Tetrahedron Letters 58 (2017) 2623–2628

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Digest paper

Anion-binding catalyst designs for enantioselective synthesis

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ARTICLE INFO

Article history:
Received 20 March 2017
Revised 11 May 2017
Accepted 11 May 2017
Available online 15 May 2017

ABSTRACT

Select hydrogen bond donors can catalyze reactions of ion pairs through the recognition of anions. This mode of action can be exploited in enantioselective catalysis if a suitable chiral hydrogen bond donor is applied. Beyond just anionic recognition, an enantioselective anion-binding catalyst often must host numerous non-covalent interactions, including hydrogen bonding, general base, π-π, and π-cation, to achieve high levels of enantiocontrol. Anion-binding catalysts can be strategically designed to support those non-covalent interactions required to render a process highly stereoselective. Tactics applied in anion-binding catalyst development include enhancing arene substituents for improved π-stacking, linking two anion-binding units together on a single scaffold, expanding types of functional groups for anion recognition, and building frameworks with bifunctional modes of action. The intent of this digest is to highlight observations that suggest as anion-binding catalyst designs advance, their associated synthetic methodologies for complex molecule construction become increasingly impressive.

Contents

Introduction

The sophistication of modern, enantioselective dual hydrogen bond donor catalysis seems almost unreal when compared to the seminal discoveries that initiated the field decades ago.[1] The earliest milestones were critical in establishing the feasibility of reaction rate acceleration in the presence of suitable hydrogen bond donors. For instance, Hine's 1,8-biphenylenediol activation of epoxides for reaction with amines revealed the unique catalytic abilities of dual hydrogen bonding groups.[2] Curran and coworkers offered key insight into the abilities of ureas to alter both the reaction rate and stereochemical outcome of organic processes.[3]

The advance of enantioselective thiourea catalysis was transformative for dual hydrogen bond donors. A 1998 report from Sigman and Jacobsen, demonstrating that peptide-based thioureas enable the highly enantioselective addition of cyanide to *N*-acylimines, verified that hydrogen bond donors can operate as excellent asymmetric catalysts.[4] Additional highly enantioselective thiourea catalyst designs reported in the early 2000s by Takemoto, Ricci, and others, contributed to an undeniable stack of evidence pointing to their synthetic utility.[5] Beyond (thio)ureas, dual hydrogen bonding scaffolds derived from other functional groups, such as squaramides and diols, were identified as promising catalysts.[6]

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http://dx.doi.org/10.1016/j.tetlet.2017.05.045
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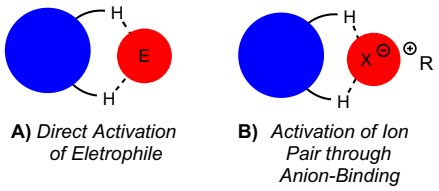


Fig. 1. Proposed modes of action for dual hydrogen bond donor catalysts.

To this day, the area of enantioselective dual hydrogen bond donor catalysis remains an intensely active and fruitful platform for investigation.

An interesting idea emerged in the mid-2000s that brought a new perspective on plausible modes of action of dual hydrogen bonding catalysts. Until this point, it was conventional to propose that dual hydrogen bond donors were directly activating electrophiles through hydrogen bonding (**A**, Fig. 1). In 2006, Schreiner and coworkers suggested that, under appropriate reaction conditions, hydrogen bond donor catalysts may bond to the anionic component of an ion pair, thereby generating a new reactive species (**B**, Fig. 1).[7] The recognition of the multiple modes of activation for dual hydrogen bond donors further widened the potential impact of the field.

Recent progress in hydrogen bond donor anion-binding catalysis has driven the field to a promising position. As will be touched on in this short contribution, there are now different families of catalysts available, clear correlations between catalyst structure and activity are documented, and mechanistic insights into reaction pathways proceeding through anion-binding catalysis have opened new doors for discovery. More than this, anion-binding catalysts are finding their unique niche in complex molecule synthesis.

Recent reviews that provide the chemistry community with thorough updates on the state of the art in anion-binding catalysis exist.[8] Therefore, it is not the purpose here to generate a detailed account of anion-binding catalysis. Instead, the goal of this digest is to draw attention to the promise of anion-binding catalyst design for the purposes of enabling enantioselective complex molecule construction. The account begins by highlighting complex target synthesis with thioureas and bis-thioureas. Heterocyclic functionalization reaction with triazoliums and triazoles as anion-binding catalysts are featured second and third, followed by using silanediols as catalysts.

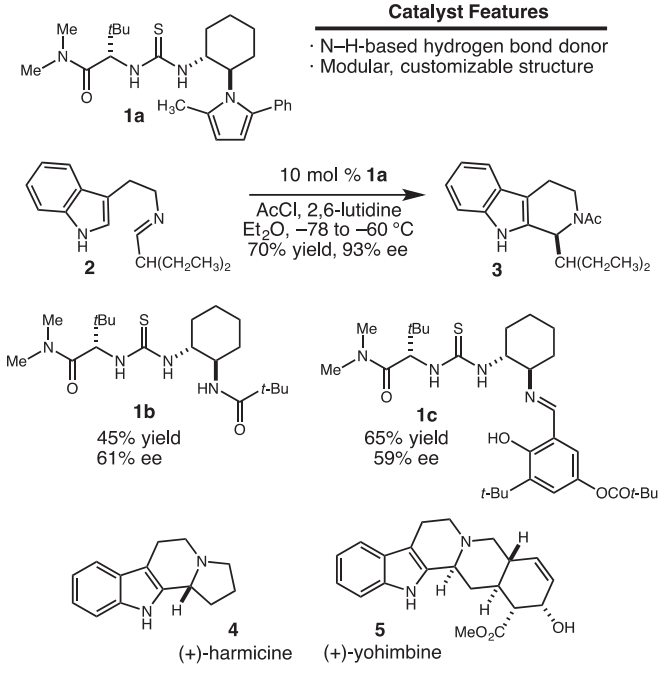
Anion-binding catalysis

(Thio)ureas

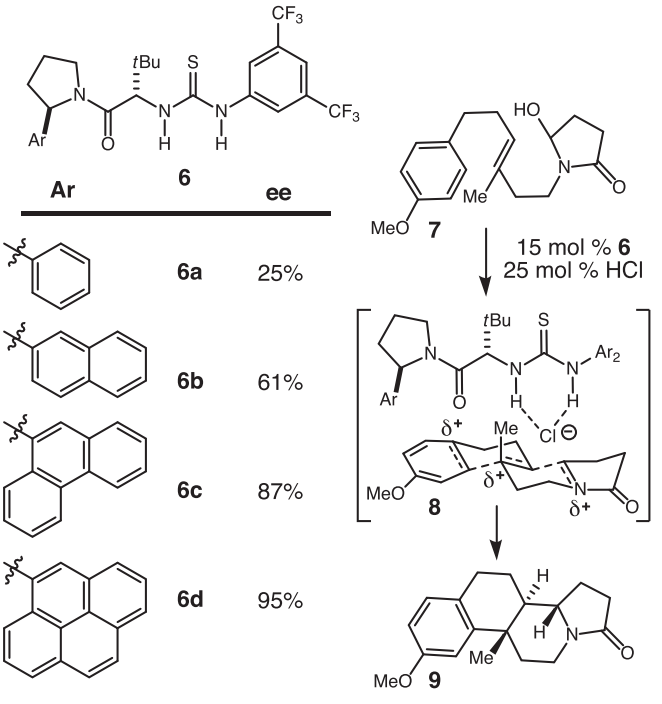
Ureas and thioureas are N–H-based hydrogen bond donors that have long been sought after for their abilities to recognize anions, such as chlorides, bromides, and acetates.[9] It has only been relatively recent that (thio)urea anion-recognition has been coupled with catalysis. The acetalization of aldehydes with triethyl orthoformate in the presence of thioureas is a seminal example.[7a] With the identification and acknowledgement of (thio)urea anion-binding catalysis emerged a research direction that has enabled the development of methodologies for complex molecule synthesis.

The Jacobsen group demonstrated the promise of anion-binding catalysis in enantioselective thiourea-catalyzed Pictet-Spengler-type cyclization reactions (Scheme 1).[10] The pyrrole-thiourea catalyst **1a** was identified by Taylor and Jacobsen as a highly selective scaffold for the cyclization reaction.[10a] For example, indole **2** was cyclized to the tetrahydro-β-carboline derivative **3** with excellent levels of enantiocontrol. The 2-methyl 5-phenyl pyrrole substituent on **1a** was found to have a significant, positive effect on the enantiocontrol of the cyclization; the amide thiourea **1b** and imine thiourea **1c** provided lower enantiomeric excesses. Harmicine (**4**) and yohimbine (**5**) were elegantly connected through enantioselective Pictet-Spengler-type reactions catalyzed by **1a**, or closely related derivatives.[10b,c]

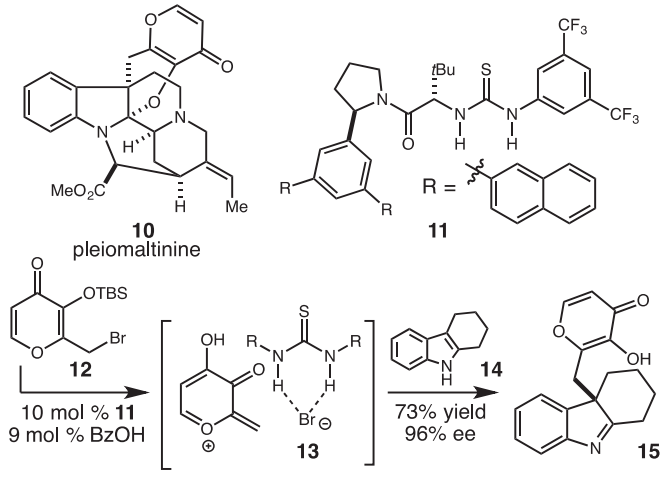
The customizable nature of the (thio)urea scaffold played a key role in the development of selective anion-binding catalysts for polyene cyclization reactions (Scheme 2).[11] In this work, a cocata-



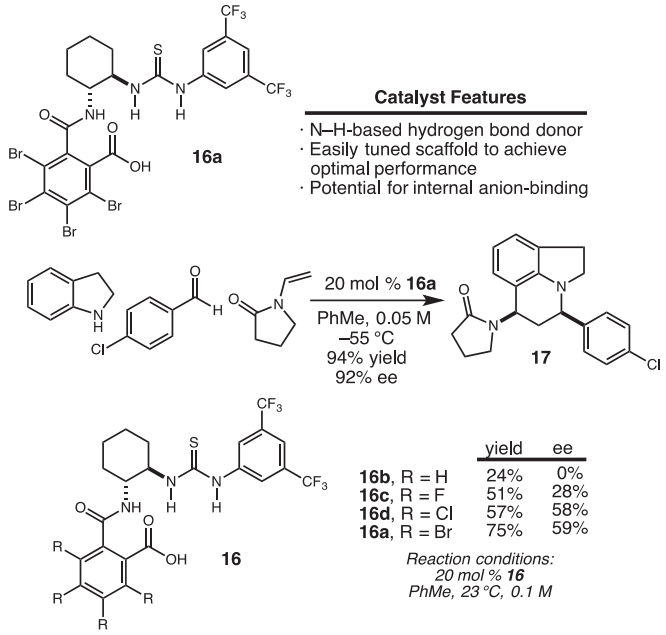
Scheme 1.



Scheme 2.



Scheme 3.

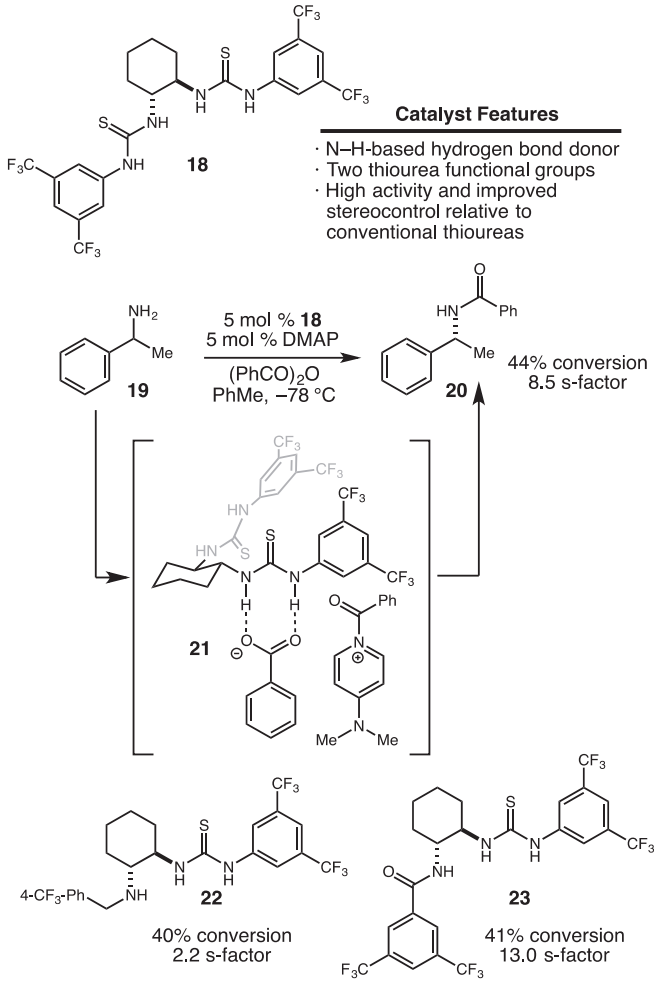


Scheme 4.

lyst system involving arylpyrrolidine thiourea catalyst **6** and HCl enables the bicyclization reaction of **7** to yield **9**. The amount of π character located on the aryl pyrrolidine of the thiourea catalyst directly correlates to reactivity: increasing the π character of the aromatic group appended to the pyrrolidine led to improved yields and enantiocontrol. The 4-pyrenyl containing scaffold **6d**, the best catalyst identified in the study, led to the synthesis of **9** as a single diastereomer in 78% yield and 95% ee. The authors invoke cation-π interactions as a major stabilizing factor in the transition state (**8**). It is worthwhile to mention that arylpyrrolidine thiourea catalyst **6** enables a number of enantioselective reactions likely proceeding through anion-binding.[12]

The potential secondary metabolites that may be targeted with arene-rich thiourea anion-binding catalysis continue to grow in complexity. A joint effort between the Jacobsen and Porco groups demonstrated thiourea catalysis may offer solutions for the enantioselective synthesis of complex alkaloid cores containing quaternary carbons, such as pleiomaltinine (**10**, Scheme 3).[13] The proposed reaction pathway involves the thiourea-assisted formation of a cationic quinone-methide-type intermediate (**13**) from **12**. Similar to the polyene cyclization described in Scheme 2, the enantiocontrol in the addition of 1,2,3,4-tetrahydrocarbazole **14** to ion-pair **13** is influenced by the π character of the aromatic substituent located on the pyrrolidine. The results of structure activity relationships studies of the catalyst (**11**) revealed the importance of the naphthyl groups in attaining high levels of enantiocontrol.

A clever internal anion-binding catalyst design was published in 2013 from Seidel and coworkers.[14] The catalyst features an anion-binding unit and Brønsted acid within the same molecule (**16**, Scheme 4). Upon deprotonation by an appropriate substrate, the conjugate base of the Brønsted acid is proposed to participate in hydrogen bonding with the thiourea functional group thereby generating a chiral anion. This anion-binding catalyst design has led to high levels of enantiocontrol and yield in the Povarov, Pictet-Spengler, and Aza-Diels-Alder reaction.[14] In the case of the Povarov reaction, a three component coupling of indoline, 4-chlorobenzaldehyde, and 1-vinylpyrrolidine-2-one gave rise to **17** in 92% enantiomeric excess under the optimal reaction conditions. Fine-tuning of the thiourea structure was critical in establishing a highly selective catalyst. The most influential catalyst design elements include the substitution pattern on the phthalic-anhydride-derived component. For instance, **16b** (R = H) and **16c** (R = F) resulted in significantly lower enantioselectivities in comparison to **16d** (R = Cl) and **16a** (R = Br).



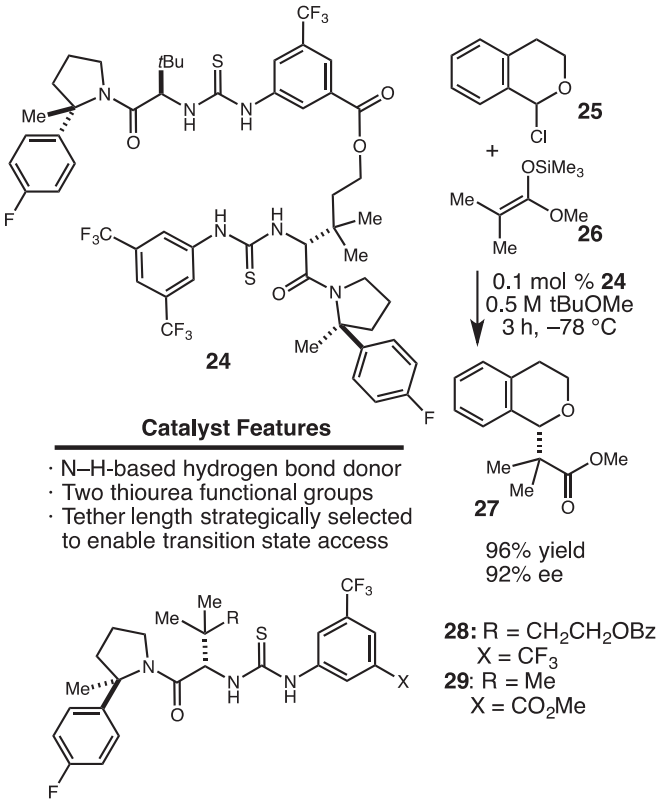
Scheme 5.

Bis-thioureas

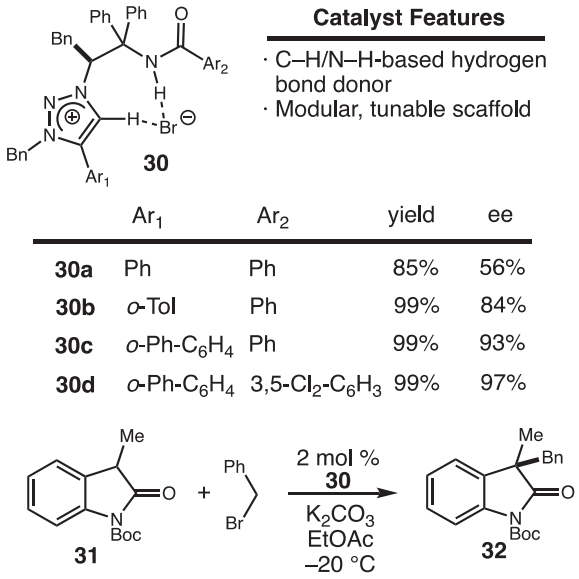
There are several merits in the strategic linking of two thiourea functional groups together to create one powerful, highly selective anion-binding catalyst. To this end, Nagasawa introduced early evidence of the unique catalytic abilities of bis-thiourea **18**, relative to a molecule with one single thiourea active site, in enantioselective Morita-Baylis-Hillman reactions.[15]

Taking advantage of the bis-thiourea scaffold in anion-binding, Seidel and coworkers developed a kinetic resolution of benzyl amines (Scheme 5).[16] Appling a cocatalyst system of 5 mol % **18** and 5 mol % 4-dimethylaminopyridine (DMAP), **20** was prepared from **19** in 44% conversion with and s-factor of 8.5. In comparison, mono-thiourea catalyst **22** yielded a similar conversion but significantly lower s-factor of 2.2. While the transition state remains undetermined, mechanistic studies provided support that intramolecular hydrogen bonding of one thiourea by the other may be partially responsible for the improved selectivity of the bis-thiourea scaffolds.[16b] The investigations eventually enabled the development of amide-thioureas **23**, a catalyst scaffold that may also benefit from intramolecular activation of the thiourea unit, as a general catalyst for the resolution of benzylic amines,[16] allylic amines,[17] diamines.[18]

Beyond achieving high levels of enantiocontrol, bis-thiourea catalysts may offer strategies to solve problems, such as high catalyst loadings and low concentrations, that are common in anion-binding processes.[19] Through dedicated mechanistic evaluations, the Jacobsen research team has identified that self-association of thiourea catalysts may be a leading cause of the undesirable catalyst loading and concentration requirements often observed in anion-binding catalysis. In addition, in certain processes, the most enantioselective anion-binding reaction pathway may proceed through transition states that require two thiourea catalysts per one anion. Strategically designing bis-thioureas that can prevent undesired self-association but facilitate transition state stabilization may overcome issues that compromise the efficiency of mono-thiourea catalysts.



Scheme 6.



Scheme 7.

The advantages of the bis-thiourea anion-binding catalyst design are clear when directly compared to mono-thioureas in the addition of silyl ketene acetals to α-chloroisochroman (Scheme 6).[19b] Specifically, 0.01 mol % of catalyst **24** enabled the formation of **27** from **25** and **26** in excellent yields and excellent levels of enantiocontrol in just 3 h in 0.5 M *tert*-butyl methyl ether. Under identical reaction conditions, catalyst **24** was 14x and 68x faster than mono-thioureas **28** and **29**, respectively.

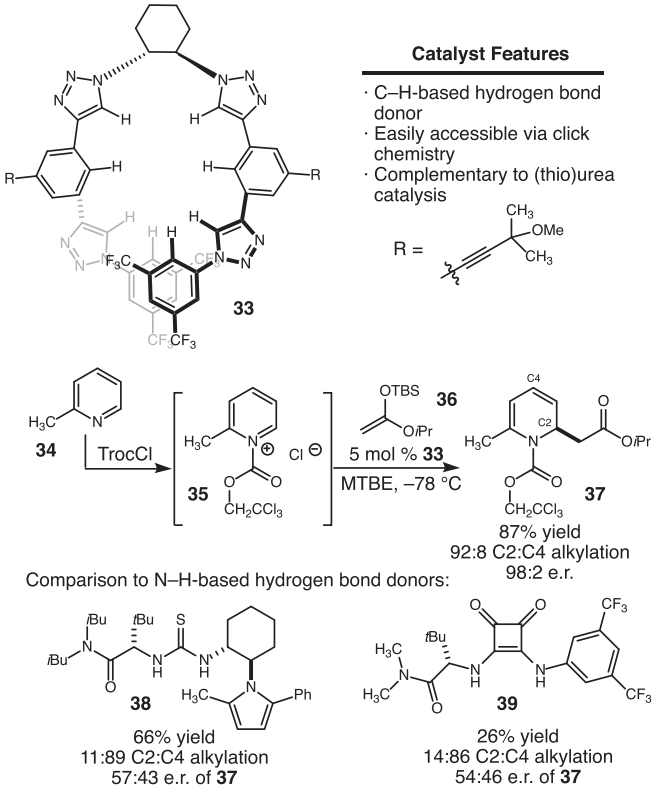
Triazoliums

1,2,3-Triazolium salts **30** introduced by Ooi and coworkers are modular, easily tuned anion-binding catalysts (Scheme 7).[20] The feasibility of the enantioselective catalytic abilities of **30** was demonstrated in the alkylation of oxindole **31**. Just 2 mol % of **30d** enabled the benzylation of **31** giving rise to **32** in quantitative yield and 97% enantiomeric excess. The catalyst structure had a significant influence on stereocontrol: both the amide and triazolium could be optimized to improve enantiocontrol. Catalyst **30a** (Ar_1, Ar_2 = Ph) afforded **32** in 56% ee while **30d** (Ar_1 = *o*-Ph-C_6H_4, Ar_2 = 3,5-Cl_2-C_6H_3) gave rise to **32** in higher yield with 97% ee. Similar triazolium salt designs have found success in catalytic enantioselective ring opening of aziridines.[21]

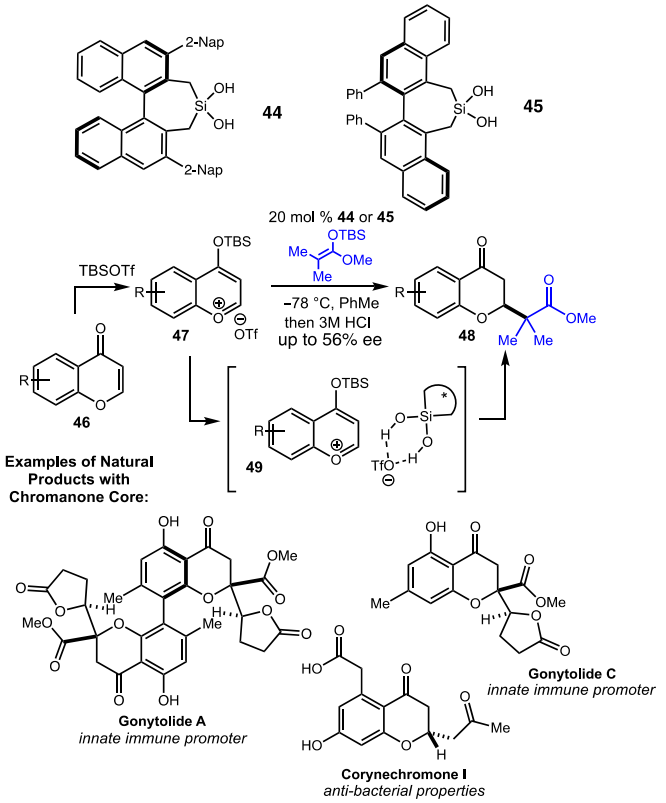
Tetrakistriazoles

Taking inspiration from the anion-recognition properties of the polarized C—H bonds found in oligotriazoles,[22] the Mancheño group designed tetrakistriazole catalysts for anion-binding (Scheme 8).[23–25] This architecturally unique family of anion-binding catalysts benefits from synthetic accessibility via Cu^1-catalyzed azide alkyne click-chemistry and stands-out from other anion-binding catalysts in regards to reactivity for select processes.

Tetrakistriazoles **33** have demonstrated success in reactions of multiple nitrogen-based heterocyclic cations, including isoquinoliniums,[23] quinoliniums,[24] and pyridiniums.[25] In their application toward pyridine dearomatization, tetrakistriazoles proved uniquely effective and thus present opportunities for the selective

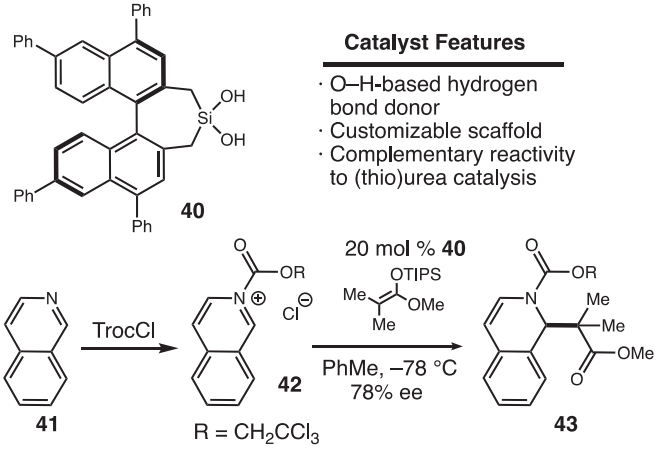


Scheme 8.



Scheme 10.

syntheses of bioactive pyridine-derived heterocycles. Specifically, 5 mol % of tetrakistriazole **33** catalyzed the addition of silylketene acetals to pyridinium ion **35**, generated in situ by the reaction of **34** and TrocCl, to yield **37** in 87% yield and 96% ee (Scheme 8). Notably, the process was highly regioselective: *C*2 alkylation was preferred over C4 alkylation. The unique advantage of **32** was apparent when compared directly to more conventional N—H hydrogen bond donors, including thiourea **38** and squaramide **39**. In both cases the tetrakistriazole is significantly more enantioselective, regioselective, and higher yielding. Evidence supporting the ability of tetrakistriazoles to accommodate a chloride ion in its helical cavity was found with NMR titration experiments of **33** and *N*-Troc quinolinium chloride.[23]



Scheme 9.

Silanediols

The silanediol functional group, a silicon with two –OH groups attached, is known for its excellent hydrogen bonding abilities.[26] In 2006, Kondo and coworkers took advantage of silanediol hydrogen bonding to recognize acetate, chloride, and bromide.[27] Motivated with the evidence of silanediol host-guest interactions, Mattson and coworkers were the first to demonstrate the feasibility of enantioselective silanediol anion-binding catalysis in reactions.[28] The silanediol anion-binding catalysts introduced by Mattson and coworkers feature molecular recognition through O—H bonds and C2-symmetric, arene-rich scaffolds. The results of structure-activity relationship studies of small libraries of cyclic and acyclic BINOL- and VANOL-derived silanediols suggest that the silanediol backbone can be tuned for optimal performance in a desired process.

The early potential of silanediol anion-binding catalysis was showcased in reactions of isoquinolinium chlorides with silyl ketene acetals (Scheme 9). Tetraphenylsilanediol **40** was found to enable the formation of **43** in nearly 80% ee. More recent advances have found that silanediols are catalysts for enantioselective chromenone functionalization reactions (Scheme 10).[29] In this process, it is proposed that the silanediol captures ion pair **47** to generate chiral ion pair **49**, which enables the enantioselective formation of **48**. This rare example of controlling the addition of carbonyl containing nucleophiles to benzopyrylium ions illustrates the potential impact silanediol anion-binding catalysis may have in complex molecule synthesis. The methodology may find direct application in natural product synthesis and drug discovery as many bioactive secondary metabolites contain the 2-alkyl-chroman-4-one core, such as the gonytolides.[30]

Conclusions

Anion-binding catalysis is a platform of promise for hydrogen bond donors. From anion-binding catalysis are emerging useful, unique methodologies that are often inaccessible to more conventional Lewis acid or transition metal-based catalysts. Moreover, the molecular targets accessed via anion-binding methodologies are becoming increasingly more complex.

The impressive current state of the art in anion-binding catalysis is a direct consequence of discoveries that have driven the field forward. For instance, the recent extension of anion-binding catalyst scaffolds beyond thioureas, to tetrakistriazoles and silanediols, seeds the inspiration to design future families of anion-binders with innovative molecular recognition elements. Experimental evidence points to the complementary nature of different types of anion-binding catalysts, which prompts the continued advance of a well-rounded collection of non-covalent anion-binding catalysts. Recent mechanistic insights draw attention to significant features of anion-binding catalysis to facilitate the development of catalysts that operate under reaction conditions more amenable to scale up. All taken together, these trends suggest impactful strategies for complex molecule synthesis are waiting to be realized from innovations in anion-binding catalyst design.

Acknowledgments

The National Science Foundation (CHE 1342030, CHE 1654396) is acknowledged for supporting our work on silanediol anion-binding catalysis.

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