Chem. Soc.* **2010**, *132*, 17370.
(8) Kobayashi, S.; Arai, K.; Yamakawa, T.; Chen, Y. J.; Salter, M. M.; Yamashita, Y. *Adv. Synth. Catal.* **2011**, *353*, 1927.
(9) Burns, N. Z.; Witten, M. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2011**, *133*, 14578.
(10) Maity, P.; Srinivas, H. D.; Watson, M. P. *J. Am. Chem. Soc.* **2011**, *133*, 17142.
(11) Rueping, M.; Volla, C. M. R.; Atodiresei, I. *Org. Lett.* **2012**, *14*, 4642.
(12) Terada, M.; Yamanaka, T.; Toda, Y. *Chem. Eur. J.* **2013**, *19*, 13658.
(13) Zi, W.; Toste, F. D. *J. Am. Chem. Soc.* **2013**, *135*, 12600.
(14) Witten, M. R.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2014**, *53*, 5912.
(15) Dasgupta, S.; Rivas, T.; Watson, M. P. *Angew. Chem. Int. Ed.* **2015**, *54*, 14154.
(16) Qian, H.; Zhao, W.; Wang, Z.; Sun, J. *J. Am. Chem. Soc.* **2015**, *137*, 560.
(17) Luan, Y.; Barbato, K. S.; Moquist, P. N.; Kodama, T.; Schaus, S. E. *J. Am. Chem. Soc.* **2015**, *137*, 3233.
(18) Gheewala, C. D.; Collins, B. E.; Lambert, T. H. *Science* **2016**, *351*, 961.
(19) Zhang, Q. W.; Fan, C. A.; Zhang, H. J.; Tu, Y. Q.; Zhao, Y. M.; Gu, P.; Chen, Z. M. *Angew. Chem. Int. Ed.* **2009**, *48*, 8572.
(20) Terada, M.; Tanaka, H.; Sorimachi, K. *J. Am. Chem. Soc.* **2009**, *131*, 3430.
(21) Coric, I.; List, B. *Nature* **2012**, *483*, 315.
(22) Borovika, A.; Tang, P.-I.; Klapman, S.; Nagorny, P. *Angew. Chem. Int. Ed.* **2013**, *52*, 13424.
(23) Lu, C.; Su, X.; Floreancig, P. E. *J. Org. Chem.* **2013**, *78*, 9366.
(24) Khomutnyk, Y. Y.; Argüelles, A. J.; Winschel, G. A.; Sun, Z.; Zimmerman, P. M.; Nagorny, P. *J. Am. Chem. Soc.* **2016**, *138*, 444.
(25) Cui, Y.; Villafane, L. A.; Clausen, D. J.; Floreancig, P. E. *Tetrahedron* **2013**, *69*, 7618.
(26) Meng, Z.; Sun, S.; Yuan, H.; Lou, H.; Liu, L. *Angew. Chem. Int. Ed.* **2014**, *53*, 543.
(27) Kim, J. H.; Čorić, I.; Vellalath, S.; List, B. *Angew. Chem. Int. Ed.* **2013**, *52*, 4474.
(28) Hsiao, C.-C.; Liao, H.-H.; Sugiono, E.; Atodiresei, I.; Rueping, M. *Chem. Eur. J.* **2013**, *19*, 9775.
(29) Lalli, C.; van de Weghe, P. *Chem. Commun.* **2014**, *50*, 7495.
(30) Tsui, G. C.; Liu, L.; List, B. *Angew. Chem. Int. Ed.* **2015**, *54*, 7703.
(31) Renzi, P.; Bella, M. *Chem. Commun.* **2012**, *48*, 6881.
(32) Morales, S.; Guijarro, F. G.; García Ruano, J. L.; Cid, M. B. *J. Am. Chem. Soc.* **2014**, *136*, 1082.
(33) Morales, S.; Guijarro, F. G.; Alonso, I.; García Ruano, J. L.; Cid, M. B. *ACS Catal.* **2016**, *6*, 84
(34) Knoevenagel, E. *Chem. Ber.* **1894**, *27*, 2345.
(35) List, B. *Angew. Chem. Int. Ed.* **2010**, *49*, 1730.
(36) Xu, D. Q.; Wang, Y. F.; Luo, S. P.; Zhang, S.; Zhong, A. G.; Chen, H.; Xu, Z. Y. *Adv. Synth. Catal.* **2008**, *350*, 2610.
(37) Wang, Y.-F.; Zhang, W.; Luo, S.-P.; Li, B.-L.; Xia, A.-B.; Zhong, A.-G.; Xu, D.-Q. *Chem. Asian J.* **2009**, *4*, 1834.

(38) Yin, G.; Zhang, R.; Li, L.; Tian, J.; Chen, L. *Eur. J. Org. Chem.* **2013**, *2013*, 5431.
(39) Luo, H.; Yan, X.; Chen, L.; Li, Y.; Liu, N.; Yin, G. *Eur. J. Org. Chem.* **2016**, *2016*, 1702.
(40) Lee, A.; Michrowska, A.; Sulzer-Mosse, S.; List, B. *Angew. Chem. Int. Ed.* **2011**, *50*, 1707.
(41) Wang, Y.; Yu, T.-Y.; Zhang, H.-B.; Luo, Y.-C.; Xu, P.-F. *Angew. Chem., Int. Ed.* **2012,** *51,* 12339.
(42) Doyle, A. G. Ph.D. Thesis, Harvard University, Cambridge, 2008.
(43) Lombardo, V. M.; Thomas, C. D.; Scheidt, K. A. *Angew. Chem. Int. Ed.* **2013**, *52*, 12910.
(44) Ascic, E.; Ohm, R. G.; Petersen, R.; Hansen, M. R.; Hansen, C. L.; Madsen, D.; Tanner, D.; Nielsen, T. E. *Chem. Eur. J.* **2014**, *20*, 3297.
(45) Larghi, E. L.; Kaufman, T. S. *Synthesis* **2006**, 187.
(46) Moyano, A.; Rios, R. *Chem. Rev.* **2011**, *111*, 4703.
(47) Larghi, E. L.; Kaufman, T. S. *Eur. J. Org. Chem.* **2011**, *2011*, 5195.
(48) Lombardo, V. M.; Thomas, C. D.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2013,** *52,* 12910.
(49) Ascic, E.; Ohm, R. G.; Petersen, R.; Hansen, M. R.; Hansen, C. L.; Madsen, D.; Tanner, D.; Nielsen, T. E. *Chem. Eur. J.* **2014,** *20,* 3297.
(50) Sohtome, Y.; Tanatani, A.; Hashimoto, Y.; Nagasawa, K. *Tetrahedron Lett.* **2004,** *45,* 5589.
(51) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243.
(52) Marigo, M.; Wabnitz, T. C.; Fielenbach, D.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2005**, *44*, 794.
(53) Schreiner, P. R.; Wittkopp, A. *Org. Lett.* **2002,** *4,* 217.
(54) Smith, P. J.; Reddington, M. V.; Wilcox, C. S. *Tetrahedron Lett.* **1992**, *33*, 6085.
(55) Fan, E.; Van Arman, S. A.; Kincaid, S.; Hamilton, A. D. *J. Am. Chem. Soc.* **1993**, *115*, 369.
(56) Leonard, N. M.; Oswald, M. C.; Freiberg, D. A.; Nattier, B. A.; Smith, R. C.; Mohan, R. S. *J. Org. Chem.* **2002,** *67,* 5202.
(57) Xu, H.; Zuend, S. J.; Woll, M. G.; Tao, Y.; Jacobsen, E. N. *Science* **2010,** *327,* 986.
(58) Das, S.; Liu, L.; Zheng, Y.; Alachraf, M. W.; Thiel, W.; De, C. K.; List, B. *J. Am. Chem. Soc.* **2016,** *138,* 9429.
(59) Zheng, C.; You, S.-L. *Chem. Soc. Rev.* **2012,** *41,* 2498.
(60) Wan, M.; Sun, S.; Li, Y.; Liu, L. *Angew. Chem., Int. Ed.* **2017,** *56,* 516
(61) Marigo, M.; Wabnitz, T. C.; Fielenbach, D.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2005**, *44*, 794.
(62) Alatorre-Santamaría, S.; Rodriguez-Mata, M.; Gotor-Fernández, V.; de Mattos, M. C.; Sayago, F. J.; Jiménez, A. I.; Cativiela, C.; Gotor, V. *Tetrahedron: Asymmetry* **2008**, *19*, 1714.
(63) Torisu, K.; Kobayashi, K.; Iwahashi, M.; Nakai, Y.; Onoda, T.; Nagase, T.; Sugimoto, I.; Okada, Y.; Matsumoto, R.; Nanbu, F.; Ohuchida, S.; Nakai, H.; Toda, M. *Bioorg. Med. Chem.* **2004**, *12*, 5361.
(64) Sohtome, Y.; Tanatani, A.; Hashimoto, Y.; Nagasawa, K. *Tetrahedron Lett.* **2004**, *45*, 5589.
(65) Karagiannidis, L. E.; Hiscock, J. R.; Gale, P. A. *Supramol. Chem.* **2013**, *25*, 626.
(66) Kotke, M.; Schreiner, P. R. *Tetrahedron* **2006**, *62*, 434.
(67) Tommasino, M. L.; Thomazeau, C.; Touchard, F.; Lemaire, M. *Tetrahedron: Asymmetry* **1999**, *10*, 1813.
(68) Gawronski, J.; Kwit, M.; Skowronek, P. *Org. Biomol. Chem.* **2009**, *7*, 1562.
(69) Brown, H. C.; McDaniel, D. H. *J. Am. Chem. Soc.* **1955**, *77*, 3752.
(70) Chrystiuk, E.; Williams, A. *J. Am. Chem. Soc.* **1987**, *109*, 3040.
(71) Collot, A.-G.; Courtney, M.; Coyne, D.; Eustace, S. E.; More O'Ferrall, R. A. *J. Org. Chem.* **2009**, *74*, 3356.

(72) Gardner, J. N.; Katritzky, A. R. *Journal of the Chemical Society* **1957**, 4375.
(73) Brown, A. R.; Kuo, W.-H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2010**, *132*, 9286.
(74) Tan, K. L.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2007**, *46*, 1315.
(75) Odabachian, Y.; Wang, Q.; Zhu, J. *Chem.–Eur. J.* **2013**, *19*, 12229.
(76) Zhao, C.; Seidel, D. *J. Am. Chem. Soc.* **2015**, *137*, 4650.

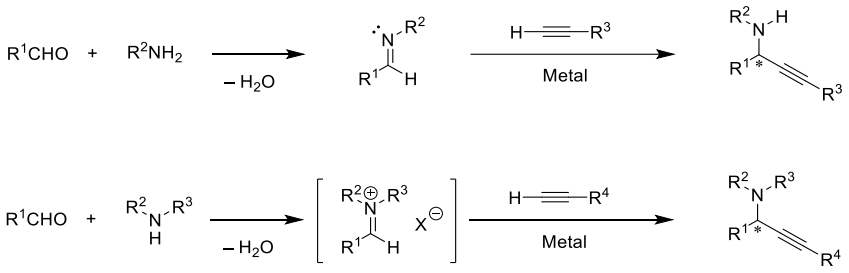
Chapter III Metal/Acid–Thiourea Cooperative Dual Catalysis

3.1 Background

3.1.1 A^3 Reactions

Propargylamines are compounds of substantial synthetic value and are most readily accessed by addition of terminal alkynes to imines or iminium ions (Scheme 3.1).[1–4] When the imine or iminium ion is prepared in situ from an aldehyde and an amine, these transformations are referred to as A^3 coupling. Pioneered by Carreira[5] and Li,[6] many transition metals have been demonstrated to catalyze the A^3 reaction featuring different substrate sets, among which Cu has been most widely used. [1–4]

Scheme 3.1 The A^3 coupling reactions with primary and secondary amines.



In 2002, Li reported the first highly enantioselective A^3 coupling between phenylacetylene and various imines generated *in situ* from anilines and aromatic aldehydes (Scheme 3.2).[7] Tridentate bis(oxazolinyl)pyridine (pybox) ligands outperformed bidentate bis(oxazoline) (box) and other chiral ligands evaluated. CuOTf and toluene proved to be optimal among other metal sources and solvents. High levels of reactivity and enantioselectivity are obtained with a wide variety of substituted aromatic aldehydes. Albeit with slight attenuated yields and ee's, water was also demonstrated as a viable solvent for these reactions with satisfactory results.

Following Li's seminal work, enantioselective A^3 reactions of primary amines has been extensively studied with various ligand types such as (py)box,[8–15] pybim,[16,17] imino[18–23] and amino[24,25] (Figure 3.1) as well as additives[26] and other metal sources such as Zn,[27–31] Zr[32] and Ag.[33]

Scheme 3.2 The first enantioselective A^3 coupling reactions by Li.

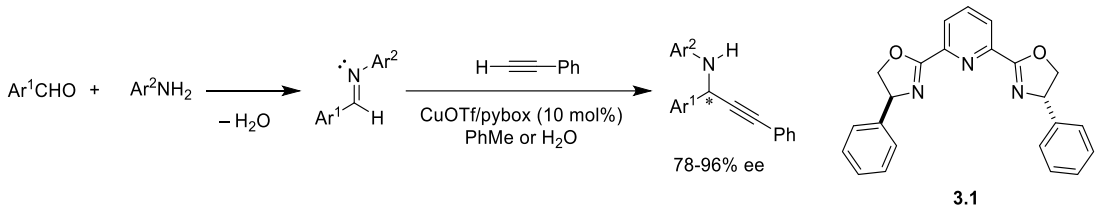
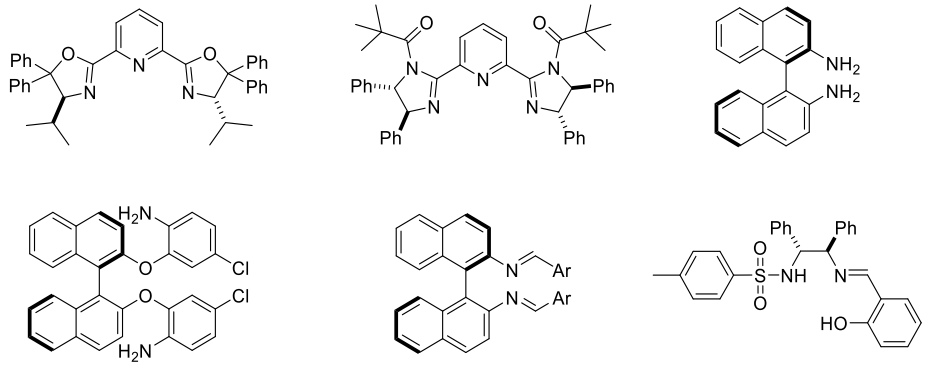


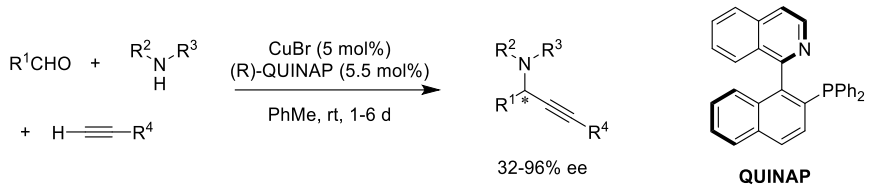
Figure 3.1 Representative ligands studied in enantioselective A^3 reactions with primary amines.



Despite the extensive reports on enantioselective A^3 reactions, methods accommodating secondary amines are rare.[34–42] The first catalytic enantioselective A^3 reaction with secondary amines was reported by Knochel and coworkers who employed CuBr in combination with QUINAP (Scheme 3.3).[34] Dibenzyl and diallyl amines are used in combination of various aldehydes and alkynes. Aliphatic aldehydes are well tolerated while aromatic ones give slightly inferior results. Electronics on the aromatic aldehydes has minor effect on the selectivity but the electron deficient *para*-CF_3 group results in considerable loss of the reactivity. Both aliphatic and aromatic alkynes are well tolerated with

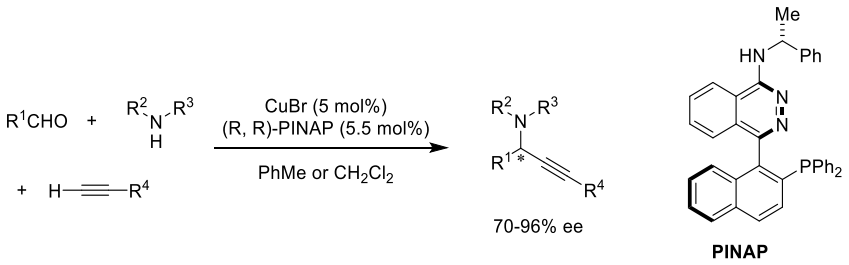
trimethylsilylacetylene affording the best selectivity. Mechanistic studies show a strong positive non-linear effect, in accord with a dimeric Cu-QUINAP crystal structure. The strong positive non-linear effect can be attributed to the heterochiral metal complex reacting at a significantly slower rate than the homochiral metal complex.

Scheme 3.3 QUINAP enabled enantioselective A^3 coupling reactions with secondary amines.



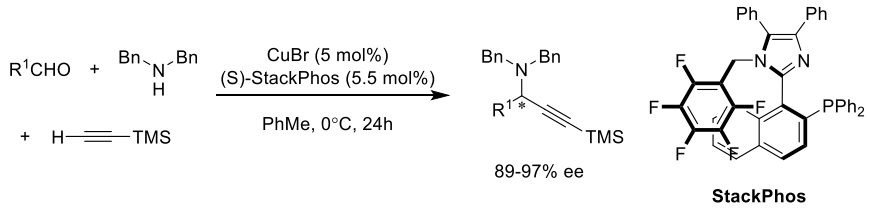
Carreira reported an important class of P, N ligands named PINAP, with the design notion that an additional chiral group would facilitate the resolution during ligand preparation by column chromatography or crystallization.[38] This is especially attracting given the popular yet expensive QUINAP ligand requires a nontrivial synthesis, including a resolution step using a preformed chiral Pd complex. The QUINAP/CuBr system shows excellent reactivity and selectivity towards the enantioselective A^3 reactions with dibenzylamine and 4-piperidone (Scheme 3.4).[39] Aliphatic aldehydes are well tolerated while benzaldehyde is considerably less reactive. Similar to Knochel's report, trimethylsilylacetylene displays highest level of selectivity.

Scheme 3.4 PINAP enabled enantioselective A^3 coupling reactions with secondary amines.



QUINAP and PINAP represent a class of atropisomeric P, N ligands featuring fused 6-membered aromatic rings.[43] When 5-membered heteroaromatic rings are used, a reduced rotation barrier is encountered, making ligand design unfavorable in terms of conformational stability.[44] In 2013, Aponick introduced a new class of P, N ligand later named StackPhos, with the design notion that stabilization of the catalyzed conformation can be realized by π-stacking (Scheme 3.5).[41] Such stabilization mechanism is further supported by the conformational instability of a nonfluorinated ligand. The StackPhos/CuBr system affords enantioselective A^3 reactions with excellent yields and ee's for both aromatic and aliphatic aldehydes in combination with trimethylsilylacetylene and dibenzylamine.

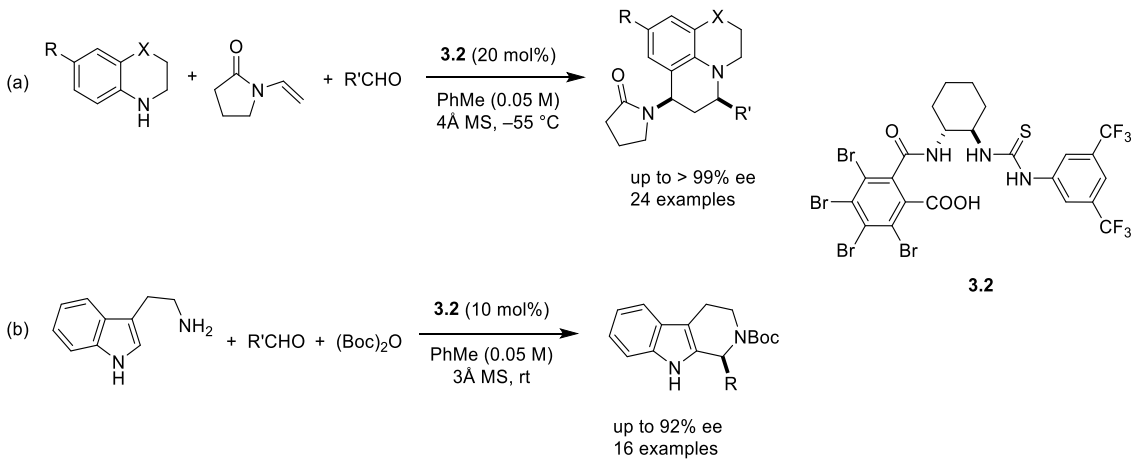
Scheme 3.5 StackPhos enabled enantioselective A^3 coupling reactions with secondary amines.



3.1.2 Conjugate-Base-Stabilized Brønsted Acids

Chiral Brønsted acid catalysis has been a versatile strategy towards numerous chemical transformations,[45] with chiral phosphoric acids being most popular.[46] On the other hand, chiral carboxylic acids, albeit abundant, are less frequently used in asymmetric catalysis.[47] One main disadvantage of carboxylic acids is their intrinsic weaker acidity compared to phosphoric acids. Our group designed a new class of chiral Brønsted acids, with the design notion that an intramolecularly tethered anion-binding moiety would bind with the conjugate base thus increasing the Brønsted acidity as well as the structure rigidity.[48] Meanwhile, the interaction between the conjugate base and cationic intermediate will be attenuated, resulting in an increased electrophilicity of the latter. A number of chiral

Brønsted acids based on this design notion were prepared and applied to the enantioselective Povarov reactions with secondary amines. Readily accessible catalyst **3.2** proved to be optimal, affording the desired products with excellent yields and ee's. With regard to the substrate scope, both aliphatic and diversely substituted aromatic aldehydes, indolines with different *para*-substituents as well as *N*-vinylacetamide as dienophile are well tolerated. The versatility of catalyst **3.2** was further demonstrated by its application in the enantioselective Pictet–Spengler reactions with unmodified tryptamine[49] and an intramolecular version of the Povarov reaction.[50]



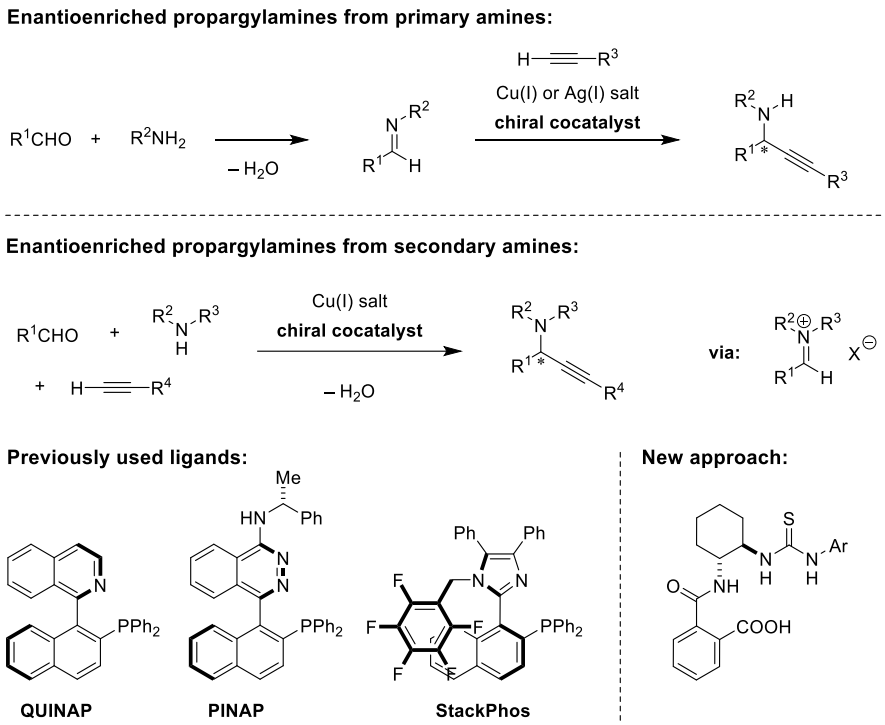
Scheme 3.6 Conjugate-base-stabilized chiral Brønsted acid and its application.

3.2 Enantioselective A^3 Reactions of Secondary Amines with a Cu(I)/Acid−Thiourea Catalyst Combination

As mentioned in previous section, the catalytic enantioselective synthesis of propargylamines derived from primary amines is a well-developed process, most commonly utilizing copper (I) catalysis and ligands such as pybox. Copper and silver salts have also been used in combination with different organocatalysts. When secondary rather than primary amines are employed, the nature of the reaction changes dramatically as do the

requirements for asymmetric catalysis. Rather than involving imines as intermediates, secondary amines by necessity require the initial formation of iminium ions. Presumably because of this added difficulty, substantially fewer reports have addressed the challenge of performing catalytic enantioselective A^3 reactions with secondary amines (Scheme 3.7). Without exception, these processes require the use of a phosphine-based ligand. Trimethylsilylacetylene is used predominantly and is often required to achieve high enantioselectivities. The conjugate-base-stabilized Brønsted acid catalyst developed by our group demonstrated high efficiency towards asymmetric Povarov reactions with secondary amines. As these reactions are thought to proceed via intermediates related to secondary iminium ion, we reasoned that such carboxylic acid-thioureas catalyst might serve as effective chiral cocatalysts in Cu(I)-catalyzed A^3 reactions.

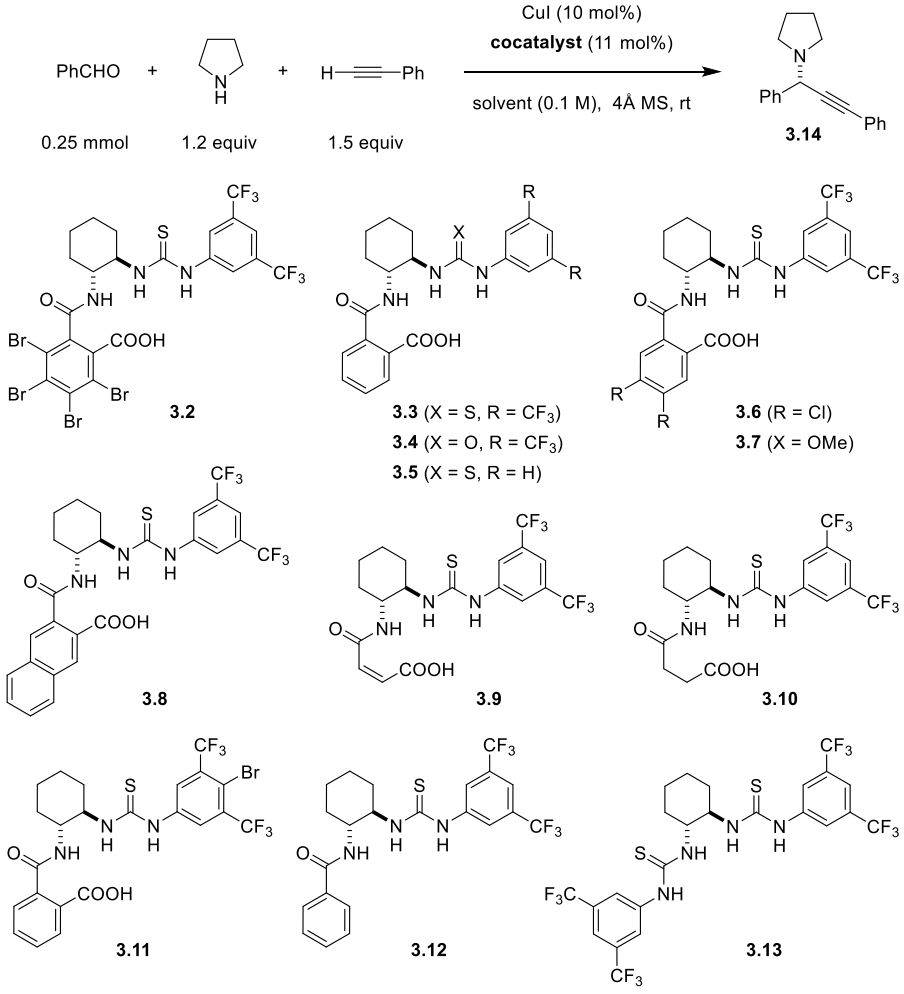
Scheme 3.7 Synthesis of enantioenriched propargylamines via A^3 coupling reactions.



3.2.1 Optimization

Benzaldehyde, pyrrolidine and phenylacetylene were selected as model substrates to evaluate the title reaction (Table 3.1). Indeed, catalyst **3.2**, when used in combination with CuI, facilitated the formation of product **3.14** in good yield albeit with only 20% ee (entry 1). Interestingly, acid-thiourea **3.3**, a poor catalyst for Povarov[48] and Pictet-Spengler[49] reactions, provided a marked increase in enantioselectivity (entry 2). Subsequent evaluation of various solvents led to further improvements with dichloromethane providing the best results (entry 3). Interestingly, replacement of CuI for either CuBr or CuCl led to inferior results (entries 4 and 5). Remarkably, and in stark contrast to our earlier studies, urea catalyst **3.4** was equally active as thiourea **3.2**. However, product **3.14** was obtained in racemic form (entry 6).

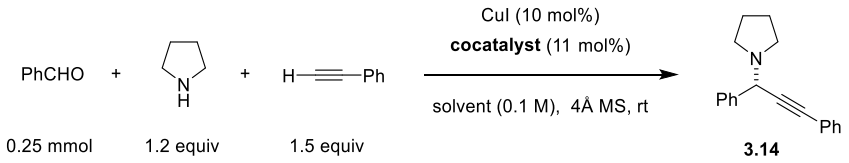
Table 3.1 Optimization of reaction conditions.



entry	cocatalyst	solvent	time [h]	yield (%)	ee (%)
1	**3.2**	$PhCH_3$	3	78	20
2	**3.3**	$PhCH_3$	6	91	60
3	**3.3**	CH_2Cl_2	2	90	73
4[a]	**3.3**	CH_2Cl_2	2	92	64
5[b]	**3.3**	CH_2Cl_2	3	82	25
6	**3.4**	CH_2Cl_2	3	92	0
7	**3.5**	CH_2Cl_2	4	89	14
8	**3.6**	CH_2Cl_2	2	92	64
9	**3.7**	CH_2Cl_2	2	92	73
10	**3.8**	CH_2Cl_2	2	94	70
11	**3.9**	CH_2Cl_2	4	96	42
12	**3.10**	CH_2Cl_2	4	94	-5
13	**3.11**	CH_2Cl_2	3	91	74
14	**3.12**	CH_2Cl_2	3	92	0
15	**3.13**	CH_2Cl_2	24	70	8
16[c]	**3.11**	CH_2Cl_2	3	92	82
17[c,d]	**3.11**	CH_2Cl_2	3	91	88
18[c,d,e]	**3.11**	CH_2Cl_2	12	92	92

[a] with CuBr. [b] with CuCl. [c] With 5 Å MS. [d] Reaction was run at a 1 mmol scale with 4 mol% CuI and 3 mol% cocatalyst. [e] Reaction was run at 0° C.

Table 3.2 Evaluation of other reaction parameters.



entry	cocatalyst	CuX	dehydrating agent	solvent	time (h)	yield (%)	ee (%)
1	**3.3**	CuI	4 Å MS	TBME	4	85	55
2	**3.3**	CuI	4 Å MS	DCE	2	94	71
3	**3.3**	Cu(OTf)·0.5 $PhCH_3$	4 Å MS	CH_2Cl_2	2	89	28

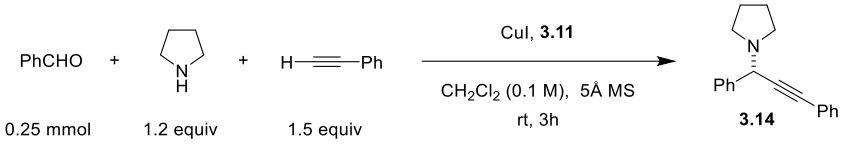
4	**3.3**	$Cu(OAc)_2 \cdot H_2O$	4 Å MS	CH_2Cl_2	2	90	–11
5	**3.3**	$Cu(CH_3CN)_4BF_4$	4 Å MS	CH_2Cl_2	3	91	–17
6	none	CuI	4 Å MS	CH_2Cl_2	3	63	-
7	none	CuI	4 Å MS	CH_2Cl_2	24	91	-
8	**3.3**	CuI	3 Å MS	CH_2Cl_2	3	91	81
9	**3.3**	CuI	Drierite[a]	CH_2Cl_2	5	57	71
10	**3.3**	CuI	Na_2SO_4	CH_2Cl_2	5	23	61
11	**3.3**	CuI	$MgSO_4$	CH_2Cl_2	5	15	57
12	**3.3**	CuI	None	CH_2Cl_2	5	10	58
13[b]	**3.11**	CuI	5 Å MS	CH_2Cl_2	12	89	92

[a] Stock# 14005, purchased from W.A. Hammond Drierite Co., Ltd. [b] Reaction was performed on a 1 mmol scale at 0 °C with 3 mol% cocatalyst, 4 mol% CuI and at a 0.05 M concentration.

Removal of the two trifluoromethyl groups on the catalyst's thiourea moiety was also detrimental (entry 7). Other modifications targeting the carboxylic acid moiety were tolerated to varying degrees but failed to provide any improvements (entries 8–12). A slightly more selective catalyst, compound **3.11**, was obtained through introduction of an additional bromine substituent between the two flanking trifluoromethyl groups (entry 13). The poor results obtained with catalyst **3.12** and the Nagasawa catalyst (**3.13**) clearly demonstrate that a carboxylic acid substituent is essential for effective catalysis (entries 14 and 15).

Further optimizations were conducted with catalyst **3.11** (Table 4.2). Replacement of 4 Å with 5 Å molecular sieves provided a boost in enantioselectivity (74 vs. 82% ee). Evaluation of various ratios of CuI and cocatalyst **3.11** led to the interesting observation that higher selectivities are obtained when CuI is used in slight excess (Table 4.3). Furthermore, the catalyst loading could be reduced and optimal results were obtained with 4 mol% of CuI and 3 mol% of **3.11**. Finally, product **3.14** was obtained with 92% ee in a reaction conducted at 0° C (entry 18).

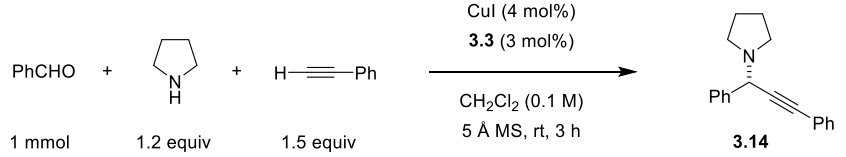
Table 3.3 Optimization of catalyst concentration and cocatalyst/metal ratio.

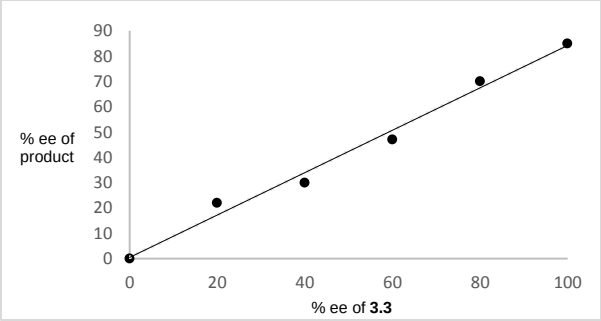


entry	**3.11** (mol%)	CuI (mol%)	yield (%)	ee (%)
1	10	10	90	83
2	4	4	92	85
3	3	3	91	87
4	2	2	88	84
5	4	3	92	80
6	3	4	91	88
7	3	5	90	88
8	3	7	92	86

It has previously been demonstrated that metal/ligand ratios can have a profound effect on the outcome of catalytic enantioselective reactions. Other cases are known in which an excess of metal salt leads to higher selectivities, due to varied aggregation behavior between the metal and the ligand.[51–53] To obtain insights into potential catalyst aggregation phenomena that might affect the catalytic process, we evaluated A^3 reactions catalyzed by **3.3** possessing varying levels of enantiopurity (Figure 3.2). However, no non-linear effects were observed.

Figure 3.2 Non-linear effect study.

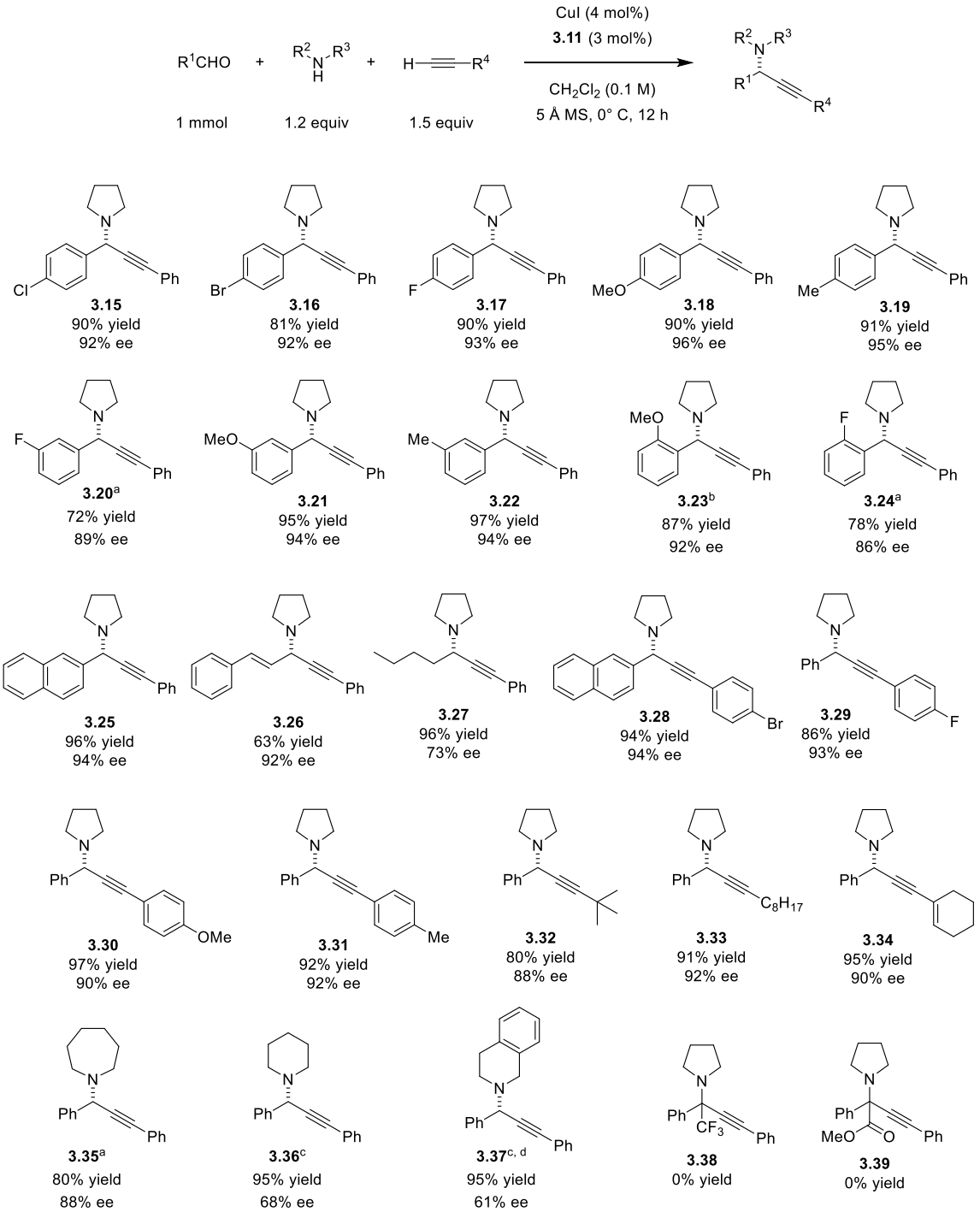




3.2.2 Substrate Scope

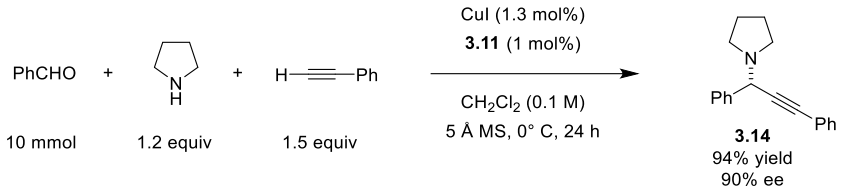
The scope of the catalytic enantioselective A^3 reaction with pyrrolidine was found to be relatively broad (Scheme 3.8). Aromatic aldehydes and terminal arylalkynes with electronically diverse substituents in different ring-positions were well tolerated. More challenging terminal alkynes with alkyl and alkenyl substituents were also viable substrates. Lower selectivities were obtained with aliphatic aldehydes. Whereas azepane performed similarly to pyrrolidine with regard to selectivity and reactivity, piperidine proved to be less reactive and provided product with reduced selectivity. Interestingly, in a reaction of 1,2,3,4-tetrahydroisoquinoline performed with CuI and **3.11** at rt for 24 h, **3.37** and its corresponding redox-A^3 product were obtained in a 6:1 ratio, and with 54% and 49% ee, respectively (77% overall yield, see Experimental Section). The use of CuBr in place of CuI allowed for the exclusive formation of **3.37**, albeit with moderate enantioselectivity. A preliminary study of ketone substrates indicated no formation of the desired products **3.38** and **3.39**. of To illustrate the utility of this process, a reaction was performed on a 10 mmol scale with only 1 mol% of **3.11** (Scheme 3.9). A high level of efficiency was maintained and product 3a was obtained in 94% yield and 90% ee.

Scheme 3.8 Substrate scope.



[a] Run at –30° C for 48 h. [b] The ee was determined after demethylation. [c] Run at rt for 24 h. [d] CuBr was used instead of CuI.

Scheme 3.9 Scale-up reaction at lower catalyst loading.

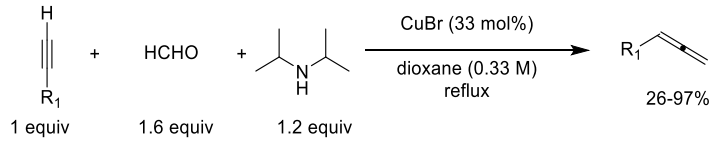


3.3 Transformation of A^3 Products to Enantioenriched Allenes

3.3.1 Background

Allenes are important synthetic intermediates as well as structural moieties incorporated in natural products and drug molecules.[54] Crabbé reported the seminal work on CuBr catalyzed allene synthesis from propargylic amines, which are synthesized via a three-component coupling reaction between formaldehyde, diisopropylamine and terminal alkynes (Scheme 3.10). It was also demonstrated that a one-pot procedure without isolating the propargylic amine also gave satisfactory results.

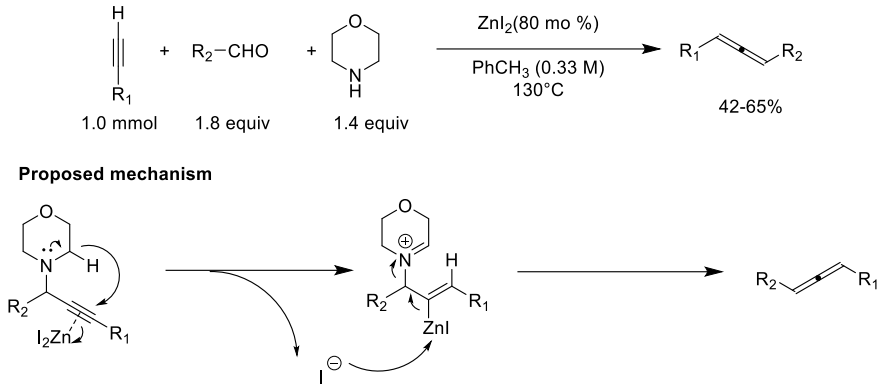
Scheme 3.10 Seminal work on allene synthesis from propargylic amines.



Following Crabbé's seminal work, many reports have emerged on this transformation, either from propargylic amines or directly from aldehydes, amines and alkynes. As a result, the substrate scope of this reaction has been largely expanded, accommodating aldehydes other than paraformaldehyde.[56,57] For example, Ma reported a one-pot procedure for 1,3-disubstituted allenes from alkynes, aldehydes, and morpholine (Scheme 3.11).[58] Cheap metal source ZnI_2 was found most efficient to promote the reaction with various aromatic and aliphatic aldehydes. Simple aliphatic alkynes, terminal propargylic alcohols as well as terminal propargylic tosylamide are all suitable substrates, affording corresponding allenes,

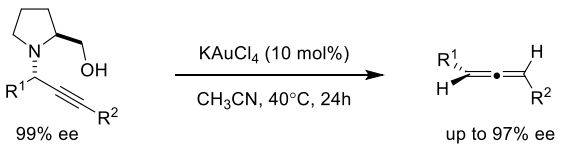
allenols and allenyl tosylamides in satisfactory yields. The authors proposed a mechanism involving a metal-promoted 1,5-hydride transfer followed by β-elimination.

Scheme 3.11 Ma's one-pot synthesis of 1,3-disubstituted allenes.



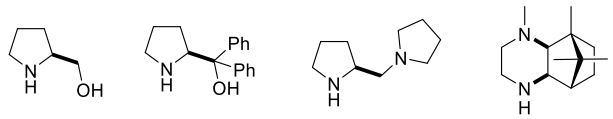
Not surprisingly, many transformations leading to enantioenriched allenes have also been reported from propargylic amines.[57] The first example was reported by Che, where the authors discovered an efficient transformation of enantioenriched propargylic amines to allenes with high level of chirality transfer (Scheme 3.12).[59] Many substituents on the aromatic ring are well tolerated including a formyl group, albeit with attenuated yield. Considerable ee loss is observed when a cyclohexenyl group is present on the alkyne. With regard to the mechanism, a peak corresponding to Au(I) adduct of the starting material is observed on electron-spray-ionization mass spectrometry, suggesting the possibility of Au(I) being the active species, presumably generated *in situ* from reduction of Au(III) by amine. Deuterium labeling experiments indicate the transferring hydride originates intramolecularly from the prolinol ring α-methylene group.

Scheme 3.12 Conversion of propargylic amines to allenes with retention of chirality by Che.

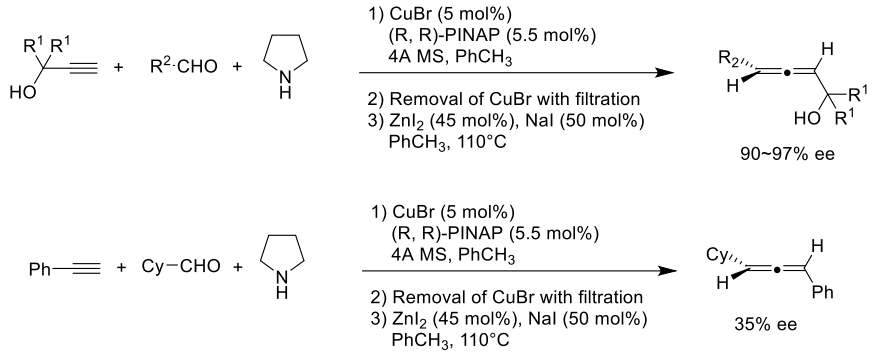


Subsequently, many similar transformations using different metals such as Ag,[60] Zn,[61,62] Cu[63] were reported, either using one-pot procedure from aldehydes, alkynes, amines or from premade propargylic amines. Without exception, the optical purity of the final allenes originate from stoichiometric use of enantioenriched cyclic amines with chirality on the 2 positions (Figure 3.3).

Figure 3.3 Commonly used enantioenriched amines for propargylamine-allene transformation.



Scheme 3.13 Catalytic enantioselective synthesis of allenes by Ma.

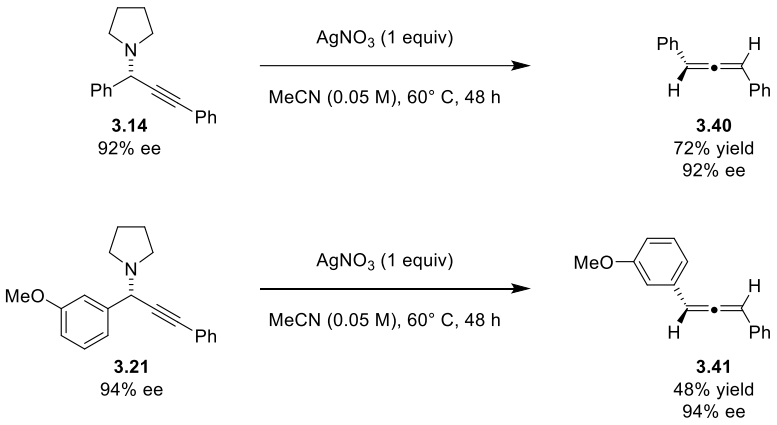


Ma reported a catalytic enantioselective synthesis of allenes from achiral aldehydes, alkynes and amines (Scheme 3.13).[64] Albeit the reaction is a two-step process, a simple filtration is sufficient between the preparation of propargylamines and the transformation into allenes. The enantiomeric excess originates from an efficient enantioselective A^3 coupling protocol enabled by CuBr/PINAP combination. The success of this method also hinges on the directing ability of a hydroxyl group on the alkyne, but it's unclear if it is involved in both steps of the reaction.

3.3.2 Results and Discussion

From the examples described above, pyrrolidine core is constantly incorporated in the propargylamine–allene transformation. With our success in enantioselective synthesis of cyclic propargylamines, we questioned the possibility of transforming them into corresponding allenes with retention of optical purity. The difference compared to all previous reported approaches is the absence of a second stereogenic center or directing group, which potentially expands the substrate scope and simplifies the starting material preparation. In preliminary experiments, we discovered $AgNO_3$ to be a suitable promoter for this transformation, albeit used in stoichiometric amount (Scheme 3.14).

Scheme 3.14 Transformation of propargylamines to allenes with retention of ee.



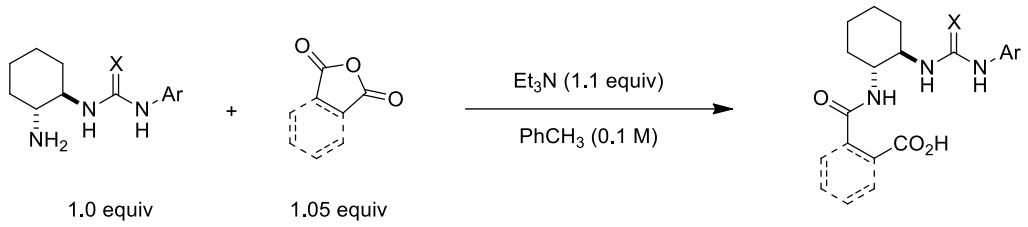
3.4 Summary

In conclusion, the cooperative catalysis between CuI and a readily available Brønsted acid cocatalyst allows for an efficient method for the synthesis of enantioenriched propargylamines from secondary amines. Propargylamines lacking directing groups can be transformed to allenes without loss of enantiopurity. This approach features the lowest catalyst loadings reported to date for catalytic enantioselective A^3 reactions with secondary amines. Incorporation of other cyclic amines as well as ketone starting materials requires a more reactive catalytic system.

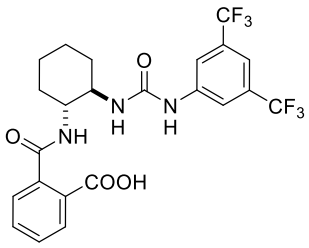
Experimental Section

General Information: Reagents and solvents were purchased from commercial sources and were purified by distillation or recrystallization prior to use. Dichloromethane was freshly distilled from calcium hydride under nitrogen prior to use. Reactions were run under a nitrogen atmosphere. Purification of reaction products was carried out by flash column chromatography using EM Reagent silica gel 60 (230–400 mesh). Analytical thin layer chromatography was performed on EM Reagent 0.25 mm silica gel 60 F_{254} plates. Visualization was accomplished with UV light, and potassium permanganate, Dragendorff-Munier and anisaldehyde stains, followed by heating. Melting points were recorded on a Thomas Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on an ATI Mattson Genesis Series FT-Infrared spectrophotometer. Proton nuclear magnetic resonance spectra (^{1}H-NMR) were recorded on a Varian VNMRS-500 MHz instrument and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 7.26 ppm, $(CD_3)_2SO$ at 2.50 ppm). Data are reported as app = apparent, s = singlet, d = doublet, t = triplet, dd = doublet of doublets, ddd = doublet of doublet of doublets, m = multiplet, comp = complex; integration; coupling constant(s) in Hz. Proton-decoupled carbon nuclear magnetic resonance spectra (^{13}C-NMR) were recorded on a Varian VNMRS-500 MHz instrument and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 77.16 ppm, $(CD_3)_2SO$ at 39.52 ppm). Mass spectra were recorded on a Finnigan LCQ-DUO mass spectrometer or on a Finnigan 2001 Fourier Transform Ion Cyclotron Resonance Mass Spectrometer. HPLC analysis was carried out on an Agilent 1100 series instrument with auto sampler and multiple wavelength detectors. Optical rotations were measured using a 1 mL cell with a 1 dm path length on a Jasco P–2000 polarimeter at 589 nm and at 20 °C. Cocatalysts **3.2**,[65] **3.3**,[65] **3.12**[66] and **3.13**[67] were prepared according to reported procedures.

General Procedure A for Catalyst Synthesis:



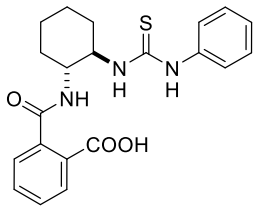
To a solution of amino(thio)urea[68,69] (2.81 mmol, 1 equiv) in toluene (28 mL, 0.1 M) in a 50 mL round bottom flask were added the corresponding anhydride (3.09 mmol, 1.1 equiv) and triethylamine (3.09 mmol, 1.1 equiv). The resulting mixture was stirred until the amino(thio)urea was consumed as indicated by TLC. The reaction mixture was concentrated and then purified by flash chromatography on silica gel using CH_2Cl_2/methanol as the eluent. The combined fractions were reduced to a volume of ca. 50 mL and washed with 1 M HCl (2 × 20 mL). The combined aqueous layers were back-extracted with ethyl acetate (2 × 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4. The solvent was then removed under reduced pressure and the resulting solid dried under high vacuum.

2-(((1*R*,2*R*)-2-(3-(3,5-Bis(trifluoromethyl)phenyl)ureido)cyclohexyl)carbamoyl)benzoic acid (3.4): 

Following the general procedure **A**, **3.4** was obtained as an off-white solid in 84% yield (1.22 g); mp > 200 ºC; R_f = 0.12 (CH_2Cl_2/MeOH 90:10 v/v); $[\alpha]_D^{20}$ +22.8 (c 1.0, EtOH); IR (KBr) 3403, 3261, 2942, 1630, 1566, 1390, 1276, 1188, 1131, 703, 681 cm^{-1}; ^1H NMR (500 MHz, $(CD_3)_2SO$) δ 12.87 (br s, 1H), 9.58 (br s, 1H), 8.21 (d, *J* = 8.8 Hz, 1H), 8.10 (s, 2H), 7.74 (app d, *J* = 7.6 Hz, 1H), 7.52 (s, 1H), 7.42 (app t, *J* = 7.5 Hz, 1H), 7.34 (app t, *J* = 7.5 Hz, 1H), 7.28 (app d, *J* = 7.4 Hz, 1H), 6.54 (br s, 1H), 3.79–3.71 (m, 1H), 3.50–3.40 (m, 1H), 2.13–2.02 (m, 1H), 1.93–1.84 (m, 1H), 1.76–1.62 (comp, 2H), 1.40–1.18 (comp, 4H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ 168.9, 168.4, 155.1, 142.8, 138.6, 131.8,

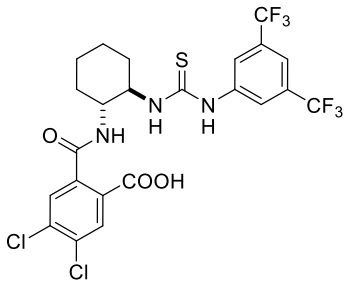
130.6 (q, $J_{C\text{-}F}$ = 32.4 Hz), 130.3, 129.2, 128.9, 127.4, 123.4 (q, $J_{C\text{-}F}$ = 272.6 Hz), 117.2, 113.2, 53.4, 52.3, 32.4, 31.5, 24.5, 24.4; *m/z* (ESI-MS) 516.1 $[M - H]^-$.

2-(((1*R*,2*R*)-2-(3-Phenylthioureido)cyclohexyl)carbamoyl)benzoic acid (3.5): Following



the general procedure **A**, **3.5** was obtained as an off-white solid in 94% yield (1.05 g); mp = 110–112 ºC; R_f = 0.30 (CH_2Cl_2/MeOH 90:10 v/v); $[\alpha]_D^{20}$ +20.4 (c 1.0, EtOH); IR (KBr) 3258, 3060, 2935, 2360, 1708, 1637, 1538, 1324, 1240, 1139, 746, 696 cm^{-1}; ^1H NMR (500 MHz, $(CD_3)_2SO$) δ 12.92 (br s, 1H), 9.59 (br s, 1H), 8.30 (d, *J* = 8.5 Hz, 1H), 7.80–7.76 (m, 1H), 7.66–7.57 (m, 1H), 7.54 (app td, *J* = 7.4, 1.3 Hz, 1H), 7.49 (app td, *J* = 7.5, 1.3 Hz, 1H), 7.46–7.41 (comp, 3H), 7.30 (app t, *J* = 7.8 Hz, 2H), 7.09 (app t, *J* = 7.3 Hz, 1H), 4.36–4.13 (m, 1H), 3.92–3.82 (m, 1H), 2.24–2.09 (m, 1H), 2.03–1.92 (m, 1H), 1.77–1.63 (comp, 2H), 1.46–1.18 (comp, 4H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ 180.0, 168.5, 167.8, 139.3, 138.7, 131.1, 130.6, 129.2, 129.1, 128.6, 124.1, 123.0, 57.2, 52.1, 31.5, 31.4, 24.4; *m/z* (ESI-MS) 396.1 $[M - H]^-$.

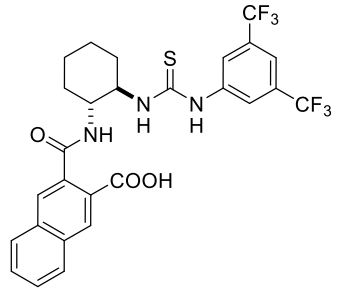
2-(((1*R*,2*R*)-2-(3-(3,5-Bis(trifluoromethyl)phenyl)thioureido)cyclohexyl)carbamoyl)-4,5-



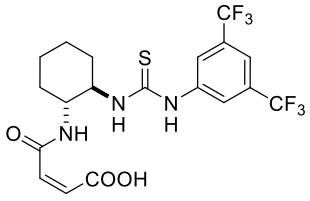
dichlorobenzoic acid (3.6): Following the general procedure **A**, **3.6** was obtained as an off-white solid in 65% yield (1.1 g); mp = 170–172 ºC; R_f = 0.42 (CH_2Cl_2/MeOH 93:7 v/v); $[\alpha]_D^{20}$ +1.31 (c 1.0, EtOH); IR (KBr) 3319, 3088, 2942, 1692, 1535, 1474, 1383, 1278, 1129, 970, 896, 682 cm^{-1}; ^1H NMR (500 MHz, $(CD_3)_2SO$) δ 13.36 (br s, 1H), 10.42 (br s, 1H), 8.49 (d, *J* = 8.0 Hz, 1H), 8.30 (s, 2H), 8.07 (br s, 1H), 7.93 (s, 1H), 7.71 (s, 1H), 7.65 (s, 1H), 4.24–4.08 (m, 1H), 3.94–3.80 (m, 1H), 2.33–2.14 (m, 1H), 1.98–1.84 (m, 1H), 1.82–1.65 (comp, 2H), 1.52–1.19 (comp, 4H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ 181.0, 167.0, 166.9, 142.7, 139.0, 133.9, 133.0, 132.3,

131.7, 130.7 (q, $J_{C\text{-}F}$ = 31.0 Hz), 130.4, 123.9 (q, $J_{C\text{-}F}$ = 272.6 Hz), 116.6, 58.1, 52.8, 32.1, 31.9, 25.1, 24.9; *m/z* (ESI-MS) 599.9 (^{35}Cl/^{35}Cl) [M – H]$^-$, 601.9 (^{35}Cl/^{37}Cl) [M – H]$^-$.

2-(((1*R*,2*R*)-2-(3-(3,5-Bis(trifluoromethyl)phenyl)thioureido)cyclohexyl)carbamoyl)-4,5-dimethoxybenzoic acid (3.7): To a solution of amino(thio)urea (0.26 mmol, 1 equiv) in toluene (13 mL, 0.02 M) in a 25 mL round bottom flask was added 4,5-dimethoxyphthalic anhydride[70] (0.27 mmol, 1.04 equiv) and triethylamine (0.27 mmol, 1.04 equiv). The resulting mixture was stirred until the aminothiourea was consumed as indicated by TLC. The solvent was removed under reduced pressure and the resulting solid was re-dissolved in a minimum amount of methanol (ca. 1 mL). To this solution was added 3 mL of methanol/HCl (aqueous 1 M) 1:1 v/v. The resulting precipitate was filtered and the collected solid was washed with cold methanol (3 × 1 mL). The resulting solid was then dried under high vacuum. Product **3.7** was obtained as an off-white solid in 51% yield (132 mg); mp > 200 ºC; R_f = 0.19 (CH_2Cl_2/MeOH 90:10 v/v); $[\alpha]_D^{20}$ –84.1 (c 0.1, acetone); IR (KBr) 3309, 3083, 2944, 1678, 1470, 1282, 1126, 1053, 970, 898, 700 cm^{-1}; ^{1}H NMR (500 MHz, $(CD_3)_2SO$) δ 12.68 (br s, 1H), 10.15 (br s, 1H), 8.24 (s, 2H), 8.17 (d, *J* = 6.7 Hz, 1H), 8.01 (s, 1H), 7.73 (s, 1H), 7.28 (s, 1H), 6.97 (s, 1H), 4.34–4.18 (m, 1H), 3.91–3.81 (m, 1H), 3.78 (s, 3H), 3.64 (s, 3H), 2.15–2.03 (m, 1H), 1.96–1.86 (m, 1H), 1.78–1.66 (comp, 2H), 1.51–1.20 (comp, 4H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ 180.1, 168.4, 167.3, 150.5, 148.5, 142.0, 132.4, 130.1 (q, $J_{C\text{-}F}$ = 33.0 Hz), 123.2 (q, $J_{C\text{-}F}$ = 272.7 Hz), 122.6, 121.8, 116.1, 112.3, 111.2, 57.5, 55.7, 55.5, 52.2, 31.3, 24.5, 24.4; *m/z* (ESI-MS) 592.0 [M – H]$^-$.

3-(((1*R*,2*R*)-2-(3-(3,5-Bis(trifluoromethyl)phenyl)thioureido)cyclohexyl)carbamoyl)-2-naphthoic acid (3.8): 

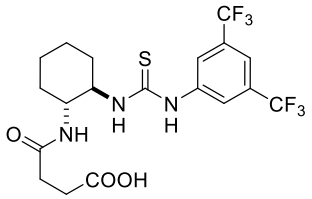
Following the general procedure **A**, **3.8** was obtained as an off-white solid in 78% yield (1.28 g); mp > 200 ºC; R_f = 0.48 (CH_2Cl_2/MeOH 90:10 v/v); $[\alpha]_D^{20}$ –22.3 (c 0.5, EtOH); IR (KBr) 3312, 3086, 2946, 1691, 1566, 1509, 1278, 1185, 1133, 766, 683 cm^{-1}; ^1H NMR (500 MHz, $(CD_3)_2SO$) δ 12.91 (br s, 1H), 10.27 (br s, 1H), 8.44 (d, *J* = 8.0 Hz, 1H), 8.36 (s, 1H), 8.28 (s, 2H), 8.13 (s, 1H), 8.07 (d, *J* = 7.8 Hz, 1H), 7.99 (s, 1H), 7.77 (s, 1H), 7.71 (s, 1H), 7.65–7.55 (m, 2H), 4.41–4.20 (m, 1H), 4.00–3.88 (m, 1H), 2.27–2.08 (m, 1H), 2.05–1.91 (m, 1H), 1.83–1.66 (comp, 2H), 1.56–1.21 (comp, 4H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ 180.3, 168.6, 168.2, 142.1, 135.1, 133.0, 132.1, 130.1 (q, J_{C-F} = 34.0 Hz), 129.2, 128.7, 128.3, 127.6, 127.5, 127.4, 123.3 (q, J_{C-F} = 272.6 Hz), 116.1, 57.5, 52.3, 31.5, 31.3, 24.4, 24.3(6); *m/z* (ESI-MS) 582.0 $[M - H]^-$.

(*Z*)-4-(((1*R*,2*R*)-2-(3-(3,5-Bis(trifluoromethyl)phenyl)thioureido)cyclohexyl)amino)-4-oxobut-2-enoic acid (3.9): 

Following the general procedure **A**, **3.9** was obtained as a white solid in 78% yield (1.06 g); mp = 191–192 ºC (decomposition); R_f = 0.23 (CH_2Cl_2/MeOH 90:10 v/v); $[\alpha]_D^{20}$ +94.2 (c 1.0, EtOH); IR (KBr) 3321, 3073, 2942, 2344, 1708, 1625, 1545, 1474, 1384, 1278, 1181, 1128, 848, 703 cm^{-1}; ^1H NMR (500 MHz, $(CD_3)_2SO$) δ 10.04 (br s, 1H), 9.17 (d, *J* = 7.9 Hz, 1H), 8.17 (s, 2H), 8.10 (s, 1H), 7.72 (s, 1H), 6.42 (d, *J* = 12.5 Hz, 1H), 6.24 (d, *J* = 12.4 Hz, 1H), 4.30–4.09 (m, 1H), 3.89–3.75 (m, 1H), 2.24–2.09 (m, 1H), 2.00–1.84 (m, 1H), 1.80–1.62 (comp, 2H), 1.42–1.17 (comp, 4H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ 180.1, 165.4, 165.3, 141.7, 133.3, 131.6, 131.1 (q, J_{C-F} =

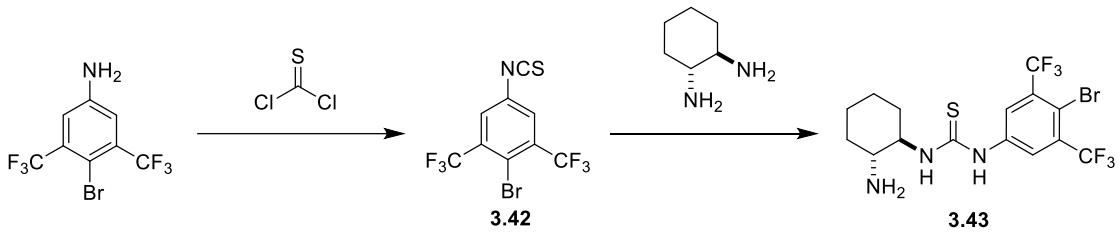
32.8 Hz), 123.2 (q, $J_{C\text{-}F}$ = 272.7 Hz), 122.0, 116.1, 56.6, 52.1, 31.3, 30.8, 24.1, 24.0; *m/z* (ESI-MS) 482.0 $[M - H]^-$.

4-(((1*R*,2*R*)-2-(3-(3,5-Bis(trifluoromethyl)phenyl)thioureido)cyclohexyl)amino)-4-oxobutanoic acid (3.10):



Following the general procedure **A**, **3.10** was obtained as a white solid in 90% yield (1.23 g); mp = 187–188 ºC (decomposition); R_f = 0.25 (CH_2Cl_2/MeOH 90:10 v/v); $[\alpha]_D^{20}$ +65.7 (c 1.0, EtOH); IR (KBr) 3323, 2935, 2861, 1712, 1618, 1551, 1386, 1278, 1178, 1134, 884, 682 cm^{-1}; ^1H NMR (500 MHz, $(CD_3)_2SO$) δ 12.02 (br s, 1H), 10.16 (br s, 1H), 8.24 (s, 2H), 7.96–7.85 (comp, 2H), 7.72 (s, 1H), 4.15–3.98 (m, 1H), 3.75–3.64 (m, 1H), 2.44–2.24 (comp, 4H), 2.21–2.07 (m, 1H), 1.87–1.76 (m, 1H), 1.74–1.58 (comp, 2H), 1.36–1.10 (comp, 4H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ 180.0, 173.8, 171.2, 142.0, 130.2 (q, $J_{C\text{-}F}$ = 32.0 Hz), 123.3 (q, $J_{C\text{-}F}$ = 272.7 Hz), 121.9, 116.0, 57.4, 51.4, 31.8, 31.0, 30.4, 29.4, 24.3, 24.2; *m/z* (ESI-MS) 484.0 $[M - H]^-$.

1-((1*R*,2*R*)-2-Aminocyclohexyl)-3-(4-bromo-3,5-bis(trifluoromethyl)phenyl)thiourea (3.43):



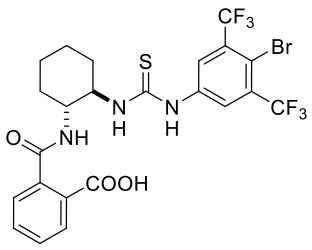
3.42 **3.43**

Compound **7** was synthesized following a modified literature procedure.[71] To a 25 mL round bottom flask was added 4-bromo-3,5-bis(trifluoromethyl)aniline (370 mg, 1.2 mmol, 1 equiv), CH_2Cl_2 (6 mL) and saturated aqueous $NaHCO_3$ (6 mL). The resulting reaction mixture was cooled to 0 ºC. Thiophosgene (0.12 mL, 1.56 mmol, 1.3 equiv) was slowly added to the organic layer via syringe. The resulting mixture was then allowed to warm to room

temperature and stirred until the aniline was consumed as indicated by TLC (4 h). The layers were then separated and the aqueous layer was extracted with CH_2Cl_2 (3 ×10 mL). The combined organic layers were then dried over Na_2SO_4 and the solvent was removed under reduced pressure. The resulting white solid (407 mg, 97%) was used directly in the next step without further purification.

To a 100 mL round bottom flask charged with a stir bar was added (1*R*,2*R*)-cyclohexane-1,2-diamine (199 mg, 1.74 mmol, 1.5 equiv) dissolved in a minimum amount of CH_2Cl_2 (ca. 0.5 mL) at 0 ºC. The crude product from the last step, dissolved in CH_2Cl_2 (46 mL), was added dropwise over 30 min. The mixture was then allowed to warm to room temperature over 15 min and concentrated under reduced pressure. Purification by flash chromatography on silica gel (CH_2Cl_2/MeOH/Et_3N 98:1:1 v/v/v to CH_2Cl_2/MeOH/Et_3N 94:5:1 v/v/v) afforded **3.43** as a white solid in 84% yield (452 mg); mp = 89–91 ºC; R_f = 0.10 (MeOH/CH_2Cl_2/Et_3N 10:89:1 v/v/v); $[\alpha]_D^{20}$ +75.74 (c 0.5, $CDCl_3$); IR (KBr) 3269, 2936, 2861, 1541, 1452, 1369, 1269, 1186, 1139, 969, 890, 678 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.10 (s, 2H), 6.60 (br s, 1H), 3.35 (br s, 1H), 2.73–2.59 (m, 1H), 2.14–2.02 (m, 1H), 2.00–1.86 (m, 1H), 1.85–1.60 (comp, 2H), 1.41–1.01 (comp, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.6, 140.2, 132.4 (q, $J_{C\text{-}F}$ = 31.1 Hz), 125.0, 122.4 (q, $J_{C\text{-}F}$ = 273.8 Hz), 112.1, 63.2, 56.6, 35.0, 32.1, 24.5; *m/z* (ESI-MS) 462.0 (^{79}Br) $[M - H]^-$, 464.0 (^{81}Br) $[M - H]^-$.

2-(((1R,2R)-2-(3-(4-bromo-3,5-bis(trifluoromethyl)phenyl)thioureido)cyclohexyl) carbamoyl)benzoic acid (3.11):



Following the general procedure **A**, **3.11** was obtained as a white solid in 92% yield (1.58 g); mp = 166–168 ºC; R_f = 0.19 (CH_2Cl_2/MeOH 90:10 v/v); $[\alpha]_D^{20}$ +48.31 (c 1.0, EtOH); IR (KBr) 3300, 3076, 2940, 1696, 1535, 1451, 1286, 1189, 1136, 972, 684 cm^{-1}; ^1H NMR (500 MHz, $(CD_3)_2SO$) δ 12.87

(br s, 1H), 10.19 (br s, 1H), 8.37 (s, 2H), 8.29 (d, J = 6.8 Hz, 1H), 8.15–8.02 (m, 1H), 7.79–7.70 (m, 1H), 7.53–7.45 (comp, 2H), 7.45–7.35 (m, 1H), 4.32–4.10 (m, 1H), 3.95–3.81 (m, 1H), 2.25–2.06 (m, 1H), 1.99–1.88 (m, 1H), 1.78–1.63 (comp, 2H), 1.50–1.18 (comp, 4H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ 180.5, 169.3, 168.5, 141.1, 139.2, 131.6, 131.4 (q, $J_{C\text{-}F}$ = 29.0 Hz), 131.3, 129.9, 129.8, 128.4, 124.9, 123.2 (q, $J_{C\text{-}F}$ = 274.0 Hz), 110.1, 58.1, 52.6, 32.0, 31.8, 25.0, 24.9; *m/z* (ESI-MS) 609.9 (^{79}Br) $[M - H]^-$, 611.9 (^{81}Br) $[M - H]^-$.

General procedure B for asymmetric A^3 reaction:

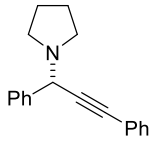
An oven dried 25 mL round bottom flask charged with a stir bar, CuI (7.6 mg, 0.04 mmol, 0.04 equiv), **3.11** (18 mg, 0.03 mmol, 0.03 equiv) and 5Å MS (600 mg) was capped with a septum. The reaction flask was gently flushed with N_2 using a needle as outlet for 15 min. Freshly distilled CH_2Cl_2 (10 mL) was added and the resulting mixture cooled to 0 °C over 15 min. Amine (1.2 mmol, 1.2 equiv), aldehyde (1 mmol, 1 equiv) and alkyne (1.5 mmol, 1.5 equiv) were added via syringe and the reaction mixture was stirred for the indicated time before being quenched by saturated aqueous NH_4Cl (10 mL). In cases where aldehydes and/or alkynes are solids, they were added before the N_2 flush. The biphasic mixture was filtered through Celite and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine (30 mL) and dried over Na_2SO_4. Following filtration, the resulting solution was concentrated under reduced pressure and purified by flash chromatography on silica gel.

General procedure C for enantioenriched allene synthesis:

Following a modified literature procedure,[72] to an oven dried 10 mL reaction vial charged with a stir bar, propargylamine (0.2 mmol, 1 equiv) and $AgNO_3$ (0.2 mmol, 1 equiv) was added MeCN (4 mL, 0.05 M). The resulting mixture was stirred at 60 ºC for 48 h in the

absence of light. The reaction mixture was then filtered through Celite, concentrated under reduced pressure and purified by flash chromatography on silica gel.

(*S*)-1-(1,3-Diphenylprop-2-yn-1-yl)pyrrolidine (3.14): Following the general procedure **B**,



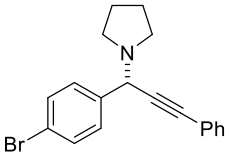
compound **3.14** was obtained as an colorless oil in 92% yield (240 mg); R_f = 0.32 (Hexanes/EtOAc 85:15 v/v); $[\alpha]^{D}_{20}$ –8.2 (c 0.5, $CHCl_3$, 92% *ee*); IR (KBr) 3060, 3030, 2966, 2874, 2807, 1489, 1449, 1129, 756, 691 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.65–7.60 (comp, 2H), 7.53–7.47 (comp, 2H), 7.41–7.35 (comp, 2H), 7.35–7.28 (comp, 4H), 4.90 (s, 1H), 2.75–2.67 (comp, 4H), 1.86–1.76 (comp, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.66, 131.91, 128.39, 128.38, 128.19, 127.67, 123.37, 87.02, 86.85, 59.26, 50.41, 23.62; *m/z* (ESI–MS) 262.1 $[M + H]^+$; HPLC: Daicel Chiralpak OJ-H, *n*-hexane/*i*-PrOH /diethylamine = 99/1/0.05, Flow rate = 1 mL/min, UV = 280 nm, t_R = 10.0 min (minor) and t_R = 13.1 min (major).

The absolute configuration was assigned by analogy.

(*S*)-1-(1-(4-Chlorophenyl)-3-phenylprop-2-yn-1-yl)pyrrolidine (3.15): Following the general procedure **B**, compound **3.15** was obtained as an orange oil in 90% yield (289 mg); R_f = 0.21 (Hexanes/EtOAc 90:10 v/v); $[\alpha]^{D}_{20}$ – 14.1 (c 0.5, $CHCl_3$, 92% *ee*); IR (KBr) 3057, 2966, 2875, 2811, 1684, 1597, 1489, 1266, 1089, 1015, 756 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.47–7.43 (d, *J* = 8.4 Hz, 2H), 7.42–7.36 (comp, 2H), 7.25–7.20 (comp, 5H), 4.89 (s, 1H), 2.72–2.58 (comp, 4H), 1.78–1.67 (comp, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.49, 133.62, 131.87, 129.82, 128.51, 128.45, 128.41, 122.85, 87.70, 85.55, 58.29, 50.11, 23.60; *m/z* (ESI–MS) 296.1 $[M + H]^+$; HPLC: Daicel Chiralpak OD-H, *n*-hexane/*i*-PrOH /diethylamine = 99/1/0.05, Flow rate = 1 mL/min, UV = 280 nm, t_R = 4.3 min (minor) and t_R = 4.8 min (major).

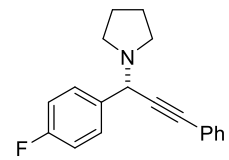
The absolute configuration was assigned by analogy.

(*S*)-1-(1-(4-Bromophenyl)-3-phenylprop-2-yn-1-yl)pyrrolidine (3.16): Following the general procedure **B**, compound **3.16** was obtained as a yellow oil in 81% yield (276 mg); R_f = 0.31 (Hexanes/EtOAc 90:10 v/v); $[\alpha]^{D}_{20}$ –13.1 (c 0.5, $CHCl_3$, 92% *ee*); IR (KBr) 3054, 2962, 2871, 2804, 1680, 1635, 1480, 1398, 1280, 1126, 758, 714 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.45–7.37 (comp, 6H), 7.27–7.22 (comp, 3H), 4.86 (s, 1H), 2.71–2.58 (comp, 4H), 1.78–1.68 (comp, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.35, 132.03, 131.62, 130.29, 128.58, 128.56, 123.04, 121.89, 87.70, 85.75, 58.57, 58.54, 50.30; *m/z* (ESI–MS) 340.1 (^{79}Br) $[M + H]^+$, 342.0 (^{81}Br) $[M + H]^+$; HPLC: Daicel Chiralpak OD-H, *n*-hexane/*i*-PrOH /diethylamine = 99/1/0.05, Flow rate = 1 mL/min, UV = 280 nm, t_R = 4.4 min (minor) and t_R = 4.9 min (major).



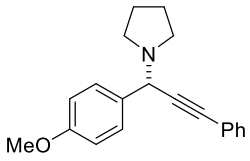
The absolute configuration was assigned by analogy.

(*S*)-1-(1-(4-Fluorophenyl)-3-phenylprop-2-yn-1-yl)pyrrolidine (3.17): Following the general procedure **B**, compound **3.17** was obtained as a yellow oil in 90% yield (251 mg); R_f = 0.25 (Hexanes/EtOAc 90:10 v/v); $[\alpha]^{D}_{20}$ –15.8 (c 0.5, $CHCl_3$, 93% *ee*); IR (KBr) 3054, 2967, 2908, 2809, 1672, 1598, 1504, 1275, 1220, 1156, 854, 751, 692 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.63–7.57 (comp, 2H), 7.53–7.47 (comp, 2H), 7.37–7.30 (comp, 3H), 7.08–7.01 (comp, 2H), 4.95 (s, 1H), 2.80–2.66 (comp, 4H), 1.89–1.76 (comp, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.42 (d, $J_{C\text{-}F}$ = 245.9 Hz), 131.91, 130.07 (d, $J_{C\text{-}F}$ = 8.1 Hz), 128.44, 128.41, 123.04, 115.20 (d, $J_{C\text{-}F}$ = 21.4 Hz), 87.50, 86.08, 58.36, 58.34, 50.20, 23.63; *m/z* (ESI–MS) 280.1 $[M + H]^+$; HPLC: Daicel Chiralpak OD-H, *n*-hexane/*i*-PrOH /diethylamine = 99/1/0.05, Flow rate = 1 mL/min, UV = 254 nm, t_R = 4.2 min (minor) and t_R = 4.5 min (major).



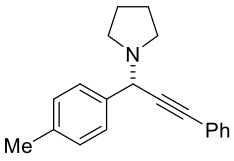
The absolute configuration was assigned by analogy.

(*S*)-1-(1-(4-Methoxyphenyl)-3-phenylprop-2-yn-1-yl)pyrrolidine (3.18): Following the general procedure **B**, compound **3.18** was obtained as a yellow oil in 90% yield (262 mg); R_f = 0.25 (Hexanes/EtOAc 70:30 v/v); $[\alpha]^{D}_{20}$ – 10.2 (c 0.5, $CHCl_3$, 96% *ee*); IR (KBr) 2960, 2908, 2878, 1685, 1603, 1579, 1452, 1334, 1242, 1030, 837, 756, 689 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.5 Hz,2H), 7.51–7.46 (comp, 2H), 7.34–7.29 (comp, 3H), 6.91–6.87 (comp, 2H), 4.91 (s, 1H), 3.81 (s, 3H), 2.79–2.68 (comp, 4H), 1.87–1.76 (comp, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.36, 132.00, 131.45, 129.73, 128.49, 128.35, 123.36, 113.84, 87.12, 86.86, 58.65, 55.51, 50.40, 23.71; *m/z* (ESI–MS) 292.1 $[M + H]^+$; HPLC: Daicel Chiralpak OJ-H, *n*-hexane/*i*-PrOH /diethylamine = 99/1/0.05, Flow rate = 1 mL/min, UV = 280 nm, t_R = 11.1 min (minor) and t_R = 12.6 min (major).



The absolute configuration was assigned by analogy.

(*S*)-1-(3-Phenyl-1-(p-tolyl)prop-2-yn-1-yl)pyrrolidine (3.19): Following the general procedure **B**, compound **3.19** was obtained as a yellow oil in 91% yield (251 mg); R_f = 0.20 (Hexanes/EtOAc 90:10 v/v); $[\alpha]^{D}_{20}$ –26.5 (c 0.5, $CHCl_3$, 95% *ee*); IR (KBr) 2960, 2876, 2802, 1601, 1509, 1490, 1114, 756, 694 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.61–7.49 (comp, 4H), 7.39–7.31 (comp, 3H), 7.24–7.18 (comp, 2H), 4.88 (s, 1H), 2.80–2.68 (comp, 4H), 2.39 (s, 3H), 1.91–1.78 (comp, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.24, 136.68, 131.85, 129.01, 128.31, 128.25, 128.08, 123.31, 87.14, 86.71, 58.98, 50.39, 23.57, 21.21; *m/z* (ESI–MS) 276.0 $[M + H]^+$; HPLC: Daicel Chiralpak OJ-H, *n*-hexane/*i*-PrOH /diethylamine = 99/1/0.05, Flow rate = 1 mL/min, UV = 254 nm, t_R = 8.0 min (minor) and t_R = 9.7 min (major).



The absolute configuration was assigned by analogy.

(*S*)-1-(1-(3-Fluorophenyl)-3-phenylprop-2-yn-1-yl)pyrrolidine (3.20): Following the general procedure **B**, compound **3.20** was obtained as an orange oil in 72% yield (201 mg); R_f = 0.46 (Hexanes/EtOAc 80:20 v/v); $[\alpha]^{D}_{20}$ –16.1 (c 0.5, $CHCl_3$, 89% *ee*); IR (KBr) 3051, 2970, 1615, 1489, 1444, 1265, 738, 707 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.54–7.48 (comp, 2H), 7.45–7.41 (m, 1H), 7.39 (dt, *J* = 10.1, 1.9 Hz, 1H), 7.37–7.30 (comp, 4H), 7.00 (td, *J* = 8.4, 2.6 Hz, 1H), 4.93 (s, 1H), 2.78–2.65 (comp, 4H), 1.89–1.76 (comp, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.96 (d, $J_{C\text{-}F}$ = 245.5 Hz), 142.40 (d, $J_{C\text{-}F}$ = 7.0 Hz), 131.92, 129.74 (d, $J_{C\text{-}F}$ = 8.1 Hz), 128.41, 128.35, 123.89 (d, $J_{C\text{-}F}$ = 2.8 Hz),, 123.10, 115.26 (d, $J_{C\text{-}F}$ = 22.7 Hz), 114.52 (d, $J_{C\text{-}F}$ = 21.2 Hz), 87.42, 85.99, 58.61, 58.59, 50.21, 23.66; *m/z* (ESI–MS) 280.1 $[M + H]^+$; HPLC: Daicel Chiralpak OJ-H, *n*-hexane/*i*-PrOH /diethylamine = 99/1/0.05, Flow rate = 1 mL/min, UV = 280 nm, t_R = 7.5 min (minor) and t_R = 8.4 min (major).

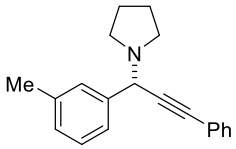
The absolute configuration was assigned by analogy.

(*S*)-1-(1-(3-Methoxyphenyl)-3-phenylprop-2-yn-1-yl)pyrrolidine (3.21): Following the general procedure **B**, compound **3.21** was obtained as a yellow oil in 95% yield (277 mg); R_f = 0.62 (Hexanes/EtOAc 70:30 v/v); $[\alpha]^{D}_{20}$ – 25.3 (c 0.5, $CHCl_3$, 94% *ee*); IR (KBr) 2963, 2875, 2807, 1599, 1489, 1464, 1310, 1278, 1150, 1050, 757, 689 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.43–7.36 (comp, 2H), 7.25–7.19 (comp, 3H), 7.19–7.15 (m, 1H), 7.14–7.09 (comp, 2H), 6.75 (dd, *J* = 8.1, 2.5 Hz, 1H), 4.78 (s, 1H), 3.73 (s, 3H), 2.67–2.58 (comp, 4H), 1.76–1.67 (comp, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.72, 141.14, 131.89, 129.30, 128.36, 128.20, 123.30, 120.80, 113.99, 113.21, 86.98, 86.72, 59.22, 55.37, 50.44, 23.64; *m/z* (ESI–MS) 292.0 [M +

H]$^+$; HPLC: Daicel Chiralpak OJ-H, *n*-hexane/*i*-PrOH /diethylamine = 99/1/0.05, Flow rate = 1 mL/min, UV = 280 nm, t_R = 11.3 min (minor) and t_R = 12.5 min (major).

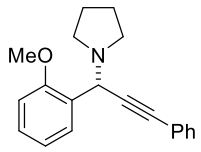
The absolute configuration was assigned by analogy.

(*S*)-1-(3-Phenyl-1-(m-tolyl)prop-2-yn-1-yl)pyrrolidine (3.22): Following the general procedure **B**, compound **3.22** was obtained as a yellow oil in 97% yield (268 mg); R_f = 0.40 (Hexanes/EtOAc 85:15 v/v); $[\alpha]^D_{20}$ –20.9 (c 0.5, $CHCl_3$, 94% *ee*); IR (KBr) 2965, 2874, 2807, 1607, 1489, 1443, 1303, 1128, 910, 756, 690 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43–7.38 (comp, 2H), 7.34–7.30 (comp, 2H), 7.26–7.21 (comp, 3H), 7.19–7.14 (m, 1H), 7.02 (app d, *J* = 7.5Hz, 1H), 4.74 (s, 1H), 2.67–2.56 (comp, 4H), 2.29 (s, 3H), 1.79–1.67 (comp, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.70, 138.14, 132.02, 129.18, 128.56, 128.47, 128.35, 128.26, 125.58, 123.55, 87.21, 86.92, 59.50, 59.48, 50.66, 23.72, 21.72; *m/z* (ESI–MS) 276.1 [M + H]$^+$; HPLC: Daicel Chiralpak OJ-H, *n*-hexane/*i*-PrOH /diethylamine = 99/1/0.05, Flow rate = 1 mL/min, UV = 254 nm, t_R = 5.8 min (minor) and t_R = 8.6 min (major).



The absolute configuration was determined by analogy.

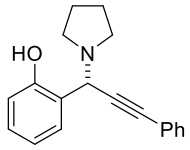
(*R*)-1-(1-(2-Methoxyphenyl)-3-phenylprop-2-yn-1-yl)pyrrolidine (3.23): Following the general procedure **B**, compound **3.23** was obtained as a colorless oil in 87% yield (254 mg); R_f = 0.20 (Hexanes/EtOAc 70:30 v/v); The ee was determined after demethylation (below); $[\alpha]^D_{20}$ +29.3 (c 0.5, $CHCl_3$, 92% *ee*); IR (KBr) 3056, 2966, 2834, 1599, 1491, 1462, 1265, 1108, 1029, 738 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.30–7.35 (comp, 2H), 7.24–7.16 (comp, 4H), 6.90 (td, *J* = 7.5, 1.1 Hz, 1H), 6.82 (app d, *J* = 8.2 Hz, 1H), 5.27 (s, 1H), 3.78 (s, 3H), 2.72–2.61 (comp, 4H), 1.76–1.65 (comp, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.70,



131.83, 129.92, 128.87, 128.27, 127.97, 127.82, 123.55, 120.45, 111.02, 88.04, 85.40, 55.88, 55.86, 51.73, 51.72, 50.56, 23.52; *m/z* (ESI–MS) 292.0 $[M + H]^+$.

The absolute configuration was assigned by analogy.

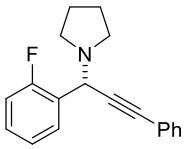
(*R*)-2-(3-Phenyl-1-(pyrrolidin-1-yl)prop-2-yn-1-yl)phenol (3.23'): Demethylation was



accomplished via a modified literature procedure.[73] To a solution of **3.23'** (73 mg, 0.25 mmol) in $PhCH_3$ (2.5 mL, 0.1 M) at 0 °C was added DIBAL (1.0 M in hexanes, 0.75 mL, 3 equiv). The resulting solution was stirred at 0 °C for 2.5 h before being quenched by saturated aqueous NH_4Cl. The resulting biphasic mixture was filtered through Celite and extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure before being purified by flash chromatography on silica gel to afford **3ja** as a colorless oil in 71% yield (49 mg); R_f = 0.27 (Hexanes/EtOAc 80:20 v/v); $[\alpha]^D_{20}$ –64.8 (c 0.5, $CHCl_3$, 92% *ee*); IR (KBr) 3397, 3049, 2968, 2843, 1592, 1492, 1460, 1406, 1259, 757 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.58–7.51 (comp, 3H), 7.40–7.32 (comp, 3H), 7.26–7.20 (m, 1H), 6.89–6.83 (comp, 2H), 5.29 (s, 1H), 2.96–2.76 (comp, 4H), 1.94–1.82 (comp, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.22, 132.01, 129.46, 128.69, 128.52, 127.97, 122.68, 122.26, 119.06, 116.35, 89.17, 83.08, 57.16, 57.13, 49.03, 23.99; *m/z* (ESI–MS) 278.0 $[M + H]^+$; HPLC: Daicel Chiralpak OJ-H, *n*-hexane/*i*-PrOH /diethylamine = 97/3/0.05, Flow rate = 1 mL/min, UV = 280 nm, t_R = 8.2 min (major) and t_R = 10.4 min (minor).

The absolute configuration was assigned by analogy.

(*R*)-1-(1-(2-Fluorophenyl)-3-phenylprop-2-yn-1-yl)pyrrolidine (3.24): Following the

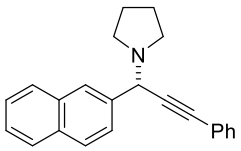


general procedure **B** compound **3.24** was obtained as a yellow oil in 78% yield (218 mg); R_f = 0.27 (Hexanes/EtOAc 90:10 v/v); $[\alpha]^D_{20}$ +15.6 (c 0.5,

$CHCl_3$, 86% *ee*); IR (KBr) 2966, 2875, 2807, 1589, 1489, 1457, 1270, 1230, 1095, 1031, 755, 690 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.73 (td, *J* = 7.5, 1.9 Hz, 1H), 7.51–7.42 (comp, 2H), 7.35–7.26 (comp, 4H), 7.16 (td, *J* = 7.5, 1.3 Hz, 1H), 7.09–7.01 (m, 1H), 5.20 (s, 1H), 2.78–2.64 (comp, 4H), 1.85–1.72 (comp, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.46 (d, J_{C-F} = 247.8 Hz), 131.92, 130.39 (d, J_{C-F} = 3.5 Hz), 129.47 (d, J_{C-F} = 8.3 Hz), 128.39, 128.31, 126.66 (d, J_{C-F} = 13.3 Hz), 124.02 (d, J_{C-F} = 3.7 Hz), 123.17, 115.59 (d, J_{C-F} = 22.1 Hz), 86.41, 86.19, 52.17, 52.14, 52.12, 50.58, 23.52; *m/z* (ESI–MS) 280.1 $[M + H]^+$; HPLC: Daicel Chiralpak OJ-H, *n*-hexane/*i*-PrOH /diethylamine = 99/1/0.05, Flow rate = 0.5 mL/min, UV = 280 nm, t_R = 14.0 min (minor) and t_R = 15.1 min (major).

The absolute configuration was assigned by analogy.

(*S*)-1-(1-(Naphthalen-2-yl)-3-phenylprop-2-yn-1-yl)pyrrolidine (3.25): Following the general procedure **B**, compound **3.25** was obtained as a light yellow solid in 96% yield (299 mg); mp = 67–69 °C; R_f = 0.25 (Hexanes/EtOAc 90:10 v/v); $[\alpha]^D_{20}$ –2.8 (c 0.5, $CHCl_3$, 94% *ee*); IR (KBr) 3046, 2962, 2873, 2807, 1630, 1598, 1502, 1485, 1438, 1354, 1260, 1129, 832, 761 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.08 (s, 1H), 7.92–7.84 (comp, 3H), 7.81–7.76 (m, 1H), 7.59–7.54 (comp, 2H), 7.53–7.46 (comp, 2H), 7.39–7.32 (comp, 3H), 5.06 (s, 1H), 2.82–2.72 (comp, 4H), 1.90–1.79 (comp, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.25, 133.34, 133.12, 131.94, 128.41, 128.24, 128.22, 128.21, 128.11, 127.71, 126.96, 126.60, 126.09, 125.99, 123.36, 87.27, 86.86, 59.48, 59.47, 50.58, 23.68; *m/z* (ESI–MS) 312.0 $[M + H]^+$; HPLC: Daicel Chiralpak OJ-H, *n*-hexane/*i*-PrOH /diethylamine = 99/1/0.05, Flow rate = 1 mL/min, UV = 280 nm, t_R = 12.2 min (minor) and t_R = 15.1 min (major).



The absolute configuration was assigned by analogy.

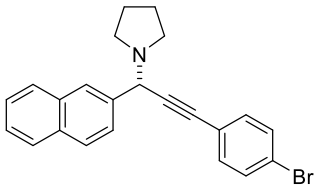
(*S,E)*-1-(1,5-Diphenylpent-1-en-4-yn-3-yl)pyrrolidine (3.26): Following the general procedure **B**, compound **3.26** was obtained as a brown oil in 63% yield (181 mg); R_f = 0.22 (Hexanes/EtOAc 70:30 v/v); $[\alpha]^{D}_{20}$ –9.76 (c 0.5, $CHCl_3$, 92% *ee*); IR (KBr) 3019, 2957, 2873, 2804, 1591, 1490, 1440, 1344, 1119, 963, 758, 689 cm^{-1}; ^1H NMR (500 MHz, CDCl3) δ 7.55–7.48 (comp, 2H), 7.47–7.41 (comp, 2H), 7.37–7.30 (comp, 5H), 7.29–7.23 (m, 1H), 6.88 (d, *J* = 15.8 Hz, 1H), 6.39 (dd, *J* = 15.8, 6.0 Hz, 1H), 4.54 (d, *J* = 6.0 Hz, 1H), 2.87–2.72 (comp, 4H), 1.91–1.80 (comp, 4H); ^{13}C NMR (125 MHz, CDCl3) δ 136.80, 132.05, 131.92, 128.66, 128.38, 128.24, 128.16, 127.79, 126.75, 123.24, 87.24, 85.77, 56.86, 50.23, 23.67; *m/z* (ESI–MS) 288.1 $[M + H]^+$; HPLC: Daicel Chiralpak OD-H, *n*-hexane/*i*-PrOH /diethylamine = 99/1/0.05, Flow rate = 1 mL/min, UV = 254 nm, t_R = 7.2 min (minor) and t_R = 7.7 min (major).

The absolute configuration was assigned by analogy.

(*S*)-1-(1-Phenylhept-1-yn-3-yl)pyrrolidine (3.27): Following the general procedure **B**, compound **3.27** was obtained as a yellow oil in 96% yield (232 mg); R_f = 0.20 (Hexanes/EtOAc 80:20 v/v); $[\alpha]^{D}_{20}$ –6.8 (c 0.5, $CHCl_3$, 73% *ee*); IR (KBr) 2957, 2872, 2807, 1598, 1489, 1458, 1362, 1293, 1136, 755 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.46–7.39 (comp, 2H), 7.32–7.26 (comp, 3H), 3.67 (dd, *J* = 9.0, 5.8 Hz, 1H), 2.81–2.64 (comp, 4H), 1.86–1.77 (comp, 4H), 1.77–1.67 (comp, 2H), 1.62–1.33 (comp, 4H), 0.93 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 131.86, 128.33, 127.92, 123.66, 88.51, 85.36, 55.27, 49.89, 35.00, 29.09, 23.64, 22.69, 14.21; *m/z* (ESI–MS) 242.1 $[M+H]^+$; HPLC: Daicel Chiralpak OJ-H, *n*-hexane/*i*-PrOH /diethylamine = 99/1/0.05, Flow rate = 1 mL/min, UV = 280 nm, t_R = 3.9 min (minor) and t_R = 4.3 min (major).

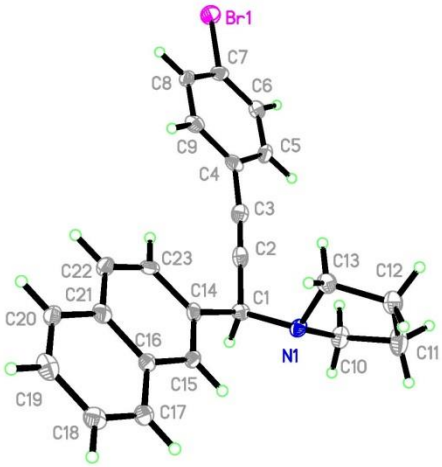
The absolute configuration was assigned by analogy.

(*S*)-1-(3-(4-Bromophenyl)-1-(naphthalen-2-yl)prop-2-yn-1-yl)pyrrolidine (3.28):



Following the general procedure **B**, compound **3.28** was obtained as a white solid in 94% yield (367 mg); mp = 63–65 °C; R_f = 0.25 (Hexanes/EtOAc 90:10 v/v); $[\alpha]^{D}_{20}$ +10.6 (c 0.5, $CHCl_3$, 94% *ee*); IR (KBr) 3049, 2967, 2824, 2792, 1507, 1482, 1349, 1260, 1240, 1067, 1005, 815 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.89–7.81 (comp, 3H), 7.76–7.71 (m, 1H), 7.51–7.44 (comp, 4H), 7.40–7.35 (comp, 2H), 4.50 (s, 1H), 2.78–2.68 (comp, 4H), 1.87–1.77 (comp, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.97, 133.40, 133.33, 133.15, 131.67, 128.21, 127,74, 126.96, 126.50, 126.17, 126.09, 122.45, 122.28, 88.27, 86.16, 59.59, 50.70, 23.67; *m/z* (ESI–MS) 389.9 (^{79}Br) $[M + H]^+$, 391.9 (^{81}Br) $[M + H]^+$; HPLC: Daicel Chiralpak OJ-H, *n*-hexane/*i*-PrOH /diethylamine = 98/2/0.05, Flow rate = 1 mL/min, UV = 280 nm, t_R = 11.0 min (minor) and t_R = 14.6 min (major).

The absolute configuration of **3.28** was assigned by X-ray crystallography:



Compound **3.28** was crystallized from MeCN through slow evaporation at room temperature. The requisite CIF has been submitted to the journal.

(*S*)-1-(3-(4-Fluorophenyl)-1-phenylprop-2-yn-1-yl)pyrrolidine (3.29): Following the general procedure **B**, compound **3.29** was obtained as a yellow oil in 86% yield (258 mg); R_f = 0.32 (Hexanes/EtOAc 80:20 v/v); $[\alpha]^{D}_{20}$ –16.9 (c 0.5, $CHCl_3$, 93% *ee*); IR (KBr) 3059, 2952, 2871, 2807, 1887, 1593, 1497, 1445, 1220, 1154, 1121, 839, 701 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.60 (d, *J* = 7.6 Hz, 2H), 7.49–7.44 (comp, 2H), 7.37 (app t, *J* = 7.6 Hz, 2H), 7.33–7.27 (m, 1H), 7.04–6.98 (comp, 2H), 4.89 (s, 1H), 2.75–2.65 (comp, 4H), 1.87–1.75 (comp, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.51 (d, J_{C-F} = 249.3 Hz), 139.37, 133.75 (d, J_{C-F} = 8.3 Hz),, 133.71, 128.41, 128.39, 127.79, 119.36 (d, J_{C-F} = 3.5 Hz), 115.63 (d, J_{C-F} = 22.0 Hz), 86.47, 85.94, 59.24, 50.45, 23.59; *m/z* (ESI–MS) 280.1 $[M+ H]^+$; HPLC: Daicel Chiralpak OJ-H, *n*-hexane/*i*-PrOH /diethylamine = 99/1/0.05, Flow rate = 1 mL/min, UV = 254 nm, t_R = 6.5 min (minor) and t_R = 11.4 min (major).

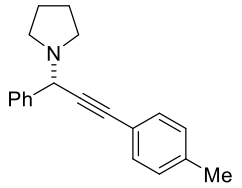
The absolute configuration was assigned by analogy.

(*S*)-1-(3-(4-Methoxyphenyl)-1-phenylprop-2-yn-1-yl)pyrrolidine (3.30): Following the general procedure **B**, compound **3.30** was obtained as an orange oil in 97% yield (311 mg); R_f = 0.26 (Hexanes/EtOAc 80:20 v/v); $[\alpha]^{D}_{20}$ –11.4 (c 0.5, $CHCl_3$, 90% *ee*); IR (KBr) 2962, 2802, 2216, 1611, 1517, 1455, 1284, 1247, 1173, 1027, 830 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.63–7.58 (comp, 2H), 7.45–7.40 (comp, 2H), 7.38–7.33 (comp, 2H), 7.32–7.27 (m, 1H), 6.86–6.83 (comp, 2H), 4.88 (s, 1H), 3.81 (s, 3H), 2.73–2.65 (comp, 4H), 1.84–1.74 (comp, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.58, 139.76, 133.31, 128.45, 128.37, 127.66, 115.50, 114.01, 86.86, 86.23, 59.31, 55.45, 50.42, 23.62; *m/z* (ESI–MS) 292.0 $[M + H]^+$; HPLC: Daicel Chiralpak

OJ-H, *n*-hexane/*i*-PrOH /diethylamine = 99/1/0.05, Flow rate = 1 mL/min, UV = 280 nm, t_R = 12.1 min (minor) and t_R = 13.8 min (major).

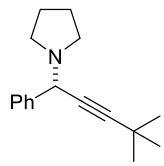
The absolute configuration was assigned by analogy.

(*S*)-1-(1-Phenyl-3-(p-tolyl)prop-2-yn-1-yl)pyrrolidine (3.31): Following the general procedure **B**, compound **3.31** was obtained as an off-white solid in 92% yield (253 mg); mp = 52–54 °C; R_f = 0.25 (Hexanes/EtOAc 90:10 v/v); $[\alpha]^D_{20}$ –16.4 (c 0.5, $CHCl_3$, 92% ee); IR (KBr) 2960, 2876, 2819, 1512, 1490, 1445, 1267, 1134, 1102, 1028, 1013 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.64–7.58 (comp, 2H), 7.41–7.32 (comp, 4H), 7.32–7.26 (m, 1H), 7.15–7.09 (comp, 2H), 4.88 (s, 1H), 2.73–2.64 (comp, 4H), 2.36 (s, 3H), 1.85–1.75 (comp, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.77, 138.25, 131.79, 129.13, 128.42, 128.35, 127.64, 120.29, 87.10, 86.06, 59.28, 50.39, 23.62, 21.59; *m/z* (ESI–MS) 276.0 $[M + H]^+$; HPLC: Daicel Chiralpak OD-H, *n*-hexane/*i*-PrOH /diethylamine = 99/1/0.05, Flow rate = 1 mL/min, UV = 280 nm, t_R = 4.9 min (minor) and t_R = 5.2 min (major).



The absolute configuration was assigned by analogy.

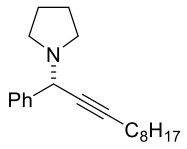
(*S*)-1-(4,4-Dimethyl-1-phenylpent-2-yn-1-yl)pyrrolidine (3.32): Following the general procedure **B**, compound **3.32** was obtained as a yellow oil in 80% yield (192 mg); R_f = 0.48 (Hexanes/EtOAc 80:20 v/v); $[\alpha]^D_{20}$ –33.6 (c 0.5, $CHCl_3$, 88% *ee*); IR (KBr) 3061, 3030, 2967, 2872, 2807, 1451, 1362, 1269, 1130, 710 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.52 (app d, *J* = 7.7 Hz, 2H), 7.31 (app t, *J* = 7.5 Hz, 2H), 7.27–7.22 (m, 1H), 4.62 (s, 1H), 2.63–2.52 (comp, 4H), 1.79–1.70 (comp, 4H), 1.27 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.25, 128.42, 128.19, 127.41, 96.94, 75.16, 58.59, 50.08, 31.48, 22.75, 23.62; *m/z* (ESI–MS) 242.1 $[M + H]^+$; HPLC: Daicel Chiralpak OJ-H,



n-hexane/*i*-PrOH /diethylamine = 99/1/0.05, Flow rate = 1 mL/min, UV = 254 nm, t_R = 4.6 min (minor) and t_R = 4.9 min (major).

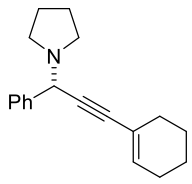
The absolute configuration was assigned by analogy.

(*S*)-1-(1-Phenylundec-2-yn-1-yl)pyrrolidine (3.33): Following the general procedure **B**, compound **3.33** was obtained as a yellow oil in 91% yield (271 mg); R_f= 0.31 (Hexanes/EtOAc 90:10 v/v); $[\alpha]^D_{20}$ –25.9 (c 0.5, $CHCl_3$, 92% *ee*); IR (KBr) 3061, 3022, 2950, 2925, 2856, 2812, 1492, 1448, 1265, 1131, 721, 694 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.57–7.51 (comp, 2H), 7.36–7.31 (comp, 2H), 7.29–7.24 (m, 1H), 4.62 (t, *J* = 1.9 Hz, 1H), 2.67–2.54 (comp, 4H), 2.29 (td, *J* = 7.0, 2.1 Hz, 2H), 1.83–1.71 (comp, 4H), 1.61–1.51 (comp, 2H), 1.50–1.39 (comp, 2H), 1.38–1.22 (comp, 8H), 0.90 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.35, 128.36, 128.21, 127.41, 87.18, 77.14, 58.95, 50.32, 31.97, 29.38, 29.23, 29.13, 29.04, 23.56, 22.81, 18.92, 14.25; *m/z* (ESI–MS) 298.1 $[M + H]^+$; HPLC: Daicel Chiralpak OJ-H, *n*-hexane/*i*-PrOH /diethylamine = 99/1/0.05, Flow rate = 1 mL/min, UV = 254 nm, t_R = 4.1 min (minor) and t_R = 5.0 min (major).



The absolute configuration was assigned by analogy.

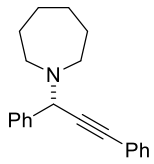
(*S*)-1-(3-(Cyclohex-1-en-1-yl)-1-phenylprop-2-yn-1-yl)pyrrolidine (3.34): Following the general procedure **B**, compound **3.34** was obtained as a yellow oil in 95% yield (252 mg); R_f = 0.48 (Hexanes/EtOAc 85:15 v/v); $[\alpha]^D_{20}$ –27.5 (c 0.5, $CHCl_3$, 90% *ee*); IR (KBr) 3027, 2931, 2873, 1449, 1345, 1271, 1128, 918, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.57–7.51 (comp, 2H), 7.36–7.30 (comp, 2H), 7.29–7.23 (m, 1H), 6.16–6.11 (m, 1H), 4.76 (s, 1H), 2.65–2.56 (comp, 4H), 2.21–2.15 (comp, 2H), 2.14–2.06 (comp, 2H), 1.82–1.71 (comp, 4H), 1.69–1.63 (comp, 2H), 1.62–1.55 (comp,



2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.06, 134.49, 134.46, 128.37, 128.27, 127.49, 120.71, 88.88, 83.77, 59.16, 50.30, 29.73, 25.73, 23.59, 22.48, 21.69; *m/z* (ESI–MS) 266.0 $[M + H]^+$; HPLC: Daicel Chiralpak OJ-H, *n*-hexane/*i*-PrOH /diethylamine = 99/1/0.05, Flow rate = 1 mL/min, UV = 254 nm, t_R = 5.6 min (minor) and t_R = 7.1 min (major).

The absolute configuration was assigned by analogy.

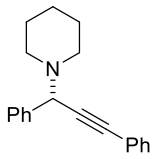
(*S*)-1-(1,3-Diphenylprop-2-yn-1-yl)azepane (3.35): Following the general procedure **B**,



compound **3.35** was obtained as a yellow oil in 80% yield (232 mg); R_f = 0.42 (Hexanes/EtOAc 90:10 v/v); $[\alpha]^D_{20}$ –1.56 (c 0.5, $CHCl_3$, 88% *ee*); IR (KBr) 3060, 2924, 2851, 1598, 1490, 1449, 1324, 1272, 1067, 755, 691 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74–7.69 (comp, 2H), 7.56–7.50 (comp, 2H), 7.40–7.32 (comp, 5H), 7.32–7.27 (m, 1H), 4.94 (s, 1H), 2.80–2.70 (comp, 4H), 1.73–1.56 (comp, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.79, 131.96, 128.42, 128.41, 128.14, 128.12, 123.59, 87.20, 86.91, 62.82, 52.83, 29.10, 27.14; *m/z* (ESI–MS) 290.1$[M + H]^+$; HPLC: Daicel Chiralpak OJ-H, *n*-hexane/*i*-PrOH /diethylamine = 99/1/0.05, Flow rate = 0.2 mL/min, UV = 280 nm, t_R = 28.0 min (minor) and t_R = 29.4 min (major).

The absolute configuration was assigned by analogy.

(*S*)-1-(1,3-Diphenylprop-2-yn-1-yl)piperidine (3.36): Following the general procedure **B**,

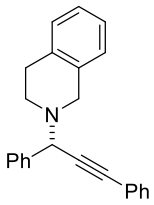


compound **3.36** was obtained as a white solid in 95% yield (262 mg); mp = 63–65 °C; R_f = 0.61 (Hexanes/EtOAc 85:15 v/v); $[\alpha]^D_{20}$ –7.8 (c 0.5, $CHCl_3$, 68% *ee*); IR (KBr) 3058, 2936, 2854, 2801, 1598, 1489, 1448, 1324, 1201, 1112, 764, 733, 694 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67–7.61 (comp, 2H), 7.55–7.48 (comp, 2H), 7.40–7.25 (comp, 6H), 4.79 (s, 1H), 2.65–2.46 (comp, 4H), 1.68–1.51 (comp, 4H), 1.50–1.38 (comp, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.92, 132.07, 128.76, 128.53,

128.31, 128.29, 123.63, 88.10, 86.37, 62.66, 50.97, 26.49, 24.73; *m/z* (ESI–MS) 276.1 $[M + H]^+$; HPLC: Daicel Chiralpak OJ-H, *n*-hexane/*i*-PrOH /diethylamine = 99/1/0.05, Flow rate = 1 mL/min, UV = 254 nm, t_R = 6.1 min (minor) and t_R = 7.5 min (major).

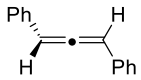
The absolute configuration was assigned by analogy.

(*S*)-2-(1,3-Diphenylprop-2-yn-1-yl)-1,2,3,4-tetrahydroisoquinoline (3.37): Following the general procedure **B**, compound **3.37** was obtained as a yellow solid in 95% yield (307 mg); mp = 87–88 °C; R_f = 0.41 (Hexanes/EtOAc 95:5 v/v); $[\alpha]^D_{20}$ –11.6 (c 0.5, $CHCl_3$, 61% *ee*); IR (KBr) 3055, 3026, 2913, 2805, 2785, 1489, 1444, 1315, 1283, 1080, 748, 701 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.79–7.74 (comp, 2H), 7.58–7.52 (comp, 2H), 7.46–7.39 (comp, 2H), 7.39–7.31 (comp, 4H), 7.18–7.11 (comp, 3H), 7.07–7.02 (m, 1H), 5.11 (s, 1H), 3.94–3.85 (comp, 2H), 3.03–2.87 (comp, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.42, 136.39, 134.53, 131.96, 128.81, 128.58, 128.43, 128.36, 128.33, 127.82, 126.86, 126.09, 125.66, 123.16, 88.68, 86.16, 61.72, 52.36, 47.37, 29.81; *m/z* (ESI–MS) 324.0 $[M + H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 99/1, Flow rate = 0.5 mL/min, UV = 254 nm, t_R = 19.0 min (major), t_R = 20.4 min (minor).



The absolute configuration was assigned by analogy.

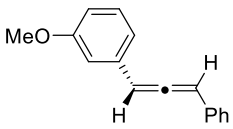
(*R*)-1,3-Diphenylpropa-1,2-diene (3.40): Following the general procedure **C**, compound **3.40** was obtained as a white solid in 72% yield (28 mg); mp = 52–54 °C; R_f = 0.33 (Hexanes/EtOAc 98:2 v/v); $[\alpha]^D_{20}$ –648.2 (c 0.5, $CHCl_3$, 92% *ee*); IR (KBr) 3059, 3022, 2923, 1934, 1593, 1490, 1450, 1252, 1070, 911, 879, 751, 692 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.37–7.30 (comp, 8H), 7.26–7.21 (comp, 2H), 6.61 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.93, 133.75, 128.88, 127.46, 127.15, 98.58; *m/z* (ESI–MS)



192.8 $[M + H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 99/1, Flow rate = 1 mL/min, UV = 254 nm, t_R = 5.8 min (major), t_R = 7.6 min (minor).

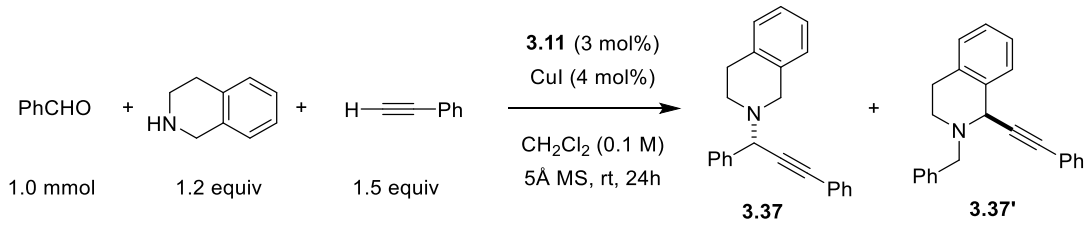
The absolute configuration was assigned by comparing the sign of the optical rotation with the reported literature value of this product (*R*): $[\alpha]^D_{25}$ –864.4 (c 0.59, $CHCl_3$, 94% *ee*).[74]

(*R*)-1-Methoxy-3-(3-phenylpropa-1,2-dien-1-yl)benzene (3.41): Following the general procedure **C**, compound **3.41** was obtained as a light yellow oil in 48% yield (21 mg); R_f = 0.31 (Hexanes/EtOAc 98:2 v/v); $[\alpha]^D_{20}$ –712.1 (c 0.5, $CHCl_3$, 94% *ee*); IR (KBr): 3027, 2931, 1937, 1701, 1596, 1490, 1452, 1264, 1152, 1043, 696 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.41–7.31 (comp, 4H), 7.22–7.22 (comp, 2H), 6.98 (d, *J* = 7.6 Hz, 1H), 6.95–6.91 (m, 1H), 6.81 (dd, *J* = 8.2, 2.5 Hz, 1H), 6.65–6.57 (comp, 2H), 3.81(s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.99, 160.11, 135.22, 133.69, 129.83, 128.88, 127.48, 127.17, 119.81, 113.25, 112.31, 104.91, 98.63, 98.56, 55.37; *m/z* (ESI–MS) 223.1 $[M + H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 99/1, Flow rate = 1 mL/min, UV = 280 nm, t_R = 9.8 min (major), t_R = 11.5 min (minor).



The absolute configuration was assigned by analogy.

Result for the CuI/3.11 catalyzed reaction with THIQ:



Products **3x** and **3x′** were not separable by standard column chromatography. According to the HPLC profile of a 1:1 mixture of racemic A^3 product **3.37** and racemic redox-A^3 product

3.37′,[75] peaks of retention times 19.2 and 28.5 min, each corresponding to one enantiomer of **3.37** and **3.37′**, have approximately the same area. Therefore, regular and redox-A^3 products have the same molar extinction coefficients at this wavelength (254 nm). ^{1}H-NMR analysis of the product mixture indicates the formation of **3.37** and **3.37′** in a 6:1 ratio. The ee's for both products were calculated based on this ratio and the corresponding HPLC data. The absolute configuration of **3.37′** was tentatively assigned based on a comparison with literature data.[75]

References

(1) Wei, C.; Li, Z.; Li, C.-J. *Synlett* **2004**, 1472.
(2) Zani, L.; Bolm, C. *Chem. Commun.* **2006**, 4263.
(3) Li, C.-J. *Acc. Chem. Res.* **2010**, *43*, 581.
(4) Peshkov, V. A.; Pereshivko, O. P.; Van der Eycken, E. V. *Chem. Soc. Rev.* **2012**, *41*, 3790.
(5) Fischer, C.; Carreira, E. M. *Org. Lett.* **2001,** *3,* 4319.
(6) Li, C.-J.; Wei, C. *Chem. Commun.* **2002,** 268.
(7) Wei, C.; Li, C.-J. *J. Am. Chem. Soc.* **2002**, *124*, 5638.
(8) Bisai, A.; Singh, V. K. *Org. Lett.* **2006**, *8*, 2405.
(9) Liu, J.; Liu, B.; Jia, X.; Li, X.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2007,** *18,* 396.
(10) Irmak, M.; Boysen, M. M. K. *Adv. Synth. Catal.* **2008,** *350,* 403.
(11) Shao, Z.; Pu, X.; Li, X.; Fan, B.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2009,** *20,* 225.
(12) Wang, J.; Shao, Z.; Ding, K.; Yu, W.-Y.; Chan, A. S. C. *Adv. Synth. Catal.* **2009,** *351,* 1250.
(13) Nakamura, S.; Ohara, M.; Nakamura, Y.; Shibata, N.; Toru, T. *Chem.–Eur. J.* **2010,** *16,* 2360.
(14) Bisai, A.; Singh, V. K. *Tetrahedron* **2012,** *68,* 3480.
(15) Balaraman, K.; Vasanthan, R.; Kesavan, V. *Tetrahedron Lett.* **2013,** *54,* 3613.
(16) Nakamura, S.; Ohara, M.; Nakamura, Y.; Shibata, N.; Torua, T. *Chem. Eur. J.* **2010,** *16,* 2360.
(17) Ohara, M.; Hara, Y.; Ohnuki, T.; Nakamura, S. *Chem.–Eur. J.* **2014,** *20,* 8848.
(18) Benaglia, M.; Negri, D.; Dell'Anna, G. *Tetrahedron Lett.* **2004,** *45,* 8705.
(19) Colombo, F.; Benaglia, M.; Orlandi, S.; Usuelli, F. *J. Mol. Catal. A: Chem.* **2006,** *260,* 128.
(20) Colombo, F.; Benaglia, M.; Orlandi, S.; Usuelli, F.; Celentano, G. *J. Org. Chem.* **2006,** *71,* 2064.
(21) Liu, B.; Huang, L.; Liu, J.; Zhong, Y.; Li, X.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2007,** *18,* 2901.
(22) Liu, B.; Liu, J.; Jia, X.; Huang, L.; Li, X.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2007,** *18,* 1124.
(23) Liu, B.; Zhong, Y.; Li, X. *Chirality* **2009,** *21,* 595.
(24) Orlandi, S.; Colombo, F.; Benaglia, M. *Synthesis* **2005,** 1689.
(25) Hatano, M.; Asai, T.; Ishihara, K. *Tetrahedron Lett.* **2008,** *49,* 379.
(26) Shao, Z.; Wang, J.; Ding, K.; Chan, A. S. C. *Adv. Synth. Catal.* **2007,** *349,* 2375.
(27) Zani, L.; Eichhorn, T.; Bolm, C. *Chem.–Eur. J.* **2007,** *13,* 2587.
(28) Blay, G.; Cardona, L.; Climent, E.; Pedro, J. R. *Angew. Chem., Int. Ed.* **2008,** *47,* 5593.
(29) Yan, W.; Li, P.; Feng, J.; Wang, D.; Zhu, S.; Jiang, X.; Wang, R. *Tetrahedron: Asymmetry* **2010,** *21,* 2037.
(30) Huang, G.; Yang, J.; Zhang, X. *Chem. Commun.* **2011,** *47,* 5587.
(31) Blay, G.; Ce-ballos, E.; Monleon, A.; Pedro, J. R. *Tetrahedron* **2012,** *68,* 2128.
(32) Traverse, J. F.; Hoveyda, A. H.; Snapper, M. L. *Org. Lett.* **2003,** *5,* 3273.
(33) Rueping, M.; Antonchick, A. P. *Angew. Chem., Int. Ed.* **2007,** *46,* 4562.
(34) Gommermann, N.; Koradin, C.; Polborn, K.; Knochel, P. *Angew. Chem. Int. Ed.* **2003**, *42*, 5763.
(35) Gommermann, N.; Knochel, P. *Chem. Commun.* **2004**, 2324.
(36) Gommermann, N.; Knochel, P. *Chem. Commun.* **2005**, 4175.
(37) Gommermann, N.; Knochel, P. *Chem. Eur. J.* **2006**, *12*, 4380.
(38) Knöpfel, T. F.; Aschwanden, P.; Ichikawa, T.; Watanabe, T.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2004**, *43*, 5971.

(39) Aschwanden, P.; Stephenson, C. R. J.; Carreira, E. M. *Org. Lett.* **2006**, *8*, 2437.
(40) Fan, W.; Ma, S. M. *Chem. Commun.* **2013**, *49*, 10175.
(41) Cardoso, F. S. P.; Abboud, K. A.; Aponick, A. *J. Am. Chem. Soc.* **2013**, *135*, 14548.
(42) Naeimi, H.; Moradian, M. *Tetrahedron: Asymmetry* **2014**, *25*, 429.
(43) Chen, Y.; Yekta, S.; Yudin, A. K. *Chem. Rev.* **2003,** *103,* 3155.
(44) Claridge, T. D. W.; Long, J. M.; Brown, J. M.; Hibbs, D.; Hursthouse, M. B. *Tetrahedron* **1997,** *53,* 4035.
(45) Rueping, M.; Nachtsheim, B. J.; Ieawsuwan, W.; Atodiresei, I. *Angew. Chem., Int. Ed.* **2011,** *50,* 6706.
(46) Terada, M. *Synthesis* **2010,** 1929.
(47) Review submitted: Asymmetric Brønsted Acid Catalysis with Chiral Carboxylic Acids.
(48) Min, C.; Mittal, N.; Sun, D. X.; Seidel, D. *Angew. Chem., Int. Ed.* **2013,** *52,* 14084.
(49) Mittal, N.; Sun, D. X.; Seidel, D. *Org. Lett.* **2014**, *16*, 1012.
(50) Min, C.; Lin, C.-T; Seidel, D. *Angew. Chem., Int. Ed.* **2015,** *54,* 6608.
(51) Rasappan, R.; Hager, M.; Gissibl, A.; Reiser, O. *Org. Lett.* **2006**, *8*, 6099.
(52) Shao, Z.; Wang, J.; Ding, K.; Chan, A. S. C. *Adv. Synth. Catal.* **2007**, *349*, 2375.
(53) Peng, F. Z.; Shao, Z. H.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2010**, *21*, 465.
(54) Hoffmann-Röder, A.; Krause, N. *Angew. Chem., Int. Ed.* **2004**, *43*, 1196.
(55) Crabbé, P.; Fillion, H.; André, D.; Luche, J.-L. *J. Chem. Soc., Chem.Commun.* **1979,** 859.
(56) Neff, R. K.; Frantz, D. E. *ACS Catal.* **2014,** *4,* 519.
(57) Ye, J.; Ma, S. *Org. Chem. Front.* **2014**, *1*, 1210.
(58) Kuang, J.; Ma, S. *J. Am. Chem. Soc.* **2010,** *132,* 1786.
(59) Lo, V. K. Y.; Wong, M. K.; Che, C. M. *Org. Lett.* **2008**, *10*, 517.
(60) Lo, V. K.-Y.; Zhou, C.-Y.; Wong, M.-K.; Che, C.-M. *Chem. Commun.* **2010**, *46*, 213.
(61) Periasamy, M.; Sanjeevakumar, N.; Dalai, M.; Gurubrahamam, R.; Reddy, P. O. *Org. Lett.* **2012**, *14*, 2932.
(62) Periasamy, M.; Reddy, P. O.; Sanjeevakumar, N. *Eur. J. Org. Chem.* **2013,** *18,* 3866.
(63) Gurubrahamam, R.; Periasamy, M. *J. Org. Chem.* **2013,** *78,* 1463.
(64) Ye, J. T.; Li, S. H.; Chen, B.; Fan, W.; Kuang, J. Q.; Liu, J. X.; Liu, Y.; Miao, B. K. Y.; Wan, B. Q.; Wang, Y. L.; Xie, X.; Yu, Q.; Yuan, W. M.; Ma, S. M. *Org. Lett.* **2012**, *14*, 1346.
(65) Min, C.; Mittal, N.; Sun, D. X.; Seidel, D. *Angew. Chem. Int. Ed*. **2013**, *52*, 14084.
(66) Klauber, E. G.; De, C. K.; Shah, T. K.; Seidel, D. *J. Am. Chem. Soc*. **2010**, *132*, 13624.
(67) Sohtome, Y.; Tanatani, A.; Hashimoto, Y.; Nagasawa, K. *Tetrahedron Lett*. **2004**, *45*, 5589.
(68) K. Dudziński, A. M. Pakulska, P. Kwiatkowski, *Org. Lett.* **2012**, *14*, 4222.
(69) K. L. Tan, E. N. Jacobsen, *Angew. Chem. Int. Ed.* **2007**, *46*. 1315.
(70) Abou-Teim, O.; Jansen, R. B.; McOmie, J. F. W.; Perry, D. H. *J. Chem. Soc., Perkin Trans. 1*. **1980**, 1841.
(71) Burns, N. Z.; Witten, M. R.; Jacobsen, E. N. *J. Am. Chem. Soc*. **2011**, *133*, 14578.
(72) Lo, V. K.-Y.; Zhou, C.-Y.; Wong, M.-K.; Che, C.-M. *Chem. Commun.* **2010**, *46*, 213.
(73) Bojack, G.; Künzer, H.; Rölfing, K.; Thiel, M. *Tetrahedron Lett*. **1996**, *37*, 6103
(74) Periasamy, M.; Sanjeevakumar, N.; Dalai, M.; Gurubrahamam, R.; Reddy, P. O. *Org. Lett*. **2012**, *14*, 2932.
(75) Racemic **3x′** was synthesized according to a known procedure: Lin, W.; Cao, T.; Fan, W.; Han, Y.; Kuang, J.; Luo, H.; Miao, B.; Tang, X.; Yu, Q.; Yuan, W.; Zhang, J.; Zhu, C.; Ma, S. *Angew. Chem. Int. Ed.* **2014**, *53*, 277.

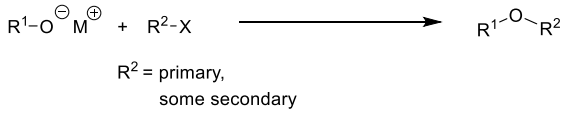
Chapter IV Direct Reductive Etherification Enabled by Cooperative Dual Catalysis of a Thiourea and a Strong Brønsted Acid

4.1 Background

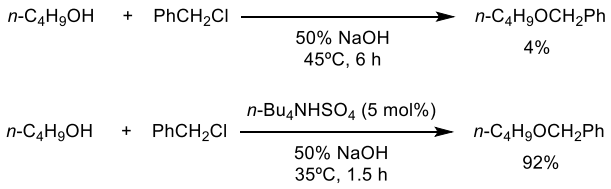
4.1.1 Williamson Ether Synthesis

The Williamson ether synthesis[1–3] has been most popular in ether formation reactions,[4–7] where a metal alkoxide undergoes an S_N2 reaction with an alkyl halide to forge the C–O bond (Scheme 4.1). Although generally no sophiscated catalyst or additive is required for such a process, the preparation of alkoxides and the generation of stoichiometric amounts of metal salt waste greatly limit its practicality. Moreover, the Williamson ether synthesis is highly sensitive to the sterics of the alkylating reagents as competitive elimination reactions can occur. Primary halides are usually viable substrates while tertiary halides mainly undergo elimination.

Scheme 4.1 Williamson ether synthesis.



Scheme 4.2 Williamson ether synthesis catalyzed by phase transfer catalyst.



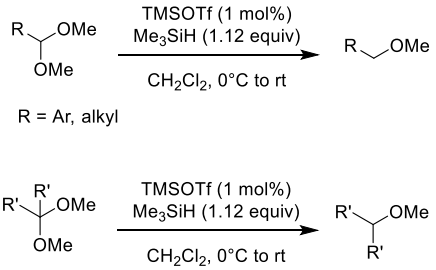
The efficiency of the Williamson ether synthesis can be improved with phase transfer catalysis (Scheme 4.2).[2] The counter anion of the phase transfer catalyst has a profound effect on the reaction rate, as its competes with the alkoxide anion in forming an ion pair with the quaternary ammonium cation. Despite the conducive effect of phase transfer catalysts,

the limitation of substrate scope, stoichiometric use of metal alkoxide and consequent generation of metal salt waste are still pressing issues with this methodology.

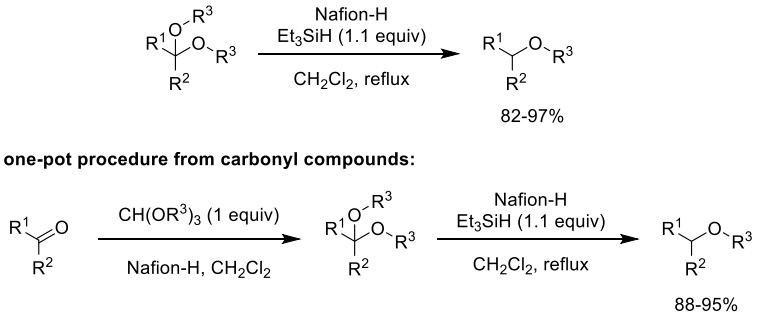
4.1.2 Reduction of Acetals

Acetals have been known for a long time to be reduced to the corresponding ethers or hydroxyl ethers by various reducing agents such as hydrogen gas,[8,9] hydrides[10–18] and silanes.[19–26] A representative work from Noyori revealed trimethylsilyl trifluoromethanesulfonate (TMSOTf) to be a viable catalyst for the reduction of dimethyl acetals (Scheme 4.3).[20] The corresponding methyl ethers are obtained in good to excellent yields with trimethylsilane as the reducing agent. Acetals derived from both aromatic and aliphatic aldehydes as well as ketones are well tolerated. However, no functional groups were evaluated for the process.

Scheme 4.3 TMSOTf catalyzed reduction of acetals to ethers by Noyori.



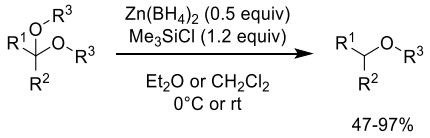
Scheme 4.4 Nafion-H catalyzed reduction of acetals and ketals.



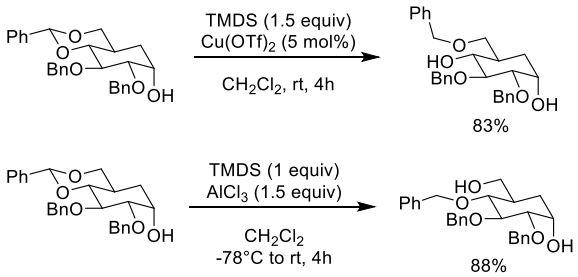
A more practical method was reported by Olah using catalytic amounts of Nafion-H (Scheme 4.4).[21] The resin-based Brønsted acid is stable towards moisture and can be regenerated easily. Various acetals and ketals can be efficiently reduced to the corresponding ethers in a few hours. A one-pot procedure was also demonstrated to convert carbonyl compounds to the corresponding ethers without isolating the dialkyl acetal intermediate.

Kotsuki reported the reduction reactions of acetals and ketals using $Zn(BH_4)_2$ as the reducing agent (Scheme 4.5).[10] Compared with Noyori's approach (Scheme 4.3), a weaker Lewis acid Me_3SiCl was used but in stoichiometric amount (1.2 equivalent). A wide variety of acetals and ketals are well tolerated and the reactions usually proceed at ambient temperature. A longer reaction time is needed for aliphatic acetals, and a *para*-nitro group on the aromatic acetal has a strong deactivating effect. The observed reaction time difference is in accord with the stability trend of the carbocation generated by acetal cleavage.

Scheme 4.5 TMSCl promoted reduction of acetals and ketals by $Zn(BH_4)_2$.



Scheme 4.6 Regioselective reductive cleavage of 4,6-*O*-benzylidene glycosyl acetals to ethers.



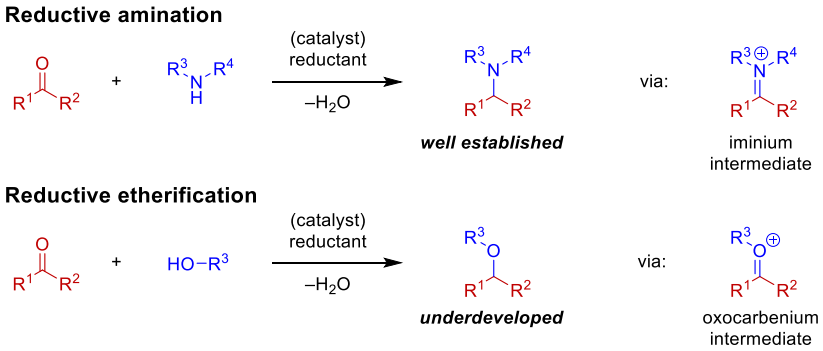
Reduction of cyclic acetals has been explored largely in sugar chemistry. Lemaire reported the regioselective reductive cleavage of 4,6-*O*-benzylidene glycosyl acetals to ethers

(Scheme 4.6).[26] Either regioisomer can be obtained with satisfactory yield by judicious choice of Lewis acid catalyst or promoter. Catalytic amount of $Cu(OTf)_2$ enables *O*-4 ring cleavage while 1.5 equivalents of $AlCl_3$ are needed for *O*-6 cleaved regioisomer.

4.1.3 Reductive Etherification

Reductive amination reactions are among the most reliable methods for amine synthesis due to starting material availability, mild reaction conditions, and broad substrate scope (Scheme 4.7).[27–29] In contrast, the corresponding reductive etherification is significantly less developed. This is despite the wide availability of the prerequisite starting materials and the advantages such an approach would offer over classical methods such as the Williamson ether synthesis.[1–7] Great efforts have been dedicated towards the development of a general method for reductive etherification. Most strategies are based on transition metal catalysts,[30–33] Lewis acids,[34–38] and Brønsted acids.[39–41] Methods relying on silylated alcohols rather than unprotected alcohols have also emerged.[42–55]

Scheme 4.7 Reductive amination and reductive etherification.

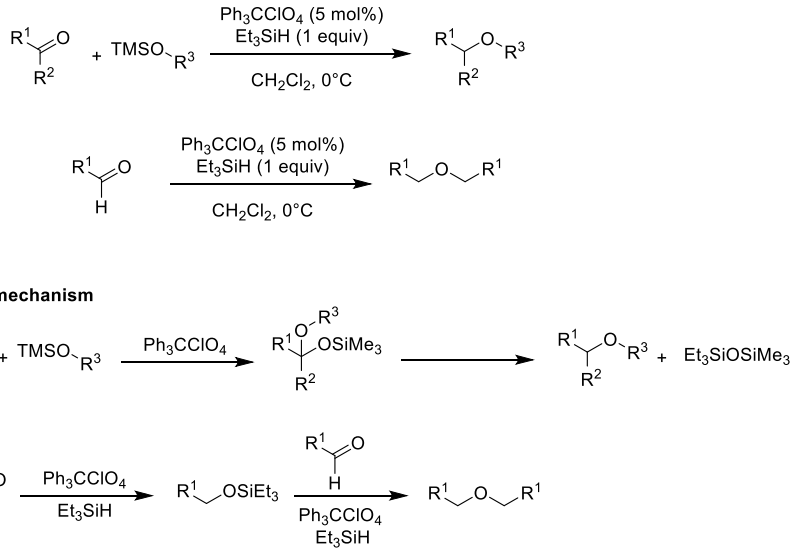


4.1.3.1 With Silylated Alcohol

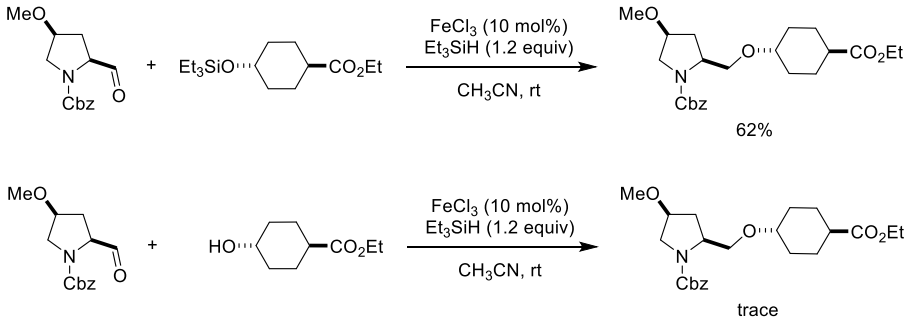
In 1985, Mukaiyama reported the first reductive etherification between aldehydes and trimethylsilyl protected alcohols (Scheme 4.8).[42] Both aliphatic and aromatic aldehydes, as

well as ketones, undergo reductive etherification reactions with silylated aliphatic alcohols to afford the corresponding ethers. A stoichiometric amount of triethylsilane is used as an efficient reducing agent in combination with catalytic amounts of trityl perchlorate. When aldehydes are used as the sole coupling partner, symmetrical ethers are generated in reasonable yields.

Scheme 4.8 Ph_3CClO_4 catalyzed reductive etherification.



Scheme 4.9 Comparison between free and protected alcohol in VLA-4 antagonist synthesis.



Subsequently, many other Lewis acids have been reported to catalyze this reaction, such as TMSI,[43] TMSOTf,[45] $BiBr_3$,[46] $Cu(OTf)_2$,[49] $B(C_6H_5)_3$,[50] $FeCl_3$,[51] and $InCl_3$.[52] Despite the versatility of these approaches, protection of the alcohol is required and the Lewis acid

catalysts employed are often moisture sensitive. In an effort to synthesize a very late antigen-4 antagonist, the reductive etherification reaction was applied by Chiba with $FeCl_3$ as catalyst (Scheme 4.9).[54] In this case, the use of an unprotected free alcohol only results in trace amount of desired product.

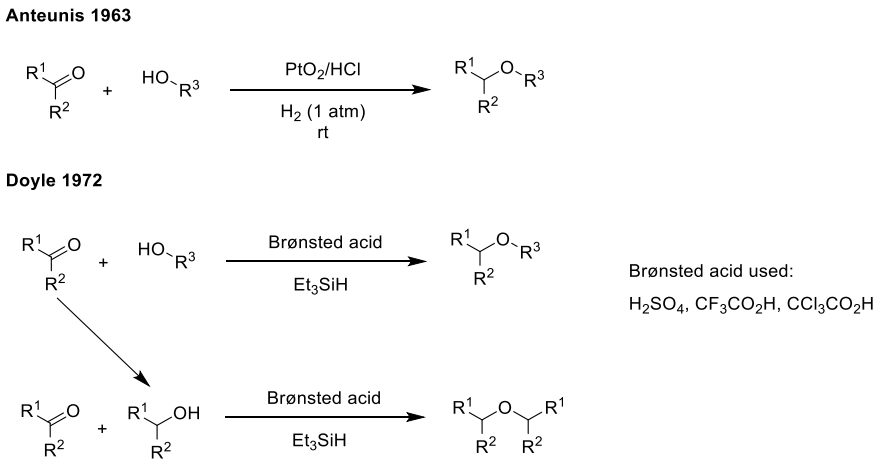
4.1.3.2 With Unprotected Alcohol

In 1963, Anteunis reported the first reductive etherification reactions between carbonyls and alcohols in the presence of platinum oxide catalyst, hydrogen and excess amounts of Brønsted acids (Scheme 4.10).[56] Despite the great importance of this method, large excess of alcohol and stoichiometric amount of hydrochloric acid are required. Although both ketones and aldehydes are tolerated, the scope of the alcohol is very limited. In 1972, Doyle reported an alternative approach using triethylsilane as the reducing agent in the absence of metal catalyst (Scheme 4.10).[39] This method also suffers from excess use of acid and limited substrate scope. Secondary and benzyl alcohols result in dramatic loss in yield and other functional groups are not tolerated. Major side products of this procedure are alcohols from aldehyde reduction and symmetrical ethers resulting from homocoupling reactions. The latter is generated via reductive coupling reaction between the carbonyl compound and the alcohol generated from carbonyl compound reduction.

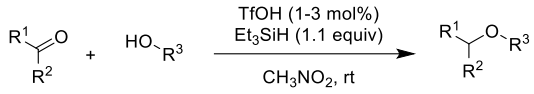
Following the seminal work described above, Lewis acids have also been reported as viable catalysts for this reaction with silane as reductant.[34–38] Large excess of TMSCl[36] and stoichiometric amounts of TMSOTf[34,37] were also used, presumably via *in situ* transformation of alcohols into the corresponding silyl ether. The first thorough evaluation of the substrate scope incorporating other functional groups was reported by Roth, where triflic acid successfully catalyzed the reaction (Scheme 4.11).[41] Alkene, alkyne, nitro, ester, carboxylic acid are all viable functional groups for this process. However, the study is light on aliphatic

aldehydes and aromatic ketones, and drastic loss in yield was observed for the latter. Moreover, when benzyl alcohol was used, considerable aldehyde reduction and subsequent homocoupling side product was observed.

Scheme 4.10 Early examples of reductive etherification with unmodified alcohols.

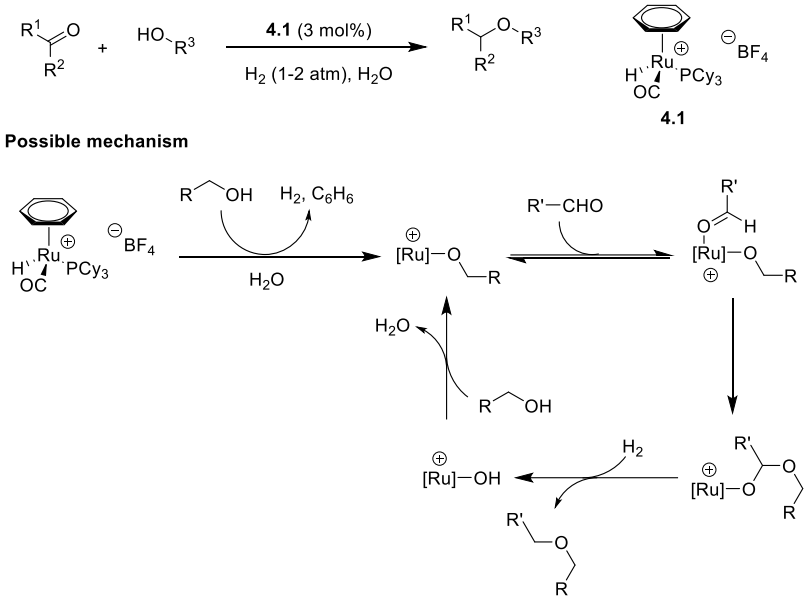


Scheme 4.11 Triflic acid catalyzed reductive etherification reactions.



Very recently, Yi reported the use of a cationic Ru-H complex for this reaction, simple hydrogen gas and water are used as the reductant and solvent (Scheme 4.12).[33] Aromatic and aliphatic aldehydes as well as ketones are all viable substrates with satisfactory yields. However, a potential disadvantage in terms of practicality is that a glovebox is required for the reaction setup. The proposed mechanism involves initial generation of a Ru-alkoxy species and coordination with the carbonyl compound. Subsequent hydrogenolysis of the hemiacetoxy species affords the final reductive coupling product.

Scheme 4.12 Ruthenium complex catalyzed reductive etherification reactions.

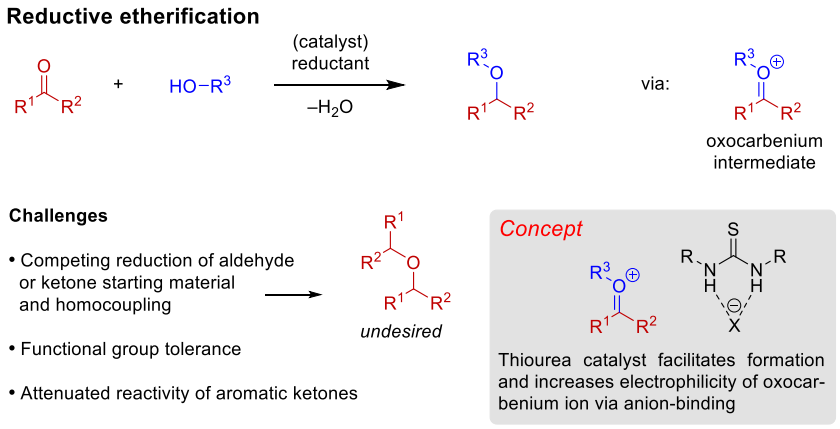


4.2 Direct Reductive Etherification Reactions Enabled by a Thiourea and a Strong Brønsted Acid Combination

Despite the advances regarding the reductive etherification reactions as mentioned above, a number of challenges have yet to be addressed to allow for broader application of this process. Remaining limitations include first and foremost functional group compatibility, but also suppression of reductive homocoupling of the aldehyde or ketone component, and applicability to challenging substrates such as aromatic ketones. We aimed to develop a new concept for the reductive etherification reactions that is based on the combination of a readily accessible organocatalyst, HCl and a simple silane reducing agent (Figure 4.1). Mirroring the requirements for reductive amination, a method for reductive etherification has to facilitate the condensation of an aldehyde/ketone with an alcohol to generate an oxocarbenium ion or related intermediate. The latter has to be reduced selectively over the aldehyde/ketone. Based on the known propensity of thiourea catalysts to increase the acidity of a Brønsted acid,[57–63] we envisioned that a combination of a simple Brønsted acid and a thiourea catalyst

in presence of an appropriate reducing agent might allow for efficient reductive etherification. Specifically, the thiourea catalyst is expected to facilitate the Brønsted acid catalysis in promoting the formation of the oxocarbenium ion intermediate and/or increasing its equilibrium concentration. Interaction of the counter anion of the oxocarbenium cation with the thiourea catalyst via anion-binding should serve to increase the electrophilicity of the oxocarbenium cation. In addition, the sulfur atom of the thiourea moiety may serve as a Lewis base capable of interacting with the reducing reagent.[64] As mentioned in Chapter I, the concept of anion-binding catalysis was first proposed by Schreiner and coworkers,[65] and is now recognized as a general activation mode.

Figure 4.1 Reductive etherification with thiourea anion-binding catalyst.

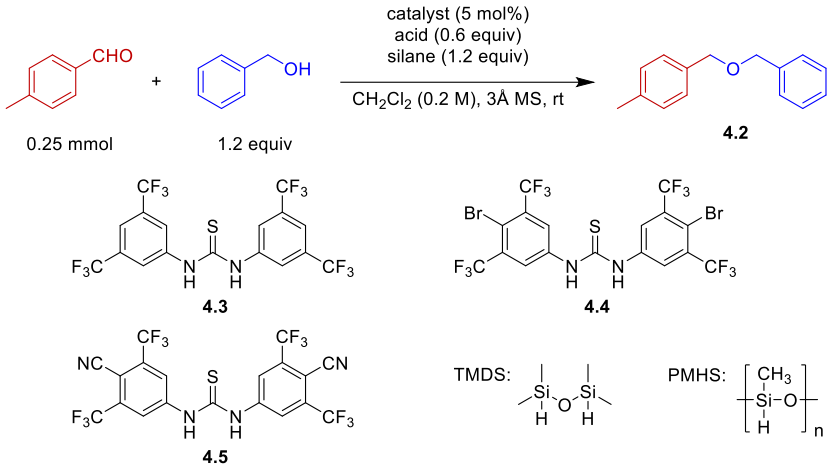


4.2.1 Optimization

Para-tolualdehyde and benzyl alcohol were selected as model substrates to evaluate the proposed reductive etherification reaction (Table 4.1). In the absence of a thiourea catalyst with TFA as the Brønsted acid promoter and Et_3SiH as the reducing reagent, only trace amounts of product **4.2** were observed after 24 hours and starting materials remained mostly unaffected (entry 1). The use of HCl in an otherwise identical experiment provided

4.2 with markedly increased yield (entry 2). As a proof of concept, addition of the well-

Table 4.1 Optimization of reaction conditions.



entry	catalyst	acid	silane	time [h]	yield (%)
1	-	TFA	Et_3SiH	24	6
2	-	HCl	Et_3SiH	24	44
3	**4.3**	HCl	Et_3SiH	24	64
4	**4.4**	HCl	Et_3SiH	24	74
5	**4.4**	HCl	$PhSiH_3$	24	21
6	**4.4**	HCl	Ph_2SiH_2	24	34
7	**4.4**	HCl	Me_2PhSiH	24	95
8	**4.4**	HCl	PMHS	24	12
9	**4.4**	HCl	Ph_3SiH	24	46
10	**4.4**	HCl	$MePhSiH_2$	24	66
11	**4.4**	HCl	$(EtO)_2MeSiH$	24	Trace
12	**4.4**	HCl	TMDS	5	98
13	**4.5**	HCl	TMDS	20 min	98 (94)
14	**4.3**	HCl	TMDS	24	92
15	-	HCl	TMDS	24	70
16[b]	**4.5**	HCl	TMDS	1	97
17[c]	**4.5**	HCl	TMDS	24	91

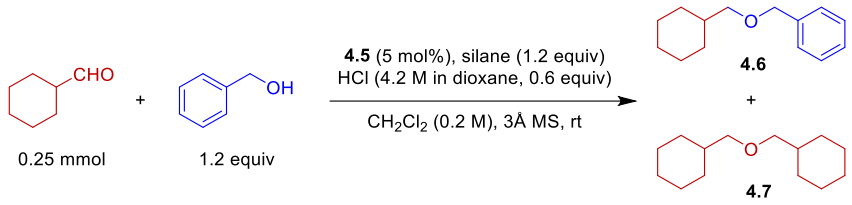
[a] NMR yields (1,3,5-trimethoxybenzene as internal standard), number in parenthesis is isolated yield; HCl was used as 4.2 M solution in dioxane. [b] with 2 mol% of thiourea. [c] with 0.3 equiv of HCl.

known Schreiner thiourea catalyst (**4.3**) at a 5 mol% loading resulted in a further substantial increase in yield (entry 3). Modified Schreiner catalyst **4.4**, bearing bromine substituents between the trifluoromethyl groups, enabled a further acceleration of the reductive etherification (entry 4). A number of different silanes were evaluated with catalyst **4.4** (entries 5–12). Among the reducing reagents, 1,1,3,3-tetramethyldisiloxane (TMDS) stood out as being highly efficient. While none of the reactions in entries 1–11 went to completion within 24 hours, the corresponding reaction with TMDS went to completion within five hours and provided **4.2** in excellent yield (entry 12). We rationalized that further improvements in efficiency may be achieved by substituting the bromo substituents in **4.4** for more electron-withdrawing cyano groups. Remarkably, the corresponding thiourea catalyst **4.5** reduced the required reaction time to 20 min with no loss in efficiency (entry 13). The difference to catalyst **4.3** is profound: under otherwise identical conditions, trace amount of starting material was still present in 24 hours (entry 14). In the absence of any thiourea catalyst, the reaction slowed down markedly (entry 15). Use of catalyst **4.5** at a loading of 2 mol% was equally efficient with regard to product yield but requiring a slightly prolonged reaction time (entry 16). However, a decrease in the amount of HCl led to a significant slowdown of the reaction (entry 17).

Under the optimized conditions of Table 4.1, reductive homocoupling of *p*-tolualdehyde was not observed. However, this undesired side reaction is known to occur in certain Brønsted acid catalyzed reductive etherification reactions. The competing reaction pathway not only compromises reaction yields, but also complicates product purification. As we were exploring the substrate scope, such homocoupling side products were observed with aliphatic aldehydes, presumably due to an increased propensity of these substrates to undergo reduction. For instance, the reaction of cyclohexanecarboxaldehyde and benzyl alcohol

provided an 8:1 mixture of desired product **4.6** and undesired homocoupling product **4.7** (Table 4.2, entry 1). We speculated that the product distribution may be shifted towards the desired product by utilizing a silane with attenuated reactivity. Indeed, upon evaluation of a number of silanes as summarized in Table 2, methylphenylsilane was found to be optimal in favoring product **4.6** (Table 2, entry 6).

Table 4.2 Optimization of conditions for an aliphatic aldehyde.



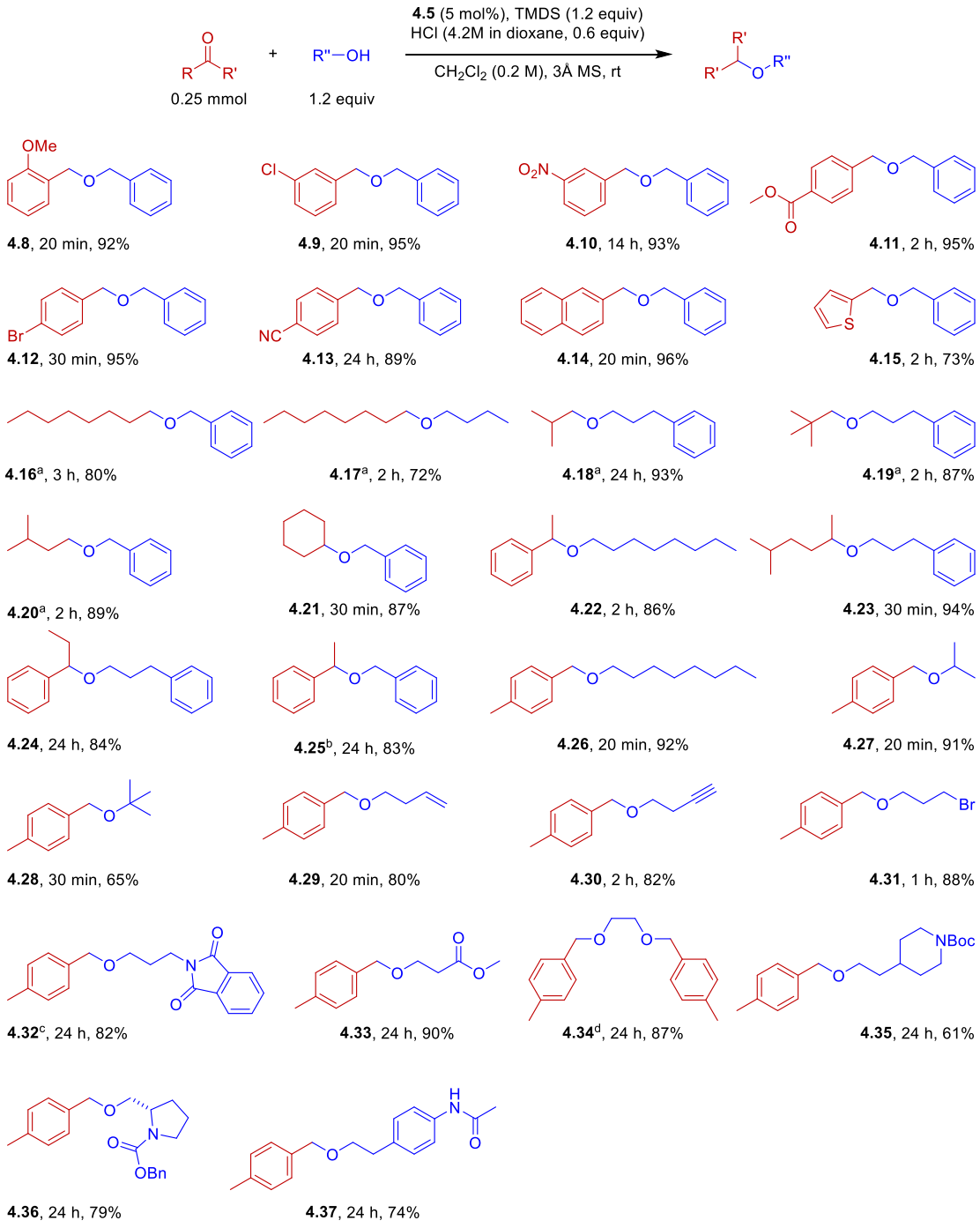
entry	silane	Time	yield of **4.6** (%)	**4.6**:**4.7**
1	TMDS	20 min	76	8:1
2	Et_3SiH	3 h	81	14:1
3	$PhSiH_3$	24 h	59	9:1
4	Ph_3SiH	24 h	66	14:1
5	Me_2PhSiH	30 min	78	15:1
6	$MePhSiH_2$	2 h	92 (87)	25:1

[a] NMR yields (1,3,5-trimethoxybenzene as internal standard), number in parenthesis is isolated yield.

4.2.2 Substrate Scope

The scope of the reductive etherification is shown in Scheme 4.13. With regard to aromatic aldehydes, different substitution patterns and electronic properties were well tolerated. Linear, α-branched, and nonenolizable aliphatic aldehydes also performed well when methylphenylsilane was used as the reductant. Cyclic and acyclic aliphatic ketones were also viable substrates. Notably, in contrast to previous reports using Brønsted and

Scheme 4.13 Substrate scope.

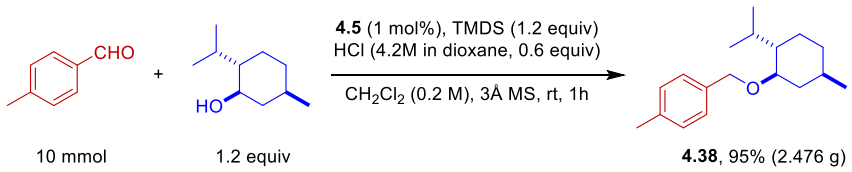


[a] MePhSiH2 was used instead of TMDS; [b] With 1.2 equiv of HCl; [c] **4.4** was used instead of **4.5**; [d] With 2.4 equiv of *p*-tolualdehyde, 10 mol% of **4.5**, 1.2 equiv of HCl and 2.4 equiv of TMDS.

Lewis acids, aromatic ketones demonstrated excellent reactivity. To the best of our knowledge, the only direct reductive etherification protocol where aromatic ketones provide

satisfactory yields calls for a ruthenium-hydride complex that requires handling in a glovebox. Various alcohols participated in reductive etherification. Ethylene glycol efficiently underwent double etherification. Importantly, the reaction was found to be compatible with a broad range of functionalities including ether, alkyl and aryl halide, nitro, ester, nitrile, thienyl, amide, imide, carbamate, alkenyl, and alkynyl groups. To further demonstrate the practicality of the process, the reductive etherification of *p*-tolualdehyde and L-menthol was performed on a 10 mmol scale with 1 mol% of **4.5** (Scheme 4.14). The reaction went to completion within one hour and provided product **4.38** in 95% yield.

Scheme 4.14 Scale-up reaction at lower catalyst loading.

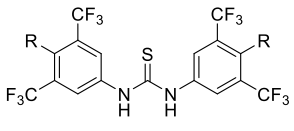


4.2.3 Further Studies

The dramatic differences in catalytic activity of the different thioureas correlate well with their chloride affinities (Table 4.3). Binding constants for chloride were determined via NMR titrations of the thiourea catalysts with tetrabutylammonium chloride in deuterated DMSO containing 0.5% water (Figures 4.2, 4.3, 4.4).[66] Consistent with the substantially greater activity of **1c**, this catalyst showed a twofold binding affinity for chloride compared to **1a** and **1b**.

Table 4.3 Chloride binding constants of thiourea catalyst.

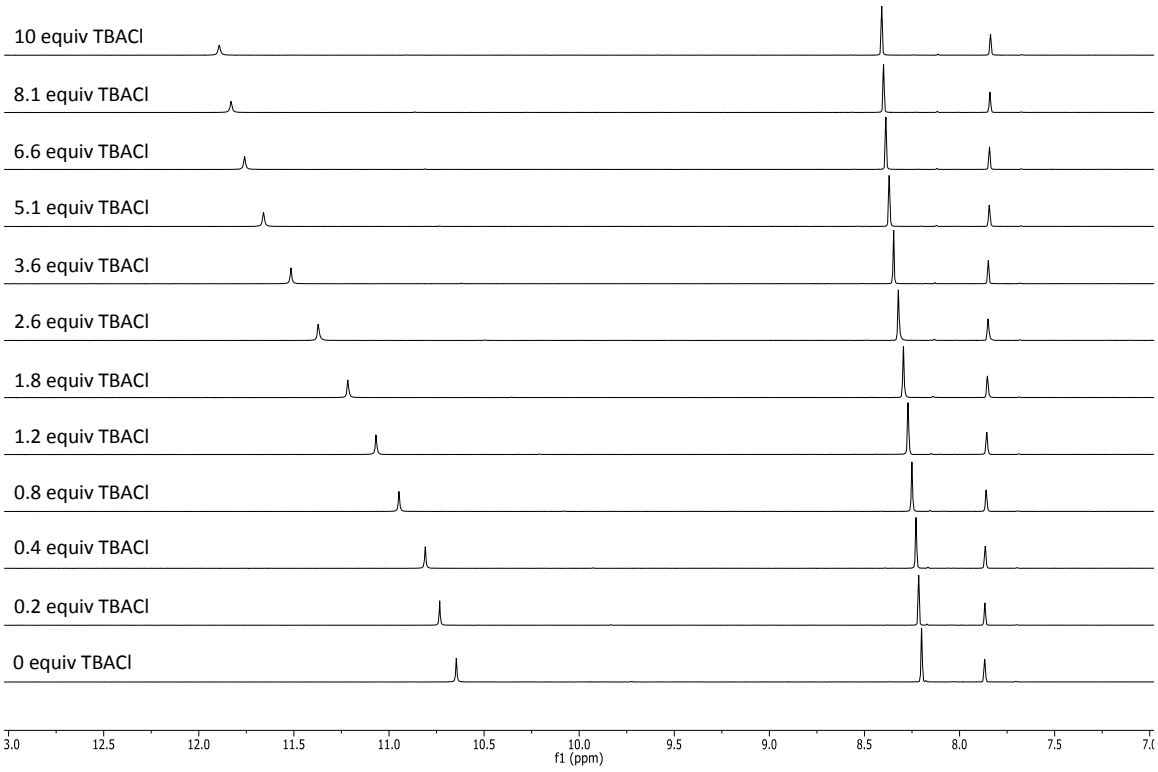
catalyst	K_a (M^{-1})
4.3	39.1±0.49 (41)[b]
4.4	41.7±0.46
4.5	81±2.2



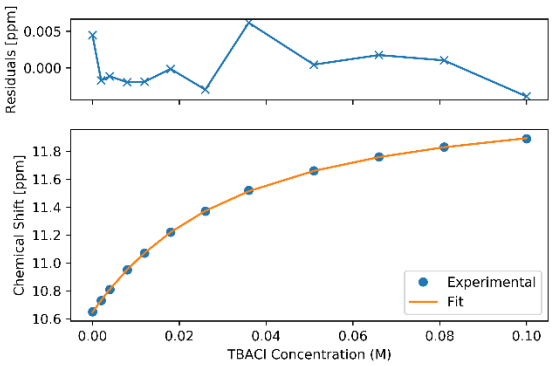
4.3 R = H
4.4 R = Br
4.5 R = CN

Figure 4.2 NMR titration of **4.3** with TBACl in DMSO-d_6/0.5% H_2O. (a) Stack plot. (b) Fitplot of N-H at δ 10.65 ppm, K_a = 39.1 ± 0.49 M^{-1}. (C) Fitplot of C-H at δ 8.20 ppm, K_a = 40 ± 2.3 M^{-1}.

(a)



(b)



(c)

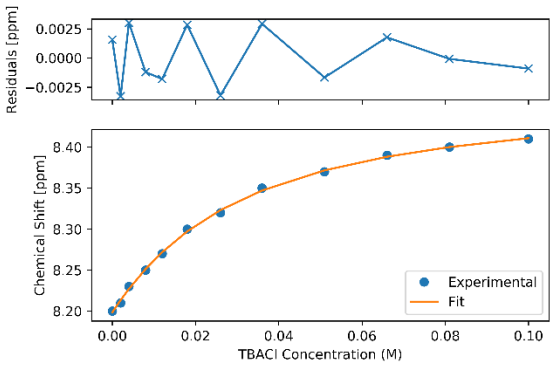
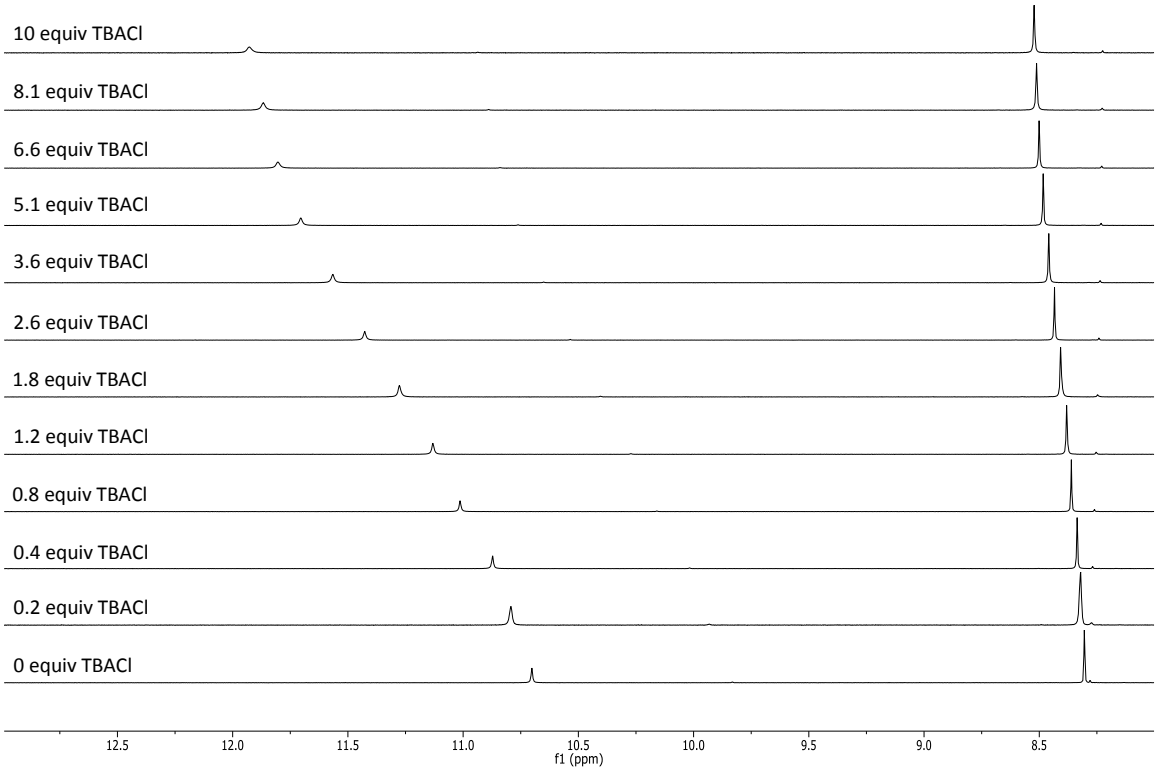


Figure 4.3 NMR titration of **4.4** with TBACl in DMSO-d_6/0.5% H_2O. (a) Stack plot. (b) Fitplot of N-H at δ 10.70 ppm, K_a = 41.7 ± 0.46 M^{-1}. (C) Fitplot of C-H at δ 8.31 ppm, K_a = 44 ± 3.0 M^{-1}.

(a)



(b) (c)

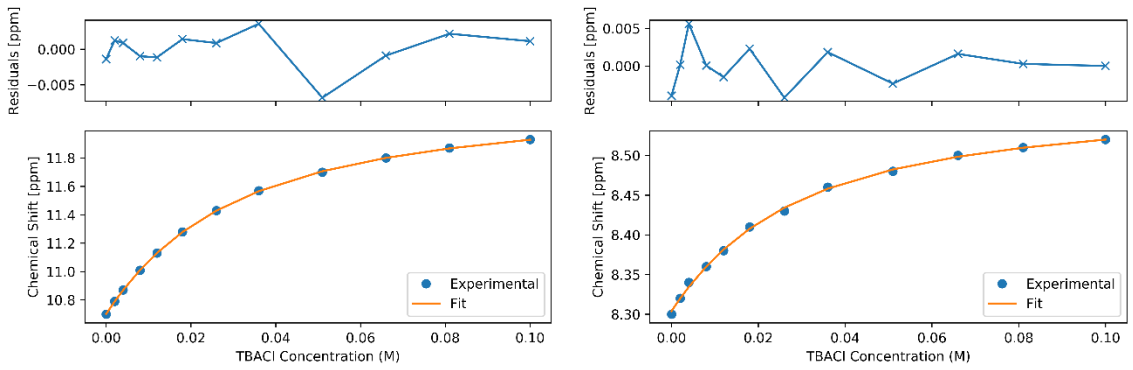
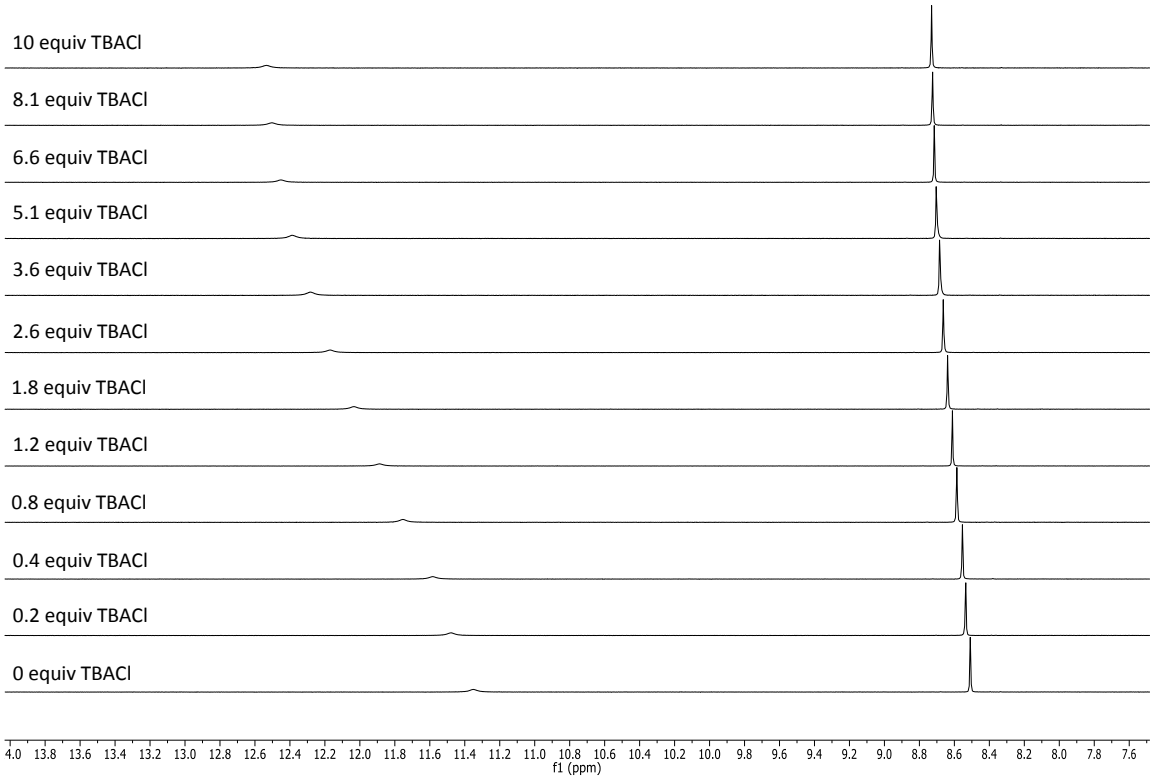
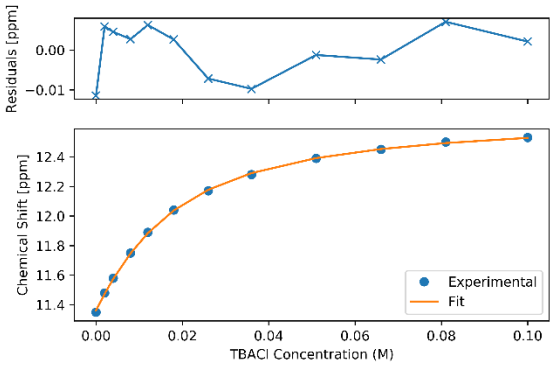


Figure 4.4 NMR titration of **4.5** with TBACl in DMSO-d_6/0.5% H_2O. (a) Stack plot. (b) Fitplot of N-H at δ 11.35 ppm, K_a = 81 ± 2.2 M^{-1}. (C) Fitplot of C-H at δ 8.51 ppm, K_a = 83 ± 7.0 M^{-1}.

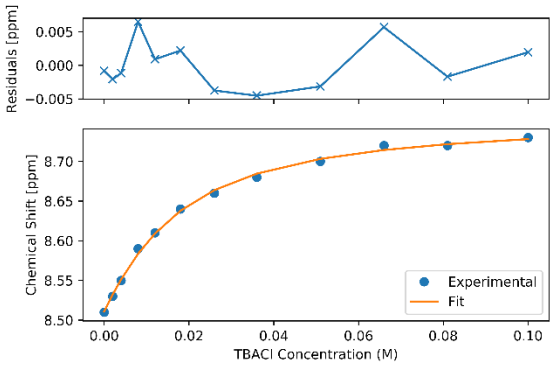
(a)



(b)

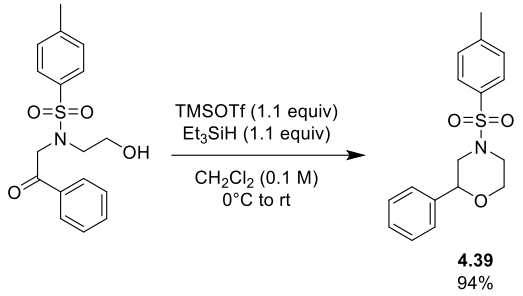


(c)



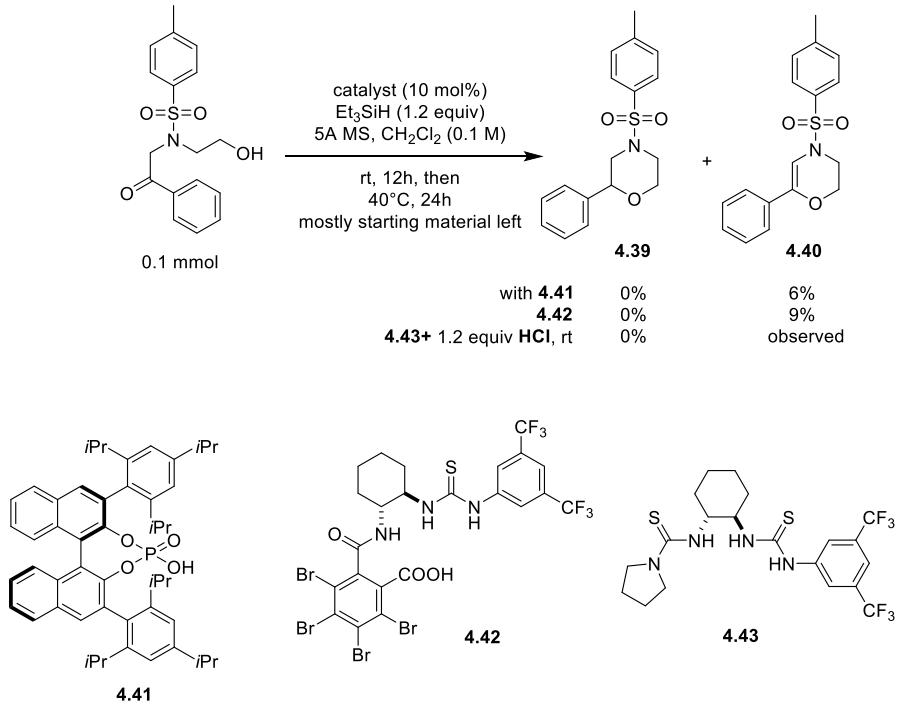
4.2.4 Efforts toward Enantioselective Reductive Etherification Reactions

Scheme 4.15 Intramolecular reductive etherification reaction reported by Gharpure.



Gharpure reported the intramolecular reductive etherification reactions of keto alcohols to synthesize substituted morpholine derivatives (Scheme 4.15).[37] Albeit stoichiometric amounts of trimethylsilyl triflate are required, the reactions are generally efficient with satisfactory yields and reaction time. We performed studies on the enantioselective version of this reaction. At the outset, we successfully reproduced the reaction almost full conversion to **4.39** in only 5 minutes. On the other hand, the use of catalytic amount of chiral Brønsted acids **4.41** or **4.42** only afforded the condensation product **4.40** even under mild heating (Scheme 4.16). The combination of bifunctional thiourea catalyst **4.43** and stoichiometric amount of HCl afforded full conversion to the condensation product **4.40** within 10 minutes. However, no detectable reduction to the desired product **4.39** was observed even with prolonged reaction time. Use of other reducing reagents such as Hantzsch ester and TMDS gave no desired product either.

Scheme 4.16 Efforts toward the enantioselective reductive etherification reactions.



4.3 Summary

In summary, we have developed an efficient method for direct reductive etherification reactions where a readily accessible thiourea organocatalyst is used in combination with a simple Brønsted acid. Challenging substrates such as aromatic ketones and various functional groups were well tolerated. Efforts toward the enantioselective reductive etherification reactions have not been successful, and a more reactive chiral catalytic system is highly in need for this purpose.

Experimental Section

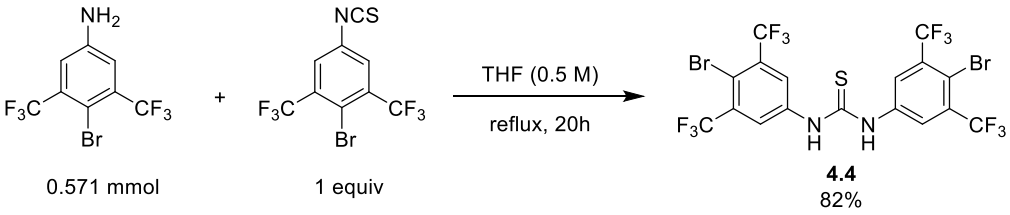
General information: Reagents and solvents were purchased from commercial sources and were purified by distillation or recrystallization prior to use. HCl in dioxane was purchased from Sigma Aldrich and titrated prior to use. 3Å powdered molecular sieves were purchased from Alfa Aesar, activated by heating in a furnace to 300 °C for 3 h and were stored in a desiccator. Purification of reaction products was carried out by flash column chromatography using EM Reagent silica gel 60 (230–400 mesh). Analytical thin layer chromatography was performed on EM Reagent 0.25 mm silica gel 60 F_{254} plates. Visualization was accomplished with UV light, potassium permanganate and phosphomolybdic acid stains, followed by heating. Melting points were recorded on a Thomas Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on an ATI Mattson Genesis Series FT-Infrared spectrophotometer. Proton nuclear magnetic resonance spectra (^{1}H-NMR) were recorded on a Varian VNMRS-500 MHz instrument and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 7.26 ppm, $(CD_3)_2SO$ at 2.50 ppm, CD_3CN at 1.94 ppm). Data are reported as app = apparent, s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sept = septet, m = multiplet, comp = complex, br = broad, and coupling constant(s) in Hz. Proton-decoupled carbon nuclear magnetic resonance spectra (^{13}C-NMR) were recorded on a Varian VNMRS-500 MHz instrument and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 77.16 ppm, $(CD_3)_2SO$ at 39.52 ppm, CD_3CN at 1.32 ppm). Mass spectra were recorded on a Finnigan LCQ-DUO mass spectrometer. Compounds **4.3**,[65] 3-phthalimidopropanol,[67] *N*-Cbz-L-prolinol[68] were prepared according to reported procedures. Compounds **4.2**,[69] **4.6**,[70] **4.8**,[69] **4.11**,[71] **4.12**,[72] **4.13**,[73] **4.14**,[74] **4.15**,[75] **4.16**,[76] **4.17**,[77] **4.18**,[78] **4.19**,[78] **4.20**,[79] **4.21**,[80] **4.22**,[81]

4.25,[82] **4.26**,[83] **4.27**,[84] **4.28**,[85] **4.38**[86] were reported before and their NMR data are consistent with ours.

Binding Constant Studies

Following a similar procedure reported by Gale,[66] aliquots of a solution of tetrabutylammonium chloride (0.2 M) and thiourea catalyst (0.01 M) in DMSO-d_6/0.5% H_2O were added to a solution of thiourea catalyst (0.01 M) in DMSO-d_6/0.5% H_2O. ^{1}H-NMR spectra were then recorded at 25 °C and binding constants were determined by fitting the chemical shift data in the SciPy package.[87] The residuals of the fits were taken as the error in the chemical shift data and used in Monte Carlo method[88] to estimate the K_a error.

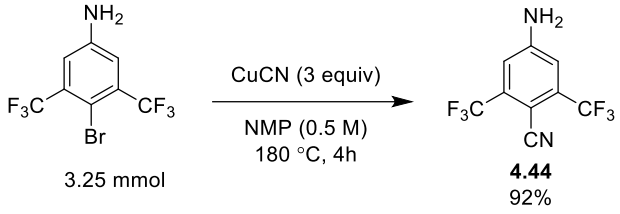
1,3-Bis(4-bromo-3,5-bis(trifluoromethyl)phenyl)thiourea



To a solution of 2-bromo-5-isothiocyanato-1,3-bis(trifluoromethyl)benzene[89] (200 mg, 0.571 mmol, 1 equiv) in THF (1.1 mL, 0.5 M) was added 4-bromo-3,5-bis(trifluoromethyl)aniline (176 mg, 0.571 mmol, 1 equiv). The resulting mixture was stirred at reflux under nitrogen for 20 hours. The solution was then cooled to room temperature, concentrated and purified via flash chromatography on silica gel to afford the desired product **4.4** in 82% yield; mp = 139–140 ºC; R_f = 0.20 (Hexanes/CH_2Cl_2 50:50 v/v); IR (KBr) 3380, 3342, 3211, 3104, 3046, 1595, 1537, 1449, 1356, 1334, 1293, 1186, 1138, 1030, 895, 838, 742, 724, 681 cm^{-1}; ^{1}H NMR (500 MHz, $(CD_3)_2SO$) δ 10.70 (br s, 2H), 8.31 (s, 4H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$) 180.16, 139.51, 131.06 (q, J_{C-F} = 30.6 Hz), 126.29 (q, J_{C-F} = 5.8 Hz), 122.41 (q,

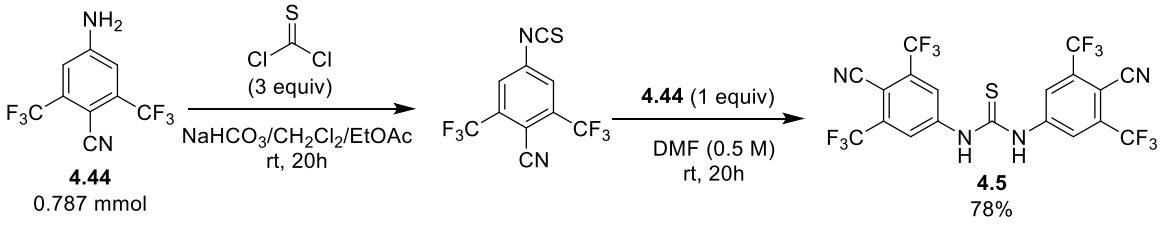
$J_{C\text{-}F}$ = 274.0 Hz), 111.78; *m/z* (ESI-MS) 654.7 (^{79}Br/^{79}Br) [M – H]$^-$, 656.7 (^{79}Br/^{81}Br) [M – H]$^-$, 658.7(^{81}Br/^{81}Br) [M – H]$^-$.

4-Amino-2,6-bis(trifluoromethyl)benzonitrile



To a solution of 4-bromo-3,5-bis(trifluoromethyl)aniline (1 g, 3.25 mmol, 1 equiv) in NMP (6.49 mL, 0.5 M) was added CuCN (0.872 g, 9.74 mmol, 3 equiv). The resulting mixture was stirred at 180 °C under nitrogen for 4 hours before being cooled to room temperature. Saturated aqueous $NaHCO_3$ (20 mL) and EtOAc (20 mL) were added and the mixture was filtered through Celite. The layers were separated and the aqueous phase was extracted with EtOAc (20 mL x 2). The combined organic layer was dried over Na_2SO_4, concentrated and purified via flash chromatography on silica gel to afford the desired product **4.44** in 92% yield; mp = 123–125 ºC; R_f = 0.29 (Hexanes/CH_2Cl_2 30:70 v/v); IR (KBr) 3483, 3372, 3246, 2672, 2221, 1639, 1612, 1491, 1404, 1286, 1185, 1142, 1065, 954, 877, 848, 730, 696, 672, 555 cm^{-1}; ^{1}H NMR (500 MHz, CD_3CN) δ 7.20 (s, 2H), 5.66 (br s, 2H); ^{13}C NMR (125 MHz, CD_3CN) δ 153.47, 136.80 (q, $J_{C\text{-}F}$ = 31.8 Hz), 123.43 (q, $J_{C\text{-}F}$ = 273.4 Hz), 114.73, 114.54 (q, $J_{C\text{-}F}$ = 5.2 Hz), 92.01; *m/z* (ESI-MS) 255.2 [M + H]$^+$.

1,3-Bis(4-cyano-3,5-bis(trifluoromethyl)phenyl)thiourea



4-Amino-2,6-bis(trifluoromethyl)benzonitrile **4.44** (200 mg, 0.787 mmol, 1 equiv) was dissolved in a mixed solvent of CH_2Cl_2 (3.5 mL) and EtOAc (0.4 mL). Saturated aqueous $NaHCO_3$ (3.9 mL) was added and the biphasic mixture was cooled to 0 °C. Thiophosgene (181 μL, 2.361 mmol, 3 equiv) was added to the organic phase and the resulting mixture was slowly warmed to room temperature and stirred until the disappearance of the starting material (20 h). The reaction mixture was extracted with CH_2Cl_2 (7 mL x 3) and the combined organic phase was dried over Na_2SO_4, concentrated and directly used in the next step. To a solution of the crude 4-isothiocyanato-2,6-bis(trifluoromethyl)benzonitrile in DMF (1.6 mL, 0.5 M) was added 4-amino-2,6-bis(trifluoromethyl)benzonitrile **4.44** (200 mg, 0.787 mmol, 1 equiv) and the solution was stirred at room temperature under nitrogen for 20 hours. EtOAc (10 mL) was added and the solution was washed with water (4 mL x 2), brine (4 mL), dried over Na_2SO_4 and concentrated. Purification via flash chromatography on silica gel afforded the desired product **4.5** as a yellow solid in 78% yield; mp = 164–166 ºC; R_f = 0.12 (Hexanes/EtOAc/HCO_2H 50:50:0.5 v/v/v); IR (KBr) 3347, 3107, 2239, 1615, 1597, 1542, 1479, 1368, 1313, 1275, 1247, 1190, 1140, 1069, 938, 893, 683 cm^{-1}; ^1H NMR (500 MHz, CD_3CN) δ 9.33 (br s, 2H), 8.43 (s, 4H); ^{13}C NMR (125 MHz, CD_3CN) δ 180.53, 144.63, 135.96 (q, $J_{C\text{-}F}$ = 32.9 Hz), 124.60 (q, $J_{C\text{-}F}$ = 5.2 Hz), 123.01 (q, $J_{C\text{-}F}$ = 273.8 Hz), 113.31, 103.12; *m/z* (ESI-MS) 548.8 $[M - H]^-$.

General Procedure for the Organocatalytic Reductive Etherification Reaction

To a flame dried vial was added thiourea catalyst **4.5** (6.9 mg, 0.013 mmol, 5 mol %), 3Å MS (100 mg) and CH_2Cl_2 (1.25 mL, 0.2 M). To this stirred suspension was added aldehyde (0.25 mmol, 1 equiv), alcohol (0.3 mmol, 1.2 equiv), HCl (4.2 M in dioxane, 36 μL, 0.6 equiv) and silane (0.3 mmol, 1.2 equiv). The vial was then capped and the resulting mixture was stirred until the disappearance of aldehyde before being quenched by Et_3N (40 μL). The resulting

mixture was concentrated and directly purified by flash chromatography on silica gel topped with Celite.

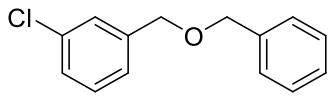
1-((Benzyloxy)methyl)-2-methoxybenzene (4.2): Following the general procedure, the reaction was run for 20 minutes and **4.2** was obtained as a colorless oil in 94% yield; R_f = 0.23 (Hexanes/CH_2Cl_2 70:30 v/v); IR (KBr) 3064, 3029, 2921, 2855, 1613, 1517, 1491, 1454, 1360, 1206, 1093, 1028, 803, 736, 697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.42–7.34 (comp, 4H), 7.33–7.26 (comp, 3H), 7.19 (d, *J* = 7.9 Hz, 2H), 4.57 (s, 2H), 4.55 (s, 2H), 2.38 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.51, 137.45, 135.34, 129.21, 128.50, 128.03, 127.90, 127.70, 72.12, 72.04, 21.32; *m/z* (ESI-MS) 212.8 $[M + H]^+$.

((Cyclohexylmethoxy)methyl)benzene (4.6): Following the general procedure, the reaction was run for 2 hours and **4.6** was obtained as a colorless oil in 87% yield; R_f = 0.30 (Hexanes/CH_2Cl_2 70:30 v/v); IR (KBr) 3062, 3030, 2923, 2851, 2787, 2136, 1946, 1496, 1451, 1361, 1258, 1120, 1097, 1073, 1028, 883, 734, 697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38–7.32 (comp, 4H), 7.31–7.26 (m, 1H), 4.51 (s, 2H), 3.29 (d, *J* = 6.5 Hz, 2H), 1.84–1.77 (comp, 2H), 1.76–1.61 (comp, 4H), 1.32–1.12 (comp, 3H), 1.01–0.91 (comp, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.98, 128.43, 127.64, 127.52, 76.45, 73.09, 38.27, 30.29, 26.78, 26.04; *m/z* (ESI-MS) 204.9 $[M + H]^+$.

1-((Benzyloxy)methyl)-2-methoxybenzene (4.8): Following the general procedure, the reaction was run for 20 minutes and **4.8** was obtained as a colorless oil in 92% yield; R_f = 0.22 (Hexanes/EtOAc 95:5 v/v); IR (KBr) 3064, 3031, 2937, 2837, 2356, 1603, 1590, 1493, 1464, 1438, 1361, 1287, 1243, 1121, 1092, 1050, 1029, 753, 697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.48–7.44 (m, 1H), 7.44–7.41 (comp, 2H), 7.40–7.35 (comp, 2H), 7.34–7.27 (comp, 2H),

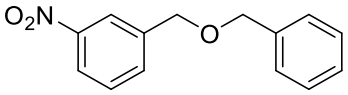
7.02–6.97 (m, 1H), 6.90 (app d, *J* = 8.2 Hz, 1H), 4.67–4.61 (comp, 4H), 3.85 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.28, 138.76, 129.07, 128.74, 128.44, 127.83, 127.60, 126.84, 120.55, 110.31, 72.48, 67.15, 55.43; *m/z* (ESI-MS) 229.0 $[M + H]^+$.

1-((Benzyloxy)methyl)-3-chlorobenzene (4.9): Following the general procedure, the



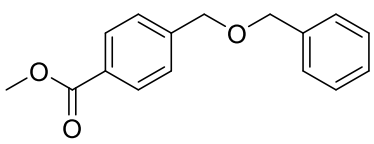
reaction was run for 20 minutes and **4.9** was obtained as a colorless oil in 95% yield; R_f = 0.29 (Hexanes/CH_2Cl_2 70:30 v/v); IR (KBr) 3069, 3029, 2857, 1946, 1871, 1603, 1576, 1474, 1454, 1432, 1356, 1206, 1101, 1075, 870, 780, 737, 697, 682 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43–7.36 (comp, 5H), 7.36–7.31 (m, 1H), 7.31–7.27 (comp, 2H), 7.27–7.24 (m, 1H), 4.59 (s, 2H), 4.55(s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.55, 138.06, 134.47, 129.81, 128.61, 127.93, 127.92, 127.87, 127.85, 125.79, 72.53, 71.43; *m/z* (ESI-MS) 233.0 $[M + H]^+$.

1-((Benzyloxy)methyl)-3-nitrobenzene (4.10): Following the general procedure, the



reaction was run for 14 hours and **4.10** was obtained as a colorless oil in 93% yield; R_f = 0.42 (Hexanes/EtOAc 90:10 v/v); IR (KBr) 3087, 3062, 3032, 2861, 1530, 1497, 1454, 1349, 1211, 1096, 1026, 890, 804, 732, 698, 672 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26–8.22 (m, 1H), 8.17–8.13 (m, 1H), 7.72–7.68 (m, 1H), 7.52 (app t, *J* = 7.9 Hz, 1H), 7.41–7.36 (comp, 4H), 7.36–7.30 (m, 1H), 4.64 (s, 2H), 4.63 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.48, 140.69, 137.68, 133.52, 129.46, 128.68, 128.08, 127.96, 122.69, 122.44, 72.93, 70.89; *m/z* (ESI-MS) 266.0 $[M + Na]^+$.

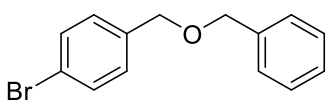
Methyl 4-((benzyloxy)methyl)benzoate (4.11): Following the general procedure, the



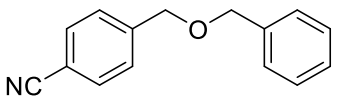
reaction was run for 2 hours and **4.11** was obtained as a colorless oil in 95% yield; R_f = 0.25 (Hexanes/EtOAc 90:10 v/v); IR (KBr) 3031, 2951, 2857, 1941, 1723, 1614, 1498,

1454, 1435, 1363, 1279, 1175, 1108, 1020, 756, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.05 (d, *J* = 8.2 Hz, 2H), 7.45 (d, *J* = 8.0 Hz, 2H), 7.41–7.35 (comp, 4H), 7.35–7.29 (m, 1H), 4.62 (s, 2H), 4.60 (s, 2H), 3.92 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.01, 143.70, 138.00, 129.80, 129.45, 128.55, 127.87, 127.34, 72.58, 71.54, 52.15; *m/z* (ESI-MS) 257.2 $[M + H]^+$.

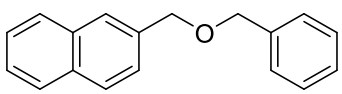
1-((Benzyloxy)methyl)-4-bromobenzene (4.12): Following the general procedure, the reaction was run for 30 minutes and **4.12** was obtained as a colorless oil in 95% yield; R_f = 0.39 (Hexanes/CH_2Cl_2 70:30 v/v); IR (KBr) 3089, 3064, 3030, 2924, 2856, 1591, 1487, 1454, 1392, 1359, 1206, 1095, 1070, 1012, 796, 736, 697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.49 (d, *J* = 8.4 Hz, 2H), 7.40–7.35 (comp, 4H), 7.35–7.29 (m, 1H), 7.26 (d, *J* = 8.6 Hz, 2H), 4.57 (s, 2H), 4.52 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.10, 137.44, 131.62, 129.48, 128.58, 127.90, 127.88, 121.59, 72.38, 71.42; *m/z* (ESI-MS) 299.2 (^{79}Br) $[M + Na]^+$, 301.1 (^{81}Br) $[M + Na]^+$.



4-((Benzyloxy)methyl)benzonitrile (4.13): Following the general procedure, the reaction was run for 24 hours and **4.13** was obtained as a colorless oil in 89% yield; R_f = 0.48 (Hexanes/EtOAc 80:20 v/v); IR (KBr) 3064, 3032, 2859, 2228, 1611, 1497, 1454, 1361, 1209, 1093, 1020, 819, 738, 699, 548 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.66–7.62 (m, 2H), 7.50–7.45 (m, 2H), 7.41–7.35 (comp, 4H), 7.35–7.30 (m, 1H), 4.62–4.59 (comp, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.03, 137.73, 132.33, 128.65, 128.05, 127.89, 118.97, 111.42, 72.87, 71.17; *m/z* (ESI-MS) 245.9 $[M + Na]^+$.

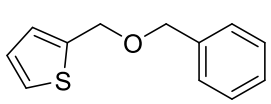


2-((Benzyloxy)methyl)naphthalene (4.14): Following the general procedure, the reaction was run for 20 minutes and **4.14** was obtained as a white solid in 96% yield; mp = 44–45 ºC; R_f = 0.26 (Hexanes/Et_2O 95:5

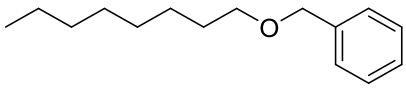


v/v); IR (KBr) 3056, 3033, 2848, 2797, 1596, 1497, 1448, 1365, 1335, 1303, 1208, 1175, 1128, 1116, 1029, 859, 819, 744, 730, 699, 477 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94–7.85 (comp, 4H), 7.59–7.55 (m, 1H), 7.55–7.50 (comp, 2H), 7.48–7.40 (comp, 4H), 7.39–7.34 (m, 1H), 4.78 (s, 2H), 4.66 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.37, 135.89, 133.41, 133.11, 128.54, 128.30, 127.99, 127.93, 127.81, 127.78, 126.59, 126.19, 125.95, 125.91, 72.32, 72.24; *m/z* (ESI-MS) 249.0 $[M + H]^+$.

2-((Benzyloxy)methyl)thiophene (4.15): Following the general procedure, the reaction was run for 2 hours and **4.15** was obtained as a colorless oil in 73% yield; R_f = 0.35 (Hexanes/CH_2Cl_2 70:30 v/v); IR (KBr) 3104, 3087, 3064, 3030, 2856, 1583, 1561, 1496, 1454, 1364, 1345, 1223, 1167, 1070, 1028, 854, 830, 737, 697 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41–7.34 (comp, 4H), 7.34–7.28 (comp, 2H), 7.03 (ddt, *J* = 3.3, 1.3, 0.7 Hz, 1H), 7.00 (dd, *J* = 5.0, 3.5 Hz, 1H), 4.73 (d, *J* = 0.7 Hz, 2H), 4.58 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.15, 138.06, 128.55, 128.00, 127.84, 126.77, 126.62, 125.98, 71.79, 66.58; *m/z* (ESI-MS) 227.0 $[M + Na]^+$.



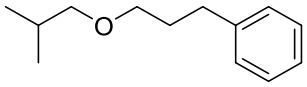
((Octyloxy)methyl)benzene (4.16): Following the general procedure, the reaction was run for 3 hours and **4.16** was obtained as a colorless oil in 80% yield; R_f = 0.21 (Hexanes/CH_2Cl_2 90:10 v/v); IR (KBr) 2927, 2855, 1636, 1455, 1362, 1103, 734, 697 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39–7.32 (comp, 4H), 7.31–7.26 (m, 1H), 4.51 (s, 2H), 3.48 (t, *J* = 6.7 Hz, 2H), 1.67–1.59 (m, 2H), 1.43–1.34 (comp, 2H), 1.33–1.21 (comp, 8H), 0.89 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.86, 128.46, 127.75, 127.58, 72.99, 70.68, 31.98, 29.93, 29.60, 29.42, 26.35, 22.80, 14.25; *m/z* (ESI-MS) 221.3 $[M + H]^+$.



1-Butoxyoctane (4.17): Following the general procedure, the reaction was run for 2 hours and **4.17** was obtained as a colorless oil in 72% yield; R_f

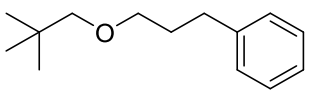
= 0.25 (Hexanes/CH_2Cl_2 90:10 v/v); IR (KBr) 2958, 2930, 2856, 1648, 1561, 1466, 1378, 1122 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.43–3.35 (comp, 4H), 1.60–1.50 (comp, 4H), 1.42–1.20 (comp, 12H), 0.91 (t, *J* = 7.4 Hz, 3H), 0.87 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 71.13, 70.79, 32.03, 31.99, 29.94, 29.62, 29.43, 26.35, 22.81, 19.53, 14.24, 14.09; *m/z* (ESI-MS) 186.8 $[M + H]^+$.

(3-Isobutoxypropyl)benzene (4.18): Following the general procedure, the reaction was run for 24 hours and **4.18** was obtained as a colorless oil in 93% yield;



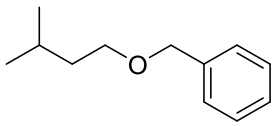
R_f = 0.32 (Hexanes/CH_2Cl_2 80:20 v/v); IR (KBr) 3027, 2954, 2856, 1603, 1493, 1455, 1381, 1361, 1116, 744, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.31–7.26 (comp, 2H), 7.22–7.16 (comp, 3H), 3.42 (t, *J* = 6.4 Hz, 2H), 3.18 (d, *J* = 6.7 Hz, 2H), 2.70 (t, *J* = 7.7 Hz, 2H), 1.94–1.82 (comp, 3H), 0.92 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.27, 128.62, 128.42, 125.84, 77.99, 70.12, 32.51, 31.49, 28.62, 19.59; *m/z* (ESI-MS) 193.3 $[M + H]^+$.

(3-(Neopentyloxy)propyl)benzene (4.19): Following the general procedure, the reaction was run for 2 hours and **4.19** was obtained as a colorless oil in 87% yield;



R_f = 0.42 (Hexanes/CH_2Cl_2 70:30 v/v); IR (KBr) 3067, 3027, 2953, 2864, 1606, 1496, 1482, 1455, 1386, 1362, 1120, 1048, 920, 744, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.33–7.27 (m, 2H), 7.24–7.18 (comp, 3H), 3.44 (t, *J* = 6.3 Hz, 2H), 3.08 (s, 2H), 2.73 (t, *J* = 7.7 Hz, 2H), 1.96–1.87 (m, 2H), 0.95 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.40, 128.65, 128.40, 125.81, 81.50, 70.54, 32.50, 32.26, 31.48, 26.95; *m/z* (ESI-MS) 207.1 $[M + H]^+$.

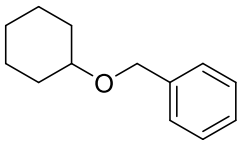
((Isopentyloxy)methyl)benzene (4.20): Following the general procedure, the reaction was run for 2 hours and **4.20** was obtained as a colorless oil in 89% yield;



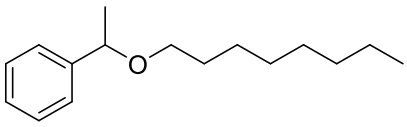
R_f = 0.15 (Hexanes/CH_2Cl_2 80:20 v/v); IR (KBr) 3062, 3030, 2956,

2926, 2868, 2789, 1496, 1467, 1454, 1366, 1101, 1028, 734, 697 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38–7.33 (comp, 4H), 7.32–7.26 (m, 1H), 4.52 (s, 2H), 3.51 (t, *J* = 6.8 Hz, 2H), 1.81–1.70 (m, 1H), 1.53 (app q, *J* = 6.8 Hz, 2H), 0.92 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.86, 128.46, 127.73, 127.58, 73.04, 68.99, 38.74, 25.24, 22.78; *m/z* (ESI-MS) 178.9 $[M + H]^+$.

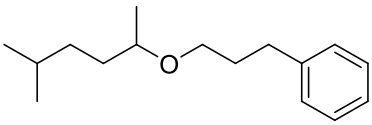
((Cyclohexyloxy)methyl)benzene (4.21): Following the general procedure, the reaction was run for 30 minutes and **4.21** was obtained as a colorless oil in 87% yield; R_f = 0.38 (Hexanes/Et_2O 95:5 v/v); IR (KBr) 3064, 3030, 2932, 2856, 1497, 1452, 1362, 1346, 1135, 1097, 1028, 954, 734, 696 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38–7.32 (comp, 4H), 7.29–7.24 (m, 1H), 4.56 (s, 2H), 3.36 (tt, *J* = 9.4, 3.8 Hz, 1H), 2.01–1.92 (m, 2H), 1.81–1.40 (m, 2H), 1.58–1.51 (m, 1H), 1.43–1.32 (m, 2H), 1.32–1.20 (comp, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.47, 128.43, 127.62, 127.42, 77.07, 69.80, 32.40, 26.00, 24.30; *m/z* (ESI-MS) 190.9 $[M + H]^+$.



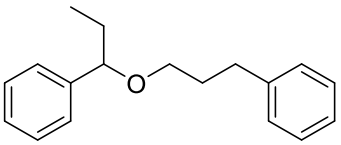
(1-(Octyloxy)ethyl)benzene (4.22): Following the general procedure, the reaction was run for 2 hours and **4.22** was obtained as a colorless oil in 86% yield; R_f = 0.30 (Hexanes/CH_2Cl_2 70:30 v/v); IR (KBr) 3064, 3024, 2928, 2856, 2359, 1493, 1452, 1369, 1351, 1206, 1105, 1070, 760, 700 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38–7.29 (comp, 4H), 7.29–7.24 (m, 1H), 4.38 (q, *J* = 6.5 Hz, 1H), 3.29 (t, *J* = 6.7 Hz, 2H), 1.61–1.50 (comp, 2H), 1.44 (d, *J* = 6.5 Hz, 3H), 1.38–1.18 (comp, 10H), 0.88 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.49, 128.48, 127.38, 126.25, 78.02, 68.94, 31.98, 30.12, 29.58, 29.41, 26.34, 24.39, 22.80, 14.24; *m/z* (ESI-MS) 235.1 $[M + H]^+$.



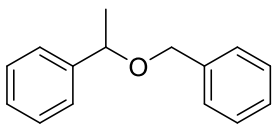
(3-((5-Methylhexan-2-yl)oxy)propyl)benzene (4.23): Following the general procedure, the reaction was run for 30 minutes and **4.23** was obtained as a colorless oil in 94% yield; R_f = 0.25 (Hexanes/CH_2Cl_2 70:30 v/v); IR (KBr) 3062, 3027, 2954, 2868, 1603, 1497, 1467, 1453, 1373, 1338, 1141, 1122, 1098, 966, 908, 745, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.31–7.27 (m, 2H), 7.23–7.17 (comp, 3H), 3.51 (dt, *J* = 9.3, 6.3 Hz, 1H), 3.40–3.33 (comp, 2H), 2.75–2.68 (comp, 2H), 1.94–1.85 (comp, 2H), 1.60–1.49 (comp, 2H), 1.45–1.36 (m, 1H), 1.35–1.25 (m, 1H), 1.23–1.16 (m, 1H), 1.14 (d, *J* = 6.1 Hz, 3H), 0.91 (d, *J* = 6.6 Hz, 3H), 0.90 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.33, 128.62, 128.40, 125.81, 75.87, 67.59, 34.95, 34.70, 32.62, 31.89, 28.31, 22.82, 22.77, 19.90; *m/z* (ESI-MS) 235.2 $[M + H]^+$.



(1-(3-Phenylpropoxy)propyl)benzene (4.24): Following the general procedure, the reaction was run for 24 hours and **4.24** was obtained as a colorless oil in 84% yield; R_f = 0.20 (Hexanes/CH_2Cl_2 70:30 v/v); IR (KBr) 3084, 3062, 3027, 2934, 2859, 2356, 2334, 1944, 1603, 1493, 1454, 1358, 1338, 1198, 1104, 983, 898, 735, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36–7.32 (m, 2H), 7.31–7.24 (comp, 5H), 7.20–7.14 (comp, 3H), 4.10 (dd, *J* = 6.8, 6.4 Hz, 1H), 3.36 (dt, *J* = 9.4, 6.3 Hz, 1H), 3.27 (dt, *J* = 9.4, 6.3 Hz, 1H), 2.75–2.62 (comp, 2H), 1.91–1.79 (comp, 3H), 1.73–1.63 (m, 1H), 0.92 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.12, 142.29, 128.58, 128.38, 128.36, 127.42, 126.84, 125.80, 83.94, 68.11, 32.59, 31.70, 31.34, 10.57; *m/z* (ESI-MS) 255.0 $[M + H]^+$.

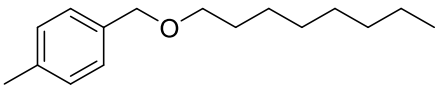


(1-(Benzyloxy)ethyl)benzene (4.25): Following the general procedure, except using 1.2 equiv of HCl, the reaction was run for 24 hours and **4.25** was obtained as a colorless oil in 83% yield; R_f = 0.28 (Hexanes/CH_2Cl_2



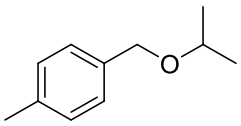
70:30 v/v); IR (KBr) 3063, 3030, 2975, 2928, 2863, 1946, 1879, 1814, 1603, 1494, 1452, 1370, 1352, 1305, 1282, 1206, 1097, 1053, 1028, 1005, 910, 761, 735, 699 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41–7.36 (comp, 4H), 7.36–7.26 (comp, 6H), 4.52 (q, *J* = 6.5 Hz, 1H), 4.47 (d, *J* = 11.9 Hz, 1H), 4.31 (d, *J* = 11.8 Hz, 1H), 1.50 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.86, 138.78, 128.63, 128.48, 127.83, 127.63, 127.60, 126.48, 77.36, 70.44, 24.36; *m/z* (ESI-MS) 213.0 $[M + H]^+$.

1-Methyl-4-((octyloxy)methyl)benzene (4.26): Following the general procedure, the



reaction was run for 20 minutes and **4.26** was obtained as a colorless oil in 92% yield; R_f = 0.25 (Hexanes/CH_2Cl_2 70:30 v/v); IR (KBr) 2959, 2927, 2855, 1894, 1516, 1457, 1360, 1201, 1100, 1022, 801 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (d, *J* = 7.9 Hz, 2H), 7.17 (d, *J* = 8.1 Hz, 2H), 4.49 (s, 2H), 3.47 (t, *J* = 6.7 Hz, 2H), 2.37 (s, 3H), 1.63 (app p, *J* = 6.7 Hz, 2H), 1.44–1.21 (comp, 10H), 0.91 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.19, 135.80, 129.12, 127.83, 72.84, 70.46, 31.98, 29.93, 29.60, 29.41, 26.35, 22.80, 21.27, 14.23; *m/z* (ESI-MS) 235.1 $[M + H]^+$.

1-(Isopropoxymethyl)-4-methylbenzene (4.27): Following the general procedure, the

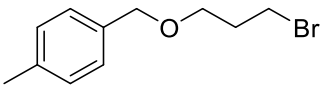


reaction was run for 20 minutes and **4.27** was obtained as a colorless oil in 91% yield; R_f = 0.24 (Hexanes/CH_2Cl_2 50:50 v/v); IR (KBr) 2972, 2927, 2865, 2629, 1904, 1518, 1468, 1379, 1335, 1175, 1127, 1067, 1022, 918, 800 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, *J* = 7.9 Hz, 2H), 7.16 (d, *J* = 7.8 Hz, 2H), 4.49 (s, 2H), 3.69 (sept, *J* = 6.1 Hz, 1H), 2.35 (s, 3H), 1.22 (d, *J* = 6.1 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.09, 136.18, 129.11, 127.75, 70.78, 69.99, 22.25, 21.27; *m/z* (ESI-MS) 164.9 $[M + H]^+$.

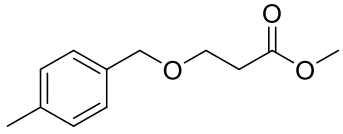
1-(*Tert*-butoxymethyl)-4-methylbenzene (4.28): Following the general procedure, the reaction was run for 30 minutes and **4.28** was obtained as a colorless oil in 65% yield; R_f = 0.25 (Hexanes/CH_2Cl_2 70:30 v/v); IR (KBr) 2974, 2926, 2866, 1517, 1473, 1389, 1379, 1362, 1236, 1196, 1178, 1082, 1021, 894, 801, 765 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.24 (d, *J* = 7.8 Hz, 2H), 7.14 (d, *J* = 7.7 Hz, 2H), 4.41 (s, 2H), 2.34 (s, 3H), 1.29 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.00, 136.81, 129.09, 127.61, 73.45, 64.15, 27.87, 21.27; *m/z* (ESI-MS) 178.7 $[M + H]^+$.

1-((But-3-en-1-yloxy)methyl)-4-methylbenzene (4.29): Following the general procedure, the reaction was run for 20 minutes and **4.29** was obtained as a colorless oil in 80% yield; R_f = 0.30 (Hexanes/CH_2Cl_2 60:40 v/v); IR (KBr) 3077, 2979, 2923, 2855, 1899, 1642, 1613, 1517, 1446, 1360, 1203, 1098, 996, 914, 802, 750 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.24 (d, *J* = 7.9 Hz, 2H), 7.16 (d, *J* = 7.7 Hz, 2H), 5.85 (ddt, *J* = 17.0, 10.1, 6.7 Hz, 1H), 5.15–5.03 (comp, 2H), 4.50 (s, 2H), 3.52 (t, *J* = 6.8 Hz, 2H), 2.42–2.34 (comp, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.34, 135.53, 135.45, 129.16, 127.90, 116.43, 72.91, 69.55, 34.39, 21.30; *m/z* (ESI-MS) 177.0 $[M + H]^+$.

1-((But-3-yn-1-yloxy)methyl)-4-methylbenzene (4.30): Following the general procedure, the reaction was run for 2 hours and **4.30** was obtained as a colorless oil in 82% yield; R_f = 0.22 (Hexanes/CH_2Cl_2 70:30 v/v); IR (KBr) 3295, 3023, 2821, 2862, 2121, 1901, 1618, 1516, 1453, 1361, 1203, 1100, 1022, 803, 748, 641 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.0 Hz, 2H), 7.17 (d, *J* = 7.8 Hz, 2H), 4.53 (s, 2H), 3.59 (t, *J* = 7.0 Hz, 2H), 2.50 (td, *J* = 7.0, 2.7 Hz, 2H), 2.36 (s, 3H), 2.00 (t, *J* = 2.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.52, 135.07, 129.21, 127.94, 81.45, 72.98, 69.40, 68.07, 21.28, 20.01; *m/z* (ESI-MS) 175.1 $[M + H]^+$.

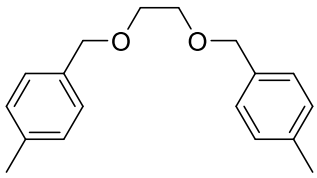
1-((3-Bromopropoxy)methyl)-4-methylbenzene (4.31): Following the general procedure,  the reaction was run for 1 hour and **4.31** was obtained as a colorless oil in 88% yield; R_f = 0.25 (Hexanes/CH_2Cl_2 70:30 v/v); IR (KBr) 3022, 2919, 2860, 2792, 1899, 1618, 1516, 1435, 1362, 1283, 1256, 1204, 1100, 1022, 878, 803, 750 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.24 (d, *J* = 7.9 Hz, 2H), 7.17 (d, *J* = 8.2 Hz, 2H), 4.49 (s, 2H), 3.60 (t, *J* = 5.8 Hz, 2H), 3.54 (t, *J* = 6.6 Hz, 2H), 2.36 (s, 3H), 2.18–2.10 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.49, 135.30, 129.21, 127.89, 73.14, 67.67, 33.08, 30.84, 21.30; *m/z* (ESI-MS) 243.1 (^{79}Br) $[M + H]^+$, 245.3 (^{81}Br) $[M + H]^+$.

2-(3-((4-Methylbenzyl)oxy)propyl)isoindoline-1,3-dione (4.32): Following the general procedure, except using thiourea catalyst **4.4**, the reaction was run for 24 hours and **4.32** was obtained as a white solid in 82% yield; mp = 32–33 ºC; R_f = 0.23 (Hexanes/EtOAc 80:20 v/v); IR (KBr) 3460, 2947, 2859, 1767, 1712, 1608, 1518, 1443, 1396, 1374, 1323, 1146, 1094, 1048, 1008, 900, 810, 755, 720, 623, 530, 470 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.83–7.79 (m, 2H), 7.71–7.66 (m, 2H), 7.18 (d, *J* = 7.9 Hz, 2H), 7.09 (d, *J* = 7.7 Hz, 2H), 4.42 (s, 2H), 3.82 (t, *J* = 6.9 Hz, 2H), 3.52 (t, *J* = 6.1 Hz, 2H), 2.31 (s, 3H), 1.99 (tt, *J* = 6.8, 6.1 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.51, 137.21, 135.32, 133.87, 132.31, 129.06, 127.87, 123.22, 73.00, 67.86, 35.79, 28.79, 21.26; *m/z* (ESI-MS) 310.1 $[M + H]^+$.

Methyl 3-((4-methylbenzyl)oxy)propanoate (4.33): Following the general procedure, the  reaction was run for 24 hours and **4.33** was obtained as a colorless oil in 90% yield; R_f = 0.22 (Hexanes/EtOAc 85:15 v/v); IR (KBr) 3027, 2952, 2867, 1743, 1516, 1437, 1364,

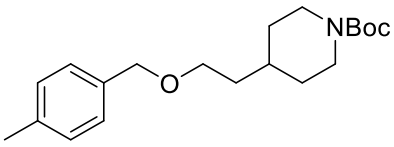
1251, 1196, 1177, 1102, 1073, 1021, 843, 804, 755 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 (d, *J* = 8.0 Hz, 2H), 7.15 (d, *J* = 7.9 Hz, 2H), 4.50 (s, 2H), 3.73 (t, *J* = 6.4 Hz, 2H), 3.69 (s, 3H), 2.61 (t, *J* = 6.4 Hz, 2H), 2.34 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.18, 137.49, 135.11, 129.19, 127.94, 73.11, 65.49, 51.80, 35.11, 21.29; *m/z* (ESI-MS) 209.2 $[M + H]^+$.

1,2-Bis((4-methylbenzyl)oxy)ethane (4.34): Following the general procedure, except using



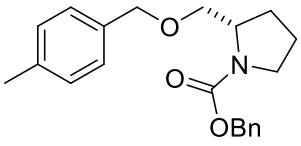
0.25 mmol of ethylene glycol, 2.4 equiv of *p*-tolualdehyde, 10 mol% of catalyst **4.5**, 1.2 equiv of HCl and 2.4 equiv of TMDS, the reaction was run for 24 hours and **4.34** was obtained as a white solid in 87% yield; mp = 34–36 ºC; R_f = 0.20 (CH_2Cl_2); IR (KBr) 3012, 2920, 2875, 2809, 1906, 1516, 1451, 1366, 1356, 1307, 1141, 1116, 1095, 1073, 1020, 905, 887, 802, 483 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.0 Hz, 4H), 7.15 (d, *J* = 7.8 Hz, 4H), 4.54 (s, 4H), 3.64 (s, 4H), 2.35 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.38, 135.37, 129.16, 127.99, 73.26, 69.48, 21.31; *m/z* (ESI-MS) 293.0 $[M + Na]^+$.

***Tert*-butyl 4-(2-((4-methylbenzyl)oxy)ethyl)piperidine-1-carboxylate (4.35):** Following



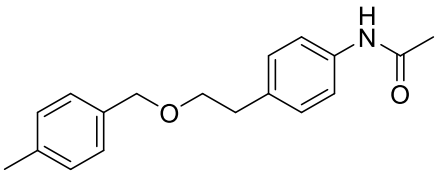
the general procedure, the reaction was run for 24 hours and **4.35** was obtained as a colorless oil in 61% yield; R_f = 0.25 (Hexanes/EtOAc 95:5 v/v); IR (KBr) 3007, 2974, 2924, 2852, 1906, 1699, 1516, 1418, 1365, 1314, 1246, 1170, 1098, 1013, 928, 868, 803, 768 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21 (d, *J* = 8.0 Hz, 2H), 7.15 (d, *J* = 7.8 Hz, 2H), 4.45 (s, 2H), 4.05 (br s, 2H), 3.48 (t, *J* = 6.3 Hz, 2H), 2.75–2.60 (m, 2H), 2.34 (s, 3H), 1.68–1.51 (comp, 5H), 1.45 (s, 9H), 1.14–1.03 (comp, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.97, 137.33, 135.53, 129.13, 127.84, 79.25, 72.91, 67.52, 43.99, 36.39, 33.01, 32.19, 28.58, 21.26; *m/z* (ESI-MS) 334.0 $[M + H]^+$.

Benzyl (*S*)-2-(((4-methylbenzyl)oxy)methyl)pyrrolidine-1-carboxylate (4.36): Following



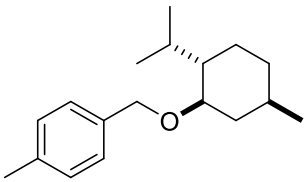
the general procedure, the reaction was run for 24 hours and **4.36** was obtained as a colorless oil in 79% yield; R_f = 0.25 (Hexanes/EtOAc 85:15 v/v); IR (KBr) 3029, 2952, 2875, 1699, 1496, 1453, 1417, 1358, 1199, 1096, 1006, 915, 804, 769, 750, 698 cm^{-1}; ^1H NMR (500 MHz, $(CD_3)_2SO$, 70 ºC) δ 7.47–7.24 (comp, 5H), 7.22–7.05 (comp, 4H), 5.14–4.98 (comp, 2H), 4.41 (s, 2H), 3.99–3.85 (m, 1H), 3.60–3.46 (m, 1H), 3.46–3.24 (comp, 3H), 2.29 (s, 3H), 2.00–1.70 (comp, 4H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$, 70 ºC) δ 153.66, 136.81, 136.09, 135.14, 128.34, 127.90, 127.24, 127.01, 126.97, 71.93, 70.07, 65.44, 56.29, 46.14, 27.69, 22.55, 20.25; *m/z* (ESI-MS) 340.2 $[M + H]^+$.

***N*-(4-(2-((4-methylbenzyl)oxy)ethyl)phenyl)acetamide (4.37):** Following the general



procedure, the reaction was run for 24 hours and **4.37** was obtained as a white solid in 74% yield; mp = 115–116 ºC; R_f = 0.40 (Hexanes/EtOAc 30:70 v/v); IR (KBr) 3310, 3264, 3197, 3133, 2943, 2866, 2802, 1684, 1663, 1609, 1550, 1515, 1410, 1364, 1322, 1266, 1102, 1000, 832, 788, 730, 525, 488 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.59 (br s, 1H), 7.41 (d, *J* = 8.4 Hz, 2H), 7.20 (d, *J* = 8.0 Hz, 2H), 7.18–7.12 (comp, 4H), 4.48 (s, 2H), 3.65 (t, *J* = 7.1 Hz, 2H), 2.88 (t, *J* = 7.1 Hz, 2H), 2.34 (s, 3H), 2.13 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.56, 137.35, 136.23, 135.34, 135.11, 129.46, 129.14, 127.85, 120.15, 72.96, 71.13, 35.85, 24.55, 21.26; *m/z* (ESI-MS) 284.1 $[M + H]^+$.

1-((((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl)oxy)methyl)-4-methylbenzene (4.38):



To a flame dried round bottom flask was added thiourea catalyst **4.5** (55 mg, 0.1 mmol, 1 mol %), 3Å MS (2 g) and CH_2Cl_2 (50 mL, 0.2 M). To this stirred suspension was added *p*-tolualdehyde

(1.2 g, 10 mmol, 1 equiv), L-menthol (1.875 g, 12 mmol, 1.2 equiv), HCl (4.2 M in dioxane, 1.43 mL, 0.6 equiv) and TMDS (1.6 g, 12 mmol, 1.2 equiv). The flask was then capped and the resulting mixture was stirred until the disappearance of *p*-tolualdehyde (1 h) before being quenched by Et_3N (1 mL). The resulting mixture was filtered through Celite, concentrated and purified by flash chromatography on silica gel to afford the desired product **4.38** as a white solid in 95% yield; mp = 37–38 ºC; R_f = 0.45 (Hexanes/CH_2Cl_2 70:30 v/v); IR (KBr) 2959, 2942, 2933, 2919, 2868, 1909, 1808, 1518, 1458, 1369, 1181, 1107, 1088, 1075, 918, 803, 588, 475 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.0 Hz, 2H), 7.14 (d, *J* = 7.8 Hz, 2H), 4.61 (d, *J* = 11.3 Hz, 1H), 4.36 (d, *J* = 11.3 Hz, 1H), 3.15 (app td, *J* = 10.6, 4.2 Hz, 1H), 2.33 (s, 3H), 2.29 (app dtd, *J* = 14.1, 7.1, 2.8 Hz, 1H), 2.18 (app dtd, *J* = 12.1, 3.9, 2.1 Hz, 1H), 1.69–1.58 (comp, 2H), 1.40–1.31 (m, 1H), 1.30–1.25 (m, 1H), 1.02–0.78 (comp, 9H), 0.71 (d, d*J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.11, 136.22, 129.07, 128.04, 78.67, 70.40, 48.47, 40.46, 34.75, 31.72, 25.63, 23.41, 22.54, 21.30, 21.18, 16.21; *m/z* (ESI-MS) 260.9 $[M + H]^+$.

References

(1) Williamson, A. *Philos. Mag.* **1850,** *37,* 350.
(2) Freedman, H. H.; Dubois, R. A. *Tetrahedron Lett.* **1975,** *16,* 3251.
(3) Peng, Y.; Song, G. *Green Chem.* **2002,** *4,* 349.
(4) Mitsunobu, O. In *Comprehensive Organic Synthesis;* Trost, B. M., Fleming, J., Eds.; Pergamon Press: New York, 1991; Vol. 6, pp 22−31.
(5) Brewster, J. A. In *Comprehensive Organic Synthesis;* Trost, B. M., Fleming, J., Eds.; Pergamon Press: New York, 1991; Vol. 8, pp 211−234.
(6) Barret, A. G. M. In *Comprehensive Organic Synthesis;* Trost, B. M., Fleming, J., Eds.; Pergamon Press: New York, 1991; Vol. 8, pp 235−257.
(7) Mandal, S.; Mandal, S.; Ghosh, S. K.; Sar, P.; Ghosh, A.; Saha, R.; Saha, B. *RSC Advances* **2016**, *6*, 69605.
(8) Howard, W. L.; Brown, J. H. *J. Org. Chem.* **1961,** *26,* 1026.
(9) Gozlan, C.; Lafon, R.; Duguet, N.; Redl, A.; Lemaire, M. *RSC Adv.* **2014,** *4,* 50653.
(10) Kotsuki, H.; Ushio, Y.; Yoshimura, N.; Ochi, M. *J. Org. Chem.* **1987,** *52,* 2594.
(11) Srikrishna, A.; Viswajanani, R. *Tetrahedron* **1995,** *51,* 3339.
(12) Takano, S.; Akiyama, M.; Sato, S.; Ogasawara, K. *Chem. Lett.* **1983,** 1593.
(13) Mori, A.; Fujiwara, J.; Maruoka, K.; Yamamoto, H. *Tetrahedron Lett.* **1983,** *24,* 4581.
(14) Ishihara, K.; Mori, A.; Yamamoto, H. *Tetrahedron* **1990,** *46,* 4595.
(15) Oikawa, M.; Liu, W. C.; Nakai, Y.; Koshida, S.; Fukase, K.; Kusumoto, S. *Synlett* **1996,** 1179.
(16) Hernández-Torres, J. M.; Achkar, J.; Wei, A. *J. Org. Chem.* **2004,** *69,* 7206.
(17) Johnsson, R.; Olsson, D.; Ellervik, U. *J. Org. Chem.* **2008,** *73,* 5226.
(18) Johnsson, R.; Ohlin, M.; Ellervik, U. *J. Org. Chem.* **2010,** *75,* 8003.
(19) Nakao, R.; Fukumoto, T.; Tsurugi, J. *J. Org. Chem.* **1972,** *37,* 4349.
(20) Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1979,** *20,* 4679.
(21) Olah, G. A.; Yamato, T.; Iyer, P. S.; Prakash, G. K. *J. Org. Chem.* **1986**, *51,* 2826.
(22) DeNinno, M. P.; Etienne, J. B.; Duplantier, K. C. *Tetrahedron Lett.* **1995,** *36,* 669.
(23) Watanabe, S.; Sueyoshi, T.; Ichihara, M.; Uehara, C.; Iwamura, M. *Org. Lett.* **2001,** *3,* 255.
(24) Ohta, T.; Michbata, T.; Yamada, K.; Omori, R.; Furukawa, I. *Chem. Commun.* **2003,** *10,* 1192.
(25) Zhang, Y. J.; Dayoub, W.; Chen, G. R.; Lemaire, M. *Green Chem.* **2011,** *13,* 2737.
(26) Zhang, Y.-J.; Dayoub, W.; Chen, G.-R.; Lemaire, M. *Eur. J. Org. Chem.* **2012,** *10,* 1960.
(27) Gomez, S.; Peters, J. A.; Maschmeyer, T. *Adv. Synth. Catal.* **2002,** *344,* 1037.
(28) Abdel-Magid, A. F.; Mehrman, S. J. *Org. Process Res. Dev.* **2006,** *10,* 971.
(29) Nugent, T. C.; El-Shazly, M. *Adv. Synth. Catal.* **2010,** *352,* 753.
(30) Wada, M.; Nagayama, S.; Mizutani, K.; Hiroi, R.; Miyoshi, N. *Chem. Lett.* **2002,** *31,* 248.
(31) Gooβen, L. J.; Linder, C. *Synlett* **2006,** *2006,* 3489.
(32) Iwanami, K.; Yano, K.; Oriyama, T. *Chem. Lett.* **2007,** *36,* 38.
(33) Kalutharage, N.; Yi, C. S. *Org. Lett.* **2015,** *17,* 1778.
(34) Nicolaou, K. C.; Hwang, C.-K.; Nugiel, D. A. *J. Am. Chem. Soc.* **1989,** *111,* 4136.
(35) Lee, S. H.; Park, Y. J.; Yoon, C. M. *Tetrahedron Lett.* **1999,** *40,* 6049.
(36) Izumi, M.; Fukase, K. *Chem. Lett.* **2005,** *34,* 594.
(37) Gharpure, S. J.; Prasad, J. V. K. *J. Org. Chem*. **2011,** *76,* 10325.
(38) Bakos, M., Gyömöre, Á.; Domján A.; Soós, T. *Angew. Chem., Int. Ed.* **2017,** *56,* 1.
(39) Doyle, M. P.; DeBruyn, D. J.; Kooistra, D. A. *J. Am. Chem. Soc.* **1972,** *94,* 3659.
(40) Rahier, N. J.; Cheng, K.; Gao, R.; Eisenhauer, B. M.; Hecht, S. M. *Org. Lett.* **2005,** *7,* 835.

(41) Gellert, B. A.; Kahlke, N.; Feurer, M.; Roth, S. *Chem. −Eur. J.* **2011,** *17,* 12203.
(42) Kato, J.; Iwasawa, N.; Mukaiyama, T. *Chem. Lett.* **1985,** *14,* 743.
(43) Sassaman, M. B.; Kotian, K. D.; Prakash, G. K. S.; Olah, G. A. *J. Org. Chem.* **1987,** *52,* 4314.
(44) Hartz, N.; Prakash, G. K. S.; Olah, G. A. *Synlett* **1992,** 569.
(45) Hatakeyama, S.; Mori, H.; Kitano, K.; Yamada, H.; Nishizawa, M. *Tetrahedron Lett.* **1994,** *35,* 4367.
(46) Komatsu, N.; Ishida, J.−Y.; Suzuki, H. *Tetrahedron Lett.* **1997,** *38,* 7219.
(47) Bajwa, J. S.; Jiang, X.; Slade, J.; Prasad. K.; Repic, O.; Blacklock, T. J. *Tetrahedron Lett.* **2002,** *43,* 6709.
(48) Miura, K.; Ootsuka, K.; Suda, S.; Nishikori, H.; Hosomi, A. *Synlett.* **2002,** *2,* 313.
(49) Yang, W.-C.; Lu, X.-A.; Kulkarni, S. S.; Hung, S.-C. *Tetrahedron Lett.* **2003,** *44,* 7837.
(50) Chandrasekhar, S.; Chandrashekar, G.; Nagendra Babu, B.; Vijeender, K.; Venkatram Reddy, K. *Tetrahedron Lett.* **2004,** *45,* 5497.
(51) Iwanami, K.; Seo, H.; Tobita, Y.; Oriyama, T. *Synthesis* **2005,** 183.
(52) Yang, M.-S.; Xu, L.-W.; Qiu, H.-Y.; Lai, G.-Q.; Jiang, J.-X. *Tetrahedron Lett.* **2008,** *49,* 253.
(53) Argouarch, G.; Grelaud, G.; Roisnel, T.; Humphrey, M. G.; Paul, F. *Tetrahedron Lett.* **2012,** *53,* 5015.
(54) Chiba, J.; Muro, F.; Setoguchi, M.; Machinaga, N. *Chem. Pharm. Bull.* **2012**, *60*, 882.
(55) Savela, R.; Leino, R. *Synthesis* **2015,** *47,* 1749.
(56) Verzele, M.; Acke, M.; Anteunis, M. *J. Chem. Soc.* **1963,** 5598.
(57) Weil, T.; Kotke, M.; Kleiner, C. M.; Schreiner, P. R. *Org. Lett.* **2008,** *10,* 1513.
(58) Klausen, R. S.; Jacobsen, E. N. *Org. Lett.* **2009,** *11,* 887.
(59) Burns, N. Z.; Witten., M. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2011,** *133,* 14578.
(60) Borovika, A.; Tang, P.-I.; Klapman, S.; Nagorny, P. *Angew. Chem., Int. Ed.* **2013,** *52,* 13424.
(61) Geng, Y.; Kumar, A.; Faidallah, H. M.; Albar, H. A.; Mhkalid, I. A.; Schmidt, R. R. *Angew. Chem., Int. Ed.* **2013,** *52,* 10089.
(62) Min, C.; Mittal, N.; Sun, D. X.; Seidel, D. *Angew. Chem., Int. Ed.* **2013,** *52,* 14084.
(63) Li, X.; Zhang, Q.; Li, Z.; Wang, X.; Liu, J.; Cui, S.; Xu, S.; Zhao, C.; Chen, C.; Guo, K. *Polymer* **2016**, *84*, 293.
(64) Park, Y.; Schindler, C.S.; Jacobsen, E.N. *J. Am. Chem. Soc.* **2016**, *138*, 14848.
(65) Kotke, M.; Schreiner, P. R. *Tetrahedron* **2006,** *62,* 434.
(66) Busschaert, N.; Kirby, I. L.; Young, S.; Coles, S. J.; Horton, P. N.; Light, M. E.; Gale, P. A. *Angew. Chem., Int. Ed.* **2012,** *51,* 4426.

(67) Levin, V. V.; Zemtsov, A. A.; Struchkova, M. I.; Dilman, A. D. *Org. Lett.* **2013,** *15,* 917.
(68) Widianti, T.; Hiraga, Y.; Kojima, S.; Abe, M. *Tetrahedron Lett.* **2010,** *21,* 1861.
(69) Karakaya, I.; Primer, D. N.; Molander, G. A. *Org. Lett.* **2015,** *17*, 3294.
(70) Taber, D. F.; Paquette, C. M.; Reddy, P. G. *Tetrahedron Lett.* **2009,** *50*, 2462.
(71) Das, A.; Chaudhuri, R.; Liu, R.-S. *Chem. Commun.* **2009,** 4046.
(72) Wang, L.; Hashidoko, Y.; Hashimoto, M. *J. Org. Chem.* **2016,** *81*, 4464.
(73) Molander, G. A.; Canturk, B. *Org. Lett.* **2008,** *10*, 2135.
(74) Iwanami, K.; Seo, H.; Tobita, Y.; Oriyama, T. *Synthesis* **2005,** *2005*, 183.
(75) Li, N.-N.; Zhang, Y.-L.; Mao, S.; Gao, Y.-R.; Guo, D.-D.; Wang, Y.-Q. *Org. Lett.* **2014,** *16*, 2732.
(76) Pan, X.; Lalevée, J.; Lacôte, E.; Curran, D. P., *Adv. Synth. Catal.* **2013,** *355*, 3522.
(77) Bethmont, V.; Fache, F.; Lemaire, M. *Tetrahedron Lett.* **1995,** *36*, 4235.
(78) Morra, N. A.; Pagenkopf, B. L. *Synthesis* **2008,** *2008*, 511.

(79) Connolly, T.; Wang, Z.; Walker, M. A.; McDonald, I. M.; Peese, K. M. *Org. Lett.* **2014,** *16*, 4444.
(80) Vo, C.-V. T.; Mitchell, T. A.; Bode, J. W. *J. Am. Chem. Soc.* **2011,** *133*, 14082.
(81) Fujii, Y.; Furugaki, H.; Tamura, E.; Yano, S.; Kita, K. *Bull. Chem. Soc. Jpn.* **2005,** *78*, 456.
(82) Xu, Q.; Xie, H.; Chen, P.; Yu, L.; Chen, J.; Hu, X. *Green Chem.* **2015,** *17*, 2774.
(83) Chu, Q.; Makhlouf Brahmi, M.; Solovyev, A.; Ueng, S.-H.; Curran, D. P.; Malacria, M.; Fensterbank, L.; Lacôte, E. *Chem.–Eur. J.* **2009,** *15*, 12937.
(84) Alonso, F.; Barba, I.; Yus, M. *Tetrahedron* **1990,** *46*, 2069.
(85) Salvati, A. E.; Hubley, C. T.; Albiniak, P. A. *Tetrahedron Lett.* **2014,** *55*, 7133.
(86) Mitchell, T. A.; Bode, J. W. *J. Am. Chem. Soc.* **2009,** *131*, 18057.
(87) Oliphant, T. E. *Comput. Sci. Eng.* **2007,** *9,* 10.
(88) Bevington, P. R.; Robinson, D. K. *Data Reduction and Error Analysis for the Physical Sciences;* McGraw-Hill: New York, 2003; pp 75−97.
(89) Zhao, C.; Seidel, D. *J. Am. Chem. Soc.* **2015,** *137,* 4650.