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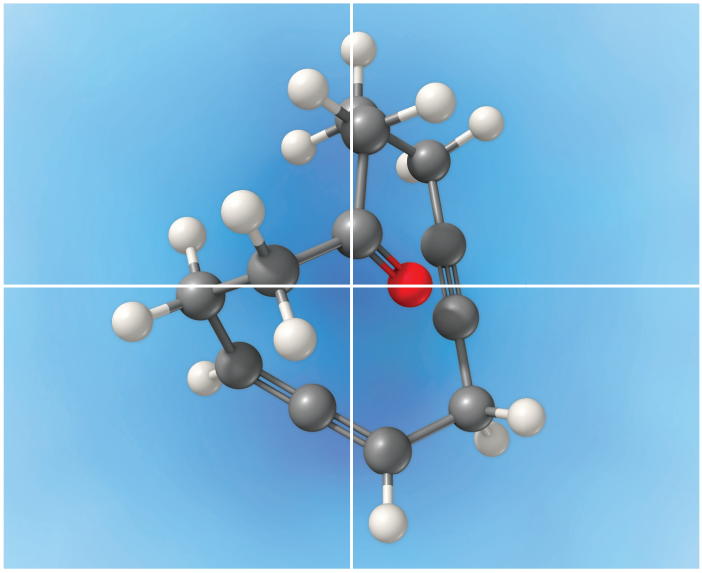

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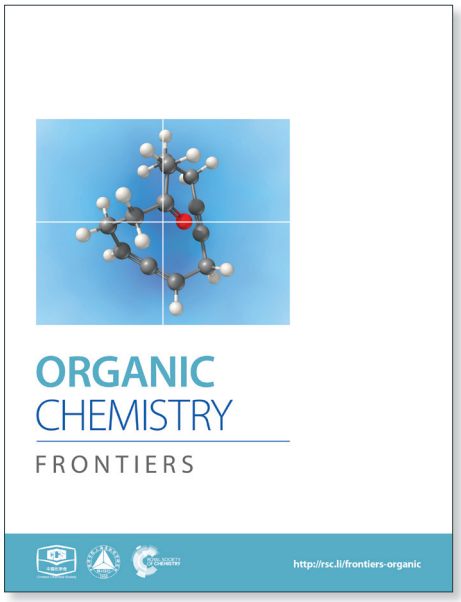

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ARTICLE

Novel strategies for catalytic asymmetric synthesis of C1-chiral 1,2,3,4-tetrahydroisoquinolines and 3,4-dihydrotetrahydroisoquinolines

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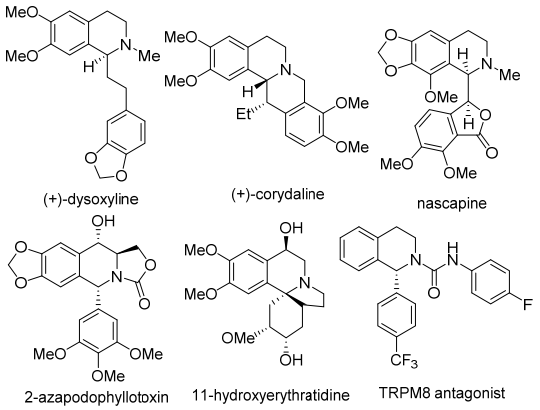
1,2,3,4-Tetrahydroisoquinoline is one of the most important "privileged scaffolds" present in natural products. C1-chiral tetrahydroisoquinolines have exhibited a wide variety of bioactivities and found applications as chiral scaffolds in asymmetric catalysis. This paper summarizes novel catalytic stereoselective strategies that emerged in the past ten years for synthesis of 1,2,3,4-tetrahydroisoquinoline and 3,4-dihydroisoquinoline scaffolds, beyond the traditional Pictet-Spengler and related protocols, as well as their applications in the total synthesis of alkaloid natural products.

1. Introduction

1,2,3,4-Tetrahydroisoquinoline (THIQ) represents one of the most prevalent "privileged scaffolds" created by nature,[1] as exemplified by the numerous identified THIQ-containing alkaloids which demonstrate a wide range of bioactivities, including anti-tumor, anti-bacteria, anti-virus, anti-inflammation, *etc.* (Scheme 1).[2] The number of bioactive small molecules bearing THIQ skeletons as potential therapeutic agents for treatment of diverse diseases, such as cancer, AIDS, Parkinson's disease *etc.* has shown an incredible increase.[3] THIQ-containing molecules have also shown increasing applications in asymmetric catalysis as chiral scaffolds.[4] Not surprisingly, strategies for the assembly of THIQ-containing molecules have garnered intensive attention in the past decades. Traditional approaches such as Pictet-Spengler reaction and Bischler-Napieralski cyclization/reduction sequence were successfully demonstrated and continue to show their power in the synthesis of isoquinoline and indole alkaloid frameworks. They are, however, intrinsically limited to electron-rich aromatic substrates.[5] Asymmetric synthesis of C1-chiral moiety containing THIQs is of particular importance due to its presence in many THIQ type alkaloids and the usually distinct bioactivities exhibited by the two antipodes of a given structure. This paper summarizes representative recent strategies for the *catalytic asymmetric* synthesis of THIQ and 3,4-dihydroisoquinoline (DHIQ) scaffolds bearing the C1-chirality. Updates in this field during the past ten years (2003-early 2014) will be included, except the above-mentioned classical methodologies. Asymmetric hydrogenation and transfer hydrogenation of isoquinoline derivatives are established powerful strategies that could be traced back to the 20th century and have been highlighted very recently.[6] Readers are referred to elegant previous reviews for summary of non-catalytic asymmetric synthesis of THIQs.[7] Reactions are discussed and classified base on their substrates and activation modes, as well as the reaction types.



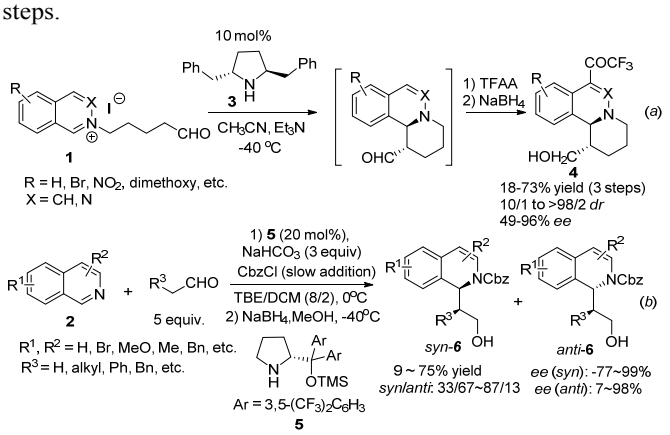
Scheme 1. Selected bioactive THIQ containing natural products and synthetic small molecules.

2. Recent strategies for catalytic asymmetric synthesis of C1-chiral THIQs and DHIQs

2.1 Nucleophilic addition to isoquinoline, 3,4-dihydroisoquinoline (DHIQ) and isoquinolinium salt.

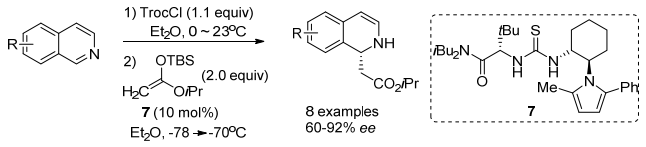
The majority of synthetic routes for 1,2,3,4-tetrahydroisoquinolines and 3,4-dihydroisoquinolines involve asymmetric addition of nucleophiles to readily available isoquinoline, 3,4-dihydroisoquinoline (DHIQ) or N-H tetrahydroisoquinolines (THIQ) core. This C1-Cα connection represents a straightforward approach for the synthesis of C1-chiral THIQs. Isoquinoline usually needs activation by an external alkylating or acylating reagent to form iminium species. Since the first catalytic enantioselective Reissert reaction reported by Shibasaki and coworkers in 2001,[8] catalytic addition of preformed or *in situ* generated nucleophiles to activated iminium species received much attention. Jørgensen *et.al.* reported in 2005 a chiral pyrrolidine derivative catalyzed intramolecular addition to isoquinolinium ions **1** (Scheme 2, *a*).[9] High enantioselectivities and good diastereoselectivities

were obtained. Mechanistic studies suggested that the reaction went through a transition state involving a crucial cation–π interaction between iminium ion with the phenyl ring in catalyst **3**. The intermolecular reaction was not realized until very recently by Cozzi and coworkers starting from isoquinoline with CbzCl as the activating reagent (Scheme 2, *b*).[10] The products **6** were obtained in moderate *dr*s and good *ee*s, but yields were moderate. Switching the solvent to pure dichloromethane afforded *anti* diastereoisomers selectively in good *ee*s. The methodology was successfully applied to the synthesis of 13-methyl tetrahydroprotoberberine in seven total steps.



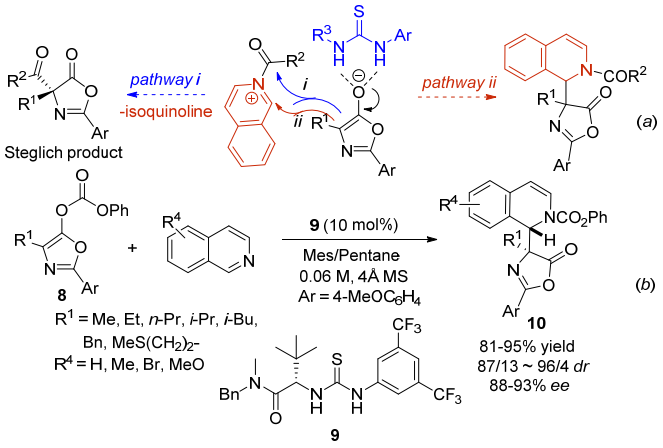
Scheme 2. Secondary amine catalyzed intra- and intermolecular asymmetric addition of aldehydes to isoquinoline

Catalyst activation of isoquinoline represents an alternative activation mode which obviates the necessity to asymmetrically activate nucleophiles. Jacobson *et. al.* reported in 2005 the intermolecular addition of preformed silyl ketene acetal to *in situ* generated *N*-acylisoquinolines catalyzed by chiral thiourea derivative **7**, inspired by their discovery of the capability of these thiourea catalysts to activate the iminium ions in the asymmetric acylative Pictet–Spengler reaction. The reaction tolerates electronically distinct substituents on both rings and affords the corresponding DHIQs with high enantioselectivities (Scheme 3).[11]



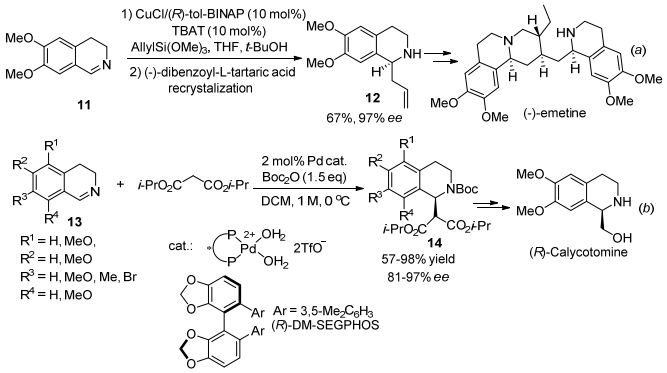
Scheme 3. Thiourea catalyzed asymmetric addition of silyl ketene acetal to isoquinoline

By combining achiral nucleophilic catalyst and chiral anion binding catalyst, Seidel and coworkers developed a novel strategy for the catalytic asymmetric Steglich rearrangement.[12] When isoquinoline was used instead of DMAP, the catalyst bound anion intermediate attacks the resultant acylated isoquinoline intermediate *via* two possible routes leading to product formation: *i*) normal attack on the carbonyl group releasing isoquinoline and the Steglich rearrangement product; and *ii*) attack on the imminium carbon atom generating THIQ product with acyl being transferred to the nitrogen in the isoquinoline (Scheme 4, *a*). Incorporation of the isoquinoline into the final product was observed at an elevated temperature with thiourea **9** *via* pathway *ii*, which delivered the products **10** in excellent yields and enantioselections despite of the significantly lower nucleophilicity of isoquinoline compared to that of DMAP. Interestingly, the facial selectivity for the azlactone addition to the acylisoquinoline was opposite to that of azlactone rearrangement (Scheme 4, *b*).



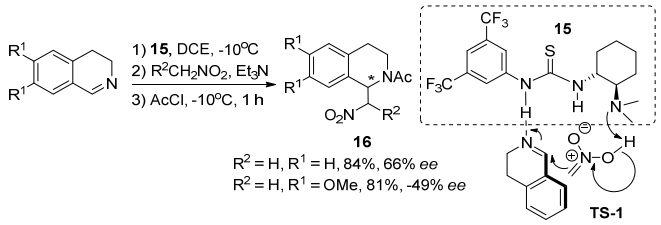
Scheme 4. Synthesis of chiral DHIQ via chiral anion binding catalysis.

The reactivity of 3,4-dihydroisoquinolines is quite similar to that of isoquinoline, except that the former might or might not require activation. Copper catalyzed asymmetric allylation of cyclic C,N-azomethine imine afforded C1-allylated THIQ with moderate enantioselectivities without activating reagent. After chemical resolution the optically pure product **12** was applied to the formal total synthesis of natural product (−)-emitine (Scheme 5, *a*).[13] Sodeoka *et.al.* disclosed an asymmetric addition of malonate to Boc_2O activated DHIQs catalyzed by chiral palladium (II) complexes (Scheme 5, *b*).[14] This reaction was applied to the facile synthesis of (*R*)-calycotomine in seven steps, which also defined the absolute configuration of the products **14**.



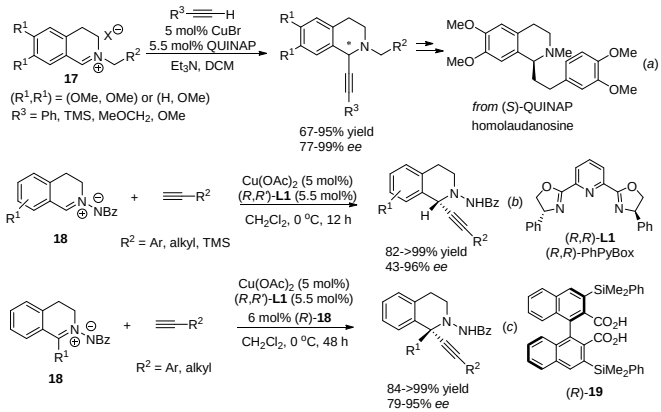
Scheme 5. Transition metal catalyzed asymmetric addition to 3,4-dihydroisoquinoline

Direct catalyst activation of 3,4-DHIQ was indicated in the asymmetric aza-Henry reaction with nitroalkanes, where thiourea derivative **15** was employed as bifunctional catalyst. However, only moderate *ee*s were obtained for the products **16** (Scheme 6).[15] This reaction works only for C1-unsubstituted cyclic imine, and the sense of asymmetric induction is sensitive to substitutions on the DHIQ (Scheme 6, abosolute configuration not shown). Based on the information obtained from catalyst screening and mechanistic studies, a transition state (**TS-1**) involving hydrogen-bonding network as depicted in Scheme 6 was proposed.



Scheme 6. Thiourea as bifunctioinal organocatalyst in the aza-Henry reaction of 3,4-DHIQ with nitroalkanes.

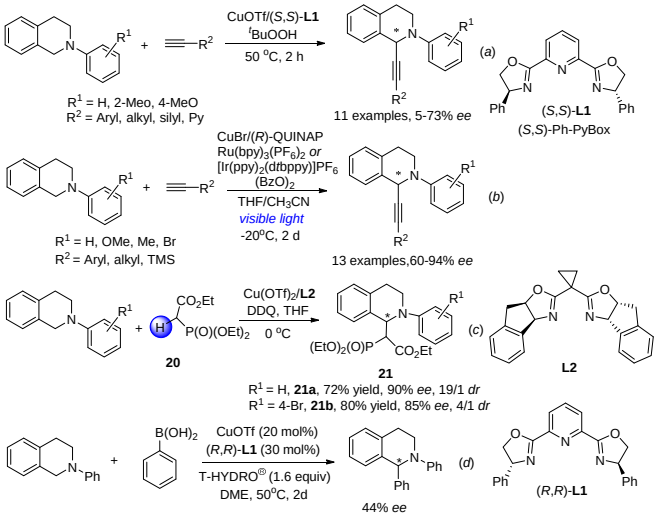
Isoquinoline iminium salts undergo facile asymmetric addition reactions with various nucleophiles. Copper catalyzed asymmetric addition of terminal alkynes was realized independently by Schreiber *et. al.* and Li *et. al.* in 2006, who found that under the catalysis of CuBr/Quinap complex, a variety of alkynes reacted with alkylated iminium salt **17** with high enantioselection.[16] This reaction was successfully applied to the concise four-step asymmetric synthesis of homolaudanosine by Schreiber and coworkers (Scheme 7, *a*). However, it showed no optical selectivity for C1-substituted substrates. The $Cu(OAc)_2$/(*R*,*R*)-**L1** combination was shown to be viable in the similar catalytic asymmetric alkynylation of C1-unsubtituted C,N-cyclic azomethine imines **18** (Scheme 7, *b*).[17] For C1-substituted substrates, products were retrieved with moderate enantioselectivities. This problem was overcome by addition of C2-symmetrical Brønsted acid as co-catalyst. The 3,3'-substituents on the acid turned out to be crucial; the bulky group substituted bisacid (*R*)-**19** led to the best enantioselectivity (Scheme 7, *c*). The high dependence of enantioselection on steric factors of the cocatalyst suggested the possible role of acid co-catalyst being to exchange with HOAc in the activation of C,N-cyclic azomethine imines, which acted cooperatively with copper catalyst to enhance enantioselection. Besides isoquinoline iminium salts, asymmetric addition of 3,4-dihydroisoquinoline *N*-oxides with organozinc species were reported to give C1-aryl and alkenyl THIQs in high enantioselections when mediated by amino acid derived amino alcohol reagents, but reactions with catalytic amount of chiral amino alcohol reagents resulted in moderate enantioselections due to competitive non-catalyzed background reactions.[18,19]



Scheme 7. Copper catalyzed asymmetric alkynylation of isoquinoline iminium salts.

2.2 Asymmetric cross dehydrogenative coupling (CDC) reactions[20] and merging organo-/metal catalysis and photoredox catalysis

The discovery of facile oxidation of *N*-aryl THIQ with various oxidants opened up new revenues for the synthesis of C1-substituted THIQs. These reactions were termed "cross dehydragenative coupling (CDC) reaction" by Li, who, along with Murahashi, pioneered this field. The combination of *N*-aryl THIQ oxidation with enantioselective addition of an external nucleophile affords C1-chiral THIQs with high efficiency. Copper/bisoxazoline catalytic system has proven successful in a series of related reactions in the activation of alkyne, dicarbonyl compounds, and arylboronic acids, *etc.* For instance, Li and coworkers discovered that in the presence of *t*-BuO_2H, the reaction of *N*-aryl THIQ with different aryl substituted alkynes afforded the CDC products in moderate to good *ee*s, while 2-pyridyl, silyl and alkyl substituted products were obtained with moderate to low *ee*s (Scheme 8, *a*).[21] The CuOTf/QUINAP combination showed comparable selectivities in a later study with TBHP as oxidant.[16b] The requirement of 50°C or higher temperature possibly impeded the development of a highly enantioselective process. High enantioselective variant of this important transformation was eventually realized very lately by Li and coworkers by merging photoredox catalysis with CuOTf/QUINAP catalyst. This synergisitic catalytic process allowed the reaction to be carried out at -20°C under low catalyst loadings, which dramatically improved the enantioselection versus the conventional oxidation condition (Scheme 8, *b*).[22] Horner-Warsworth-Emmons (HWE) reagent **20** could be activated by a $Cu(OTf)_2$/**L2** complex and react with the oxidatively generated THIQ iminium ion to delivere the CDC products **21a** with high eantio- and diastereoselectivities, as reported by Wang and coworkers in 2011 (Scheme 8, *c*).[23] Related reaction with aryl boronic acids was studied by Li and coworkers in 2008. The asymmetric version of such transformation was preliminarily studied in this work with (*R*,*R*)-**L1**, but moderate enantioselection was observed (Scheme 8, *d*).[24]

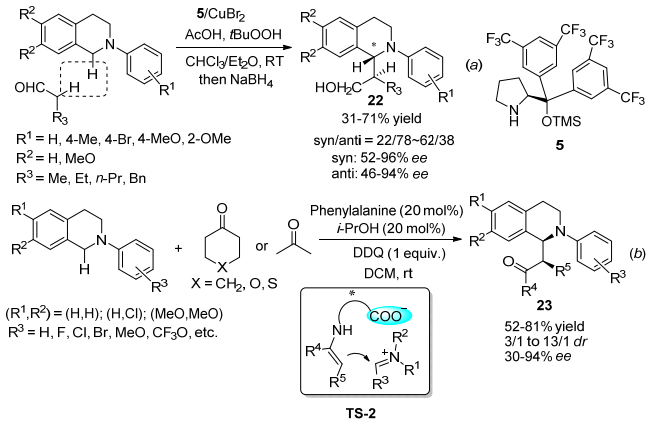


Scheme 8. Transition metal involved CDC reactions of *N*-aryl THIQ.

Under the catalysis of Hayashi-Jørgensen catalyst **5**, aliphatic aldehydes add to the *in situ* generated THIQ iminium ion intermediates in an enantioselective fashion (Scheme 9, *a*).[25] The selectivity outcome turned out to be very sensitive to the reaction conditions. Under the optimized conditions the products **22** were obtained with only moderate *dr*s but good to excellent *ee*s. A related work with ketone by Wang and coworkers employed phenylalanine as catalyst to form the enamine intermediate with ketone, while its pendent carboxylic acid moiety forms chiral ion pair with the

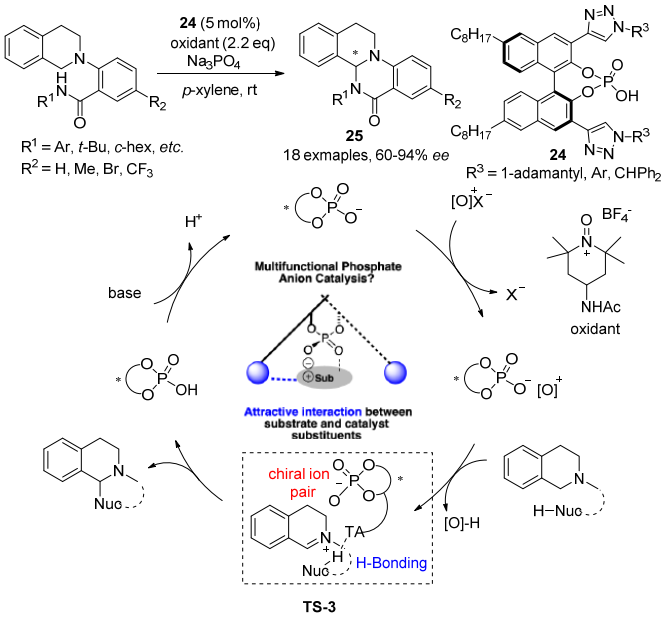
iminium ion intermediate (**TS-2**, Scheme 9, *b*).[26] This bifunctional catalyst brings both reacting intermediates in close proximity and is expected to improve selectivity. Indeed, the metal free reaction between cyclic ketones and *N*-aryl THIQ afforded the CDC producst **23** with good *dr* and *ee*s, while acetone, the only reported acyclic ketone, afforded the corresponding product with only 30% *ee*.

Almost at the same time, Toste and coworkers realized an enantioselective intramolecular CDC amidation reaction with multifunctional chiral phosphoric acid catalysts, featuring activation of both reaction components.[27] Realization of high enantioselection hinges on the design of a 3,3'-(1,2,3-triazole)-containing phosphoric acid catalyst **24**. The chiral phosphoric acid catalyst was proposed to form ion pairs with the cationic oxidant and remained attached to the resulting iminium intermediate post to its formation. The triazole moiety in the catalysts was proposed to interact with the amide in the nucleophile, thus rendering a more rigid transition state (**TS-3**, Scheme 10) for asymmetric induction. Attack of the iminium intermediate by the activated amide nitrogen implements the annulation furnishing enantioenriched tricyclic THIQ products **25** (Scheme 10). This bio-inspired transition state-lowering strategy with hydrogen-bonding interaction was shown to be advantageous than the traditional one which relies purely on steric factors at the 3,3'-position of the phosphoric acid catalyst.



Scheme 9. Chiral amine catalyzed CDC reaction of *N*-aryl THIQ

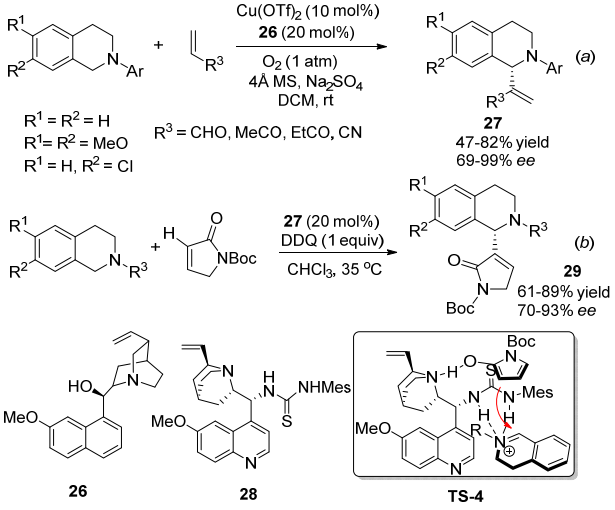
In contrast to the great success being made in the asymmetric construction of C_{sp3}–C1 juncture as mentioned above, examples wherein nucleophiles bearing sp^2 hybridized carbon centers are less explored. The combined CDC-Morita Baylis Hillman (MBH) reaction was first reported by Li and coworkers as early as 2006,[28] but its asymmetric reaction was not realized until 2012, when Wang and coworkers reported the enantioselective aerobic oxidative coupling between THIQ and electron-deficient alkenes (Scheme 11, *a*).[29] This reaction combines copper catalyzed aerobic oxidation of THIQ with asymmetric nucleophilic catalysis to produce **27** with high enantioselection. The reaction seemed to proceed *via* classical MBH mechanism, since hydroxy tertiary amines and tertiary phosphines were also able to induce moderate enantioselections. Very lately, Wang and coworkers reported the related reaction with α,β-unsaturated γ-butyrolactam catalyzed by chiral quinine derived bifunctional thiourea catalyst **28**. The reaction afforded a series of C1-heterocyclic substituted THIQs **29**, featuring α-position functionalization of α,β-unsaturated γ-butyrolactam. A putative transition state **TS-4** involving an activated enamine generated *in situ* from α,β-unsaturated γ-butyrolactam was provided to explain



Scheme 10. Chiral phosphoric acid catalyzed intramolecular CDC-amidation of *N*-aryl THIQ.

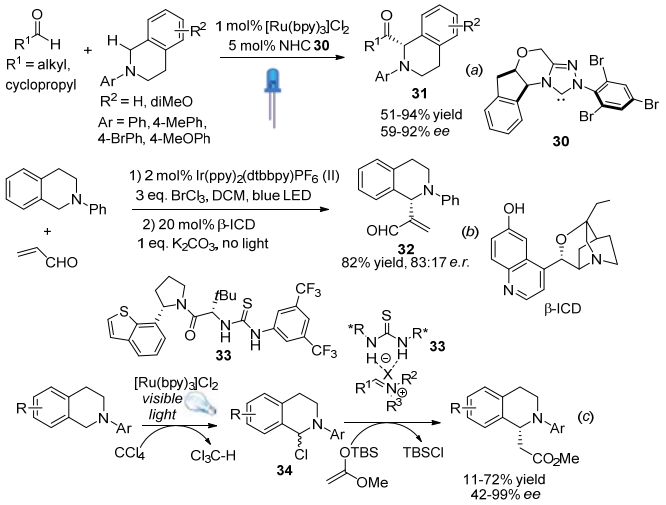
this unique regioselectivity (Scheme 11, *b*).[30]

Photooxidation of *N*-aryl THIQ represents a greener and often more ambient alternative compared to traditional oxidation processes, as exemplified by the successful development of highly enantioselective asymmetric C1-alkynlyation of THIQ by merging photoredox catalysis with asymmetric copper catalysis (Scheme 8, *b*). The enantioselective functionalization of *N*-aryl THIQ by sequential photoredox-metal/organocatalysis achieved low enantioselection as observed by Tan and coworkers in the Mannich reaction of acetone with *N*-PMP substituted THIQ, wherein Rose Bengal, an organic dye, was used as photocatalyst.[31] Shortly after, Rovis *et. al.* merged photoredox and NHC catalysis to realize the catalytic asymmetric α-acylation of THIQs (Scheme 12, *a*).[32] The *in situ* generated acyl anion via *N*-heteocyclic carbene (NHC) umpolung catalysis reacted with the photoredox generated iminium ion to form C1-acylated products **31** in high enantioselectivities. Notably, low catalyst loadings were required in this process.



Scheme 11. Catalytic CDC-Morita-Baylis-Hillman reaction.

Xiao *et.al.* recently described one-pot sequential photo catalysis/nucleophilic catalysis for the construction of C1-functionalized THIQs.[33] Using O_2 as the oxidant the reaction between *N*-phenyl THIQ with acrolein resulted in formation of oxidized isoquinoline. Instead, with $BrCCl_3$ as oxidant the desired product was obtained in moderate yield. Catalytic asymmetric reaction β-isocupreidine (β-ICD) as nucleophilic catalyst and an iridium complex as photoredox catalyst retrieved product **32** with a moderate 66% *ee* (Scheme 12, *b*). This is reminiscent of Wang's work in 2011 which employed Cu/O_2 oxidation, in which high enantioselectivities were achieved (Scheme 11, *a*). Noticing the usually concomitant reductive generation of halide anions during light photocatalysis, Stepheson and coworkers recently combined photocatalysis with chiral anion binding catalysis to realize oxidative enantioselective C−H functionalization of THIQs with silyl ketene acetals (Scheme 12, *c*).[34] The thiourea **33** was proposed to activate

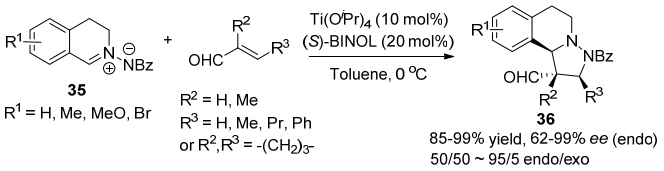


Scheme 12. CDC processes involving visible photoredox catalysis for synthesis of THIQs.

the resultant intermediate α-haloamine **34**, by binding to the halide ion and the resultant counterion was proposed to induce enantioselectivity. Similarly, this two-step sequential process is reminiscent of Jacobsen's chiral thiourea catalyzed addition of silyl ketene acetals to isoquinolines, which also achieved good enantioselection (Scheme 3). This process, however, does not require bulkier isopropyl ester to attain good enantioselection, albeit the yields are moderate.

2.3 1,3-Dipolar cycloaddition reactions

1,3-Dipolar cycloaddition reactions with C,N-cyclic azomethine imine or their analogues create ring fused THIQs bearing multiple stereogenic centers. The titanium-binolate complex catalyzed asymmetric dipolar cycloaddition of C,N-cyclic azomethine imine **35** with α,β-unsaturated aldehydes developed by Maruoka and coworkers in 2010 generates chiral THIQs **36** with 1,3-diamine moiety (Scheme 13).[35] Excellent *exo*/*endo* ratio and *ee*s were achieved when a 2/1 ratio of BINOL and $Ti(OiPr)_4$ was employed. Substitution of β position (R^3) on the aldehyde was crucial for the high *exo* selectivity, while good *ee*s were observed in most cases with or without α- or β-substitutions.

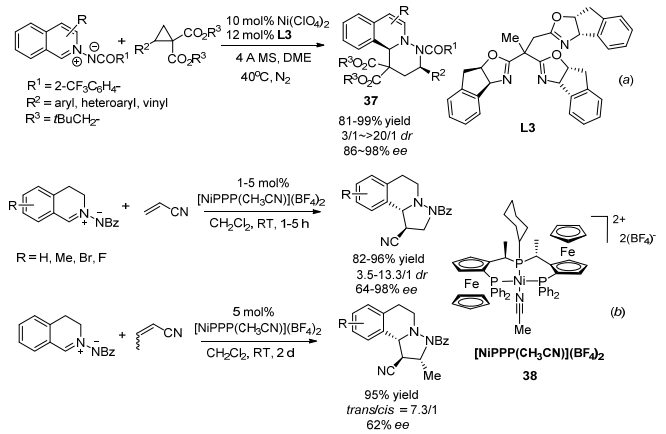


Scheme 13. Titanium Lewis acid catalyzed asymmetric 1,3-dipolar cycloaddition of C,N-cyclic methine imine with α,β-unsaturated aldehyde

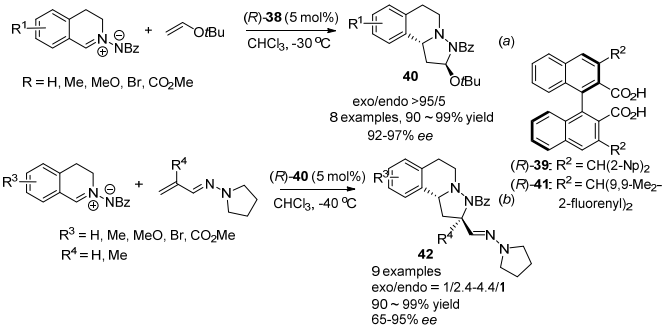
Since Maruoka's pioneering work, the 1,3-DC reaction of C,N-cyclic methine imines has received intensive study in the past a few years. Tang and coworkers realized a Ni^{II}/trioxazoline complex catalyzed highly enantioselective [3+3] cycloaddition of azomethine imine with activated cyclopropane (Scheme 14, *a*).[36] The reaction is tolerant of a variety of different substitutions on the cyclopropane and delivers a variety of six membered heterocycle fused DHIQ **37**. The reaction with R^2 being H was high yielding but completely racemic. DFT calculation indicated the existence of π−π stacking interaction between the indane side arm in the ligand **L3** and the phenyl group in the cyclopropane substrate, which is corroborated with experimental evidences. Another nickel based catalyst $Ni[(R,S_p)\text{-PigiPhos}][BF_4]_2$ **38** was recently applied by Togni to the normal electron demand dipolar cycloaddition between C,N-cyclic methine imines and unsaturated nitriles in 2013 (Scheme 14, *b*).[37] The reaction with acrylonitrile afforded products with high diastereoselectivities and essentially the same enantioselectivities with 1 mol% catalyst loading within 5 hours. The reaction of crotonitrile turned out to be much slower and went to completion in 2 days to afford the product at a moderate 62% *ee*. Mechanistic studies indicated that besides the unquestionable coordination of nitrile to the catalyst, interaction of azomethine imine with the catalyst was also nonnegligible.

Maruoka *et. al.* also realized inverse electron demand (IED) dipolar cycloaddition reaction of C,N-cyclic azomethine imine with electron rich *t*-butyl vinyl ether and vinylougous aza-enamines by activation of the 1,3-dipole, following their observation of facile protonation of such C,N-cyclic azomethine imines.[38] For the reaction with vinyl ether, high *exo* selectivities and enantioselectives were achieved with bisacid (*R*)-**39** (Scheme 15, *a*).After optimization, the reaction with acrolein derived vinylogous aza-enamines afforded the corresponding products **42** with moderate *exo*/*endo* selectivities but generally high *ee*s under the catalysis of bulkier catalyst (*R*)-**41** (Scheme 15, *b*). Notably, when R' = Me instead of H, *endo* isomer became the major product (*exo*/*endo* = 1/2.4) and lower enantioselectivity of the *exo* isomer (68% *ee*) was observed. These two types of remarkable cycloaddition reactions provide tricyclic THIQ compounds with three contingent stereogenic centers efficeiently in one step.

Proline derivatives have been well established in the asymmetric organocatalytic reaction of aldehyde/ketone with C,N-cyclic methine imines, as one of the strategies for nucleophile activation. Catalyst **5** was able to catalyze the three component dipolar cycloaddition featuring *in situ* generation of 1,3-dipole from α-haloketone with isoquinoline salt, as reported by Jørgensen and coworkers in 2012 (Scheme 16, *a*).[39] Substituted phenyl, 2-furyl, 2-napthyl substituted enal all reacted efficiently to afford the corresponding products with high *ee*s. With the same strategy, Wang and coworkers reported in 2014 two examples realizing the IED cycloaddition of C,N-cyclic methine imine with enamine[40] and dienamine[41] (Scheme 16, *c*)



Scheme 14. Nickel Lewis acid catalyzed 1,3-dipoolar cycloaddition of C,N-cyclic methine imines

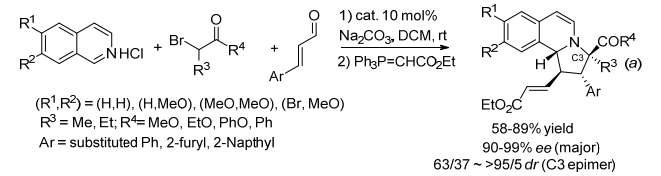


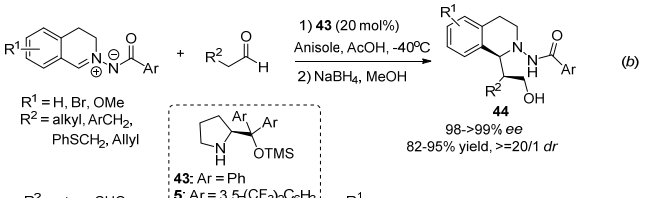
Scheme 15. Chiral Brønsted acid catalyzed asymmetric 1,3-dipolar cycloaddition reaction of C,N-cyclic methine imines

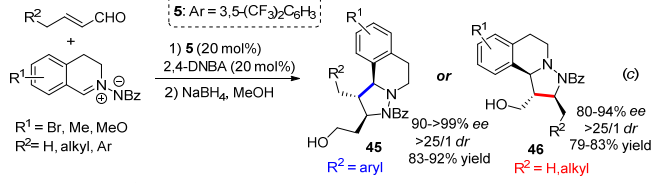
intermediates generated from aliphatic aldehydes and α,β-unsaturated aldehydes, respectively. The reaction of aldehydes proceeds *via* the formation of an enamine intermediate which undergoes inverse electron demand [3+2] cycloaddition (Scheme 16, *b*). For the latter, the initially formed iminium intermediate **A** between the aldehyde and proline silyl ether catalyst forms an equilibrium with the dienamine **B**. With R^2 being aromatic substituents, cycloaddition occurs at the C4−C5 double bond and forms final product **45** via intermediate **B**. For substrates with R^2 being hydrogen or alkyl groups the [3+2] cycloadducts occurred selectively at C3−C4 double bond of the aldehyde, affording **46** in high enantio- and diastereoselectivities. In this case the iminium ion **A** was speculated to play a key role in triggering the normal electron demand cycloaddition, leading to the C3−C4 addition product *via* the LUMO-lowering mechanism (Scheme 16, *d*).

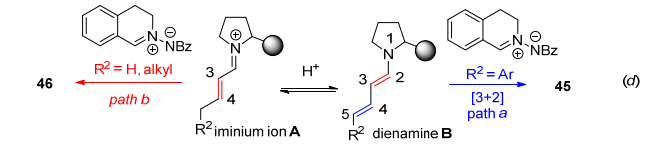
2.4 De novo construction of THIQ by asymmetric annulation

2.4.1 Asymmetric intramolecular allylic amination. The strategy of *de novo* construction of THIQ *via* intramolecular asymmetric allylic amination was realized by Ito, Katsuki *etc.* in 2003 under palladium catalysis, which showed moderate to good eantioselectivities in the C1-vinylated products (Scheme 17, *a*).[42] Use of (*R*)-BINAP **L5** as ligand instead of (*R*)-Phox ligand **L4** gave opposite sense of enantioselection a different solvent. A similar palladium catalyzed reaction by Ojima *et. al.* in 2007 used monodentate phosphoramidite ligands and obtained comparable enantioselectivities.[43] Feringa and coworkers developed the iridium catalyzed transformation in 2011 and achieved high enantioselection (Scheme 17, *b*).[44] Using this methodology the same group completed

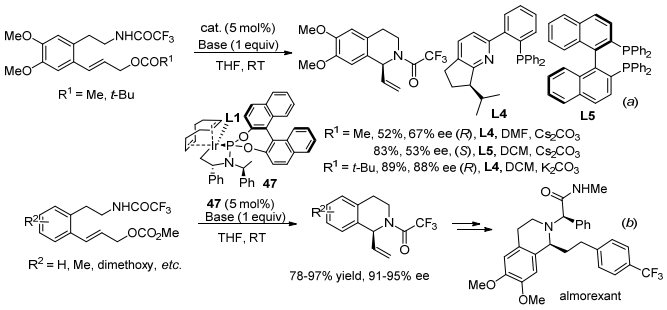








Scheme 16. Proline derivatives activated HOMO-raising and LUMO-lowering stratetigies in the 1,3-DC of C,N-cyclic methine imine



Scheme 17. Construction of C1-chiral THIQ *via* transition metal catalyzed asymmetric allylic amination

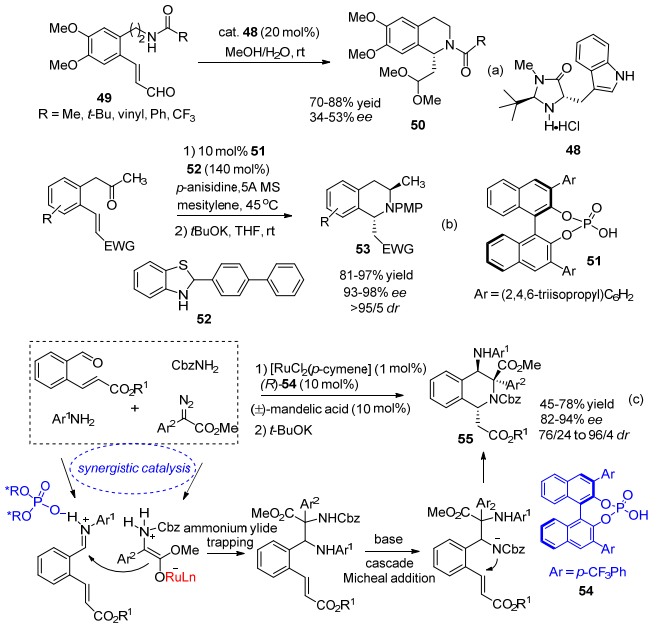
a straightforward four step total synthesis of natural product almorexant.[45]

2.4.2 Asymmetric intramolecular aza-Michael addition reaction. The asymmetric intramolecular aza-Michael addition reaction constitutes another important *de novo* synthetic approach toward construction of important nitrogen containing heterocycles, including C1-chiral THIQs. In 2003 Ihara *et.al.* reported the use of MacMillan catalyst **48** to trigger the aza-Michael reaction of substrate **49** affording the acetal product **50** in moderate enantioselectivities (Scheme 18, *a*).[46] This strategy, however, received more success in the synthesis of C3-chiral THIQs, wherein high enantioselectivities were achieved with Jørgenson-Hayashi prolinol silyl ether catalyst in 2008.[47]

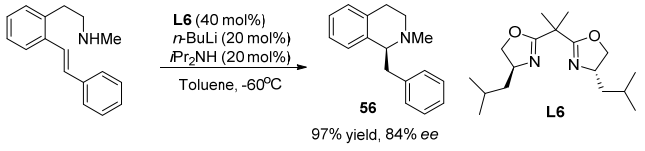
Alternatively, by preinstallation of the C3 stereochemistry, the stereochemistry of C1 in the aza-Micheal addition could be elegantly controlled in a diastereoselective manner. Enders and coworkers realized a chiral Brønsted acid catalyzed reductive amination/aza-Micheal addition sequence for the synthesis of 1,3-disubstituted THIQs in 2010.[48] The reductive amination afforded products with high conversion and selectivity using List's TRIP catalyst **51**. Upon

deprotonation, the 1,3-*trans*-substituted THIQ products **53** were obtained with high enantio- and diastereoselectivities (Scheme 18, *b*). More recently, in a cascade four-component ylide trapping/aza-Micheal addition reaction, 1,3,4-tetrasubstitued THIQs were produced with high enantio- and diastereoselectivities. The successful combination of ruthenium and chiral phosphoric acid catalysts **54** enabled synergistic interaction of the ruthenium associated ammonium ylide with the chiral phosphoric acid activated iminium intermediate, creating the key C3−C4 bond with concomitant formation of two stereogenic centers.[49] Subsequent treatment of base deprotonates the aniline N−H bond and triggers a diastereoselective Michael addition to afford the final product **55** (Scheme 18, *c*).

2.4.3 Asymmetric hydroamination. Due to their high reactivity, asymmetric reactions involving organolithium reagents usually proceed with stoichiometric amounts of chiral reagents. Nevertheless, intramolecular asymmetric addition of lithium amide to styrene was realized by Tomioka *et. al.* in a catalytic manner in 2007 (Scheme 19).[50] Under optimal conditions this reaction affords *N*-methyl C1-benzylated THIQ **56** in high enantioselectivity with



Scheme 18. Direct (*a*) and diastereoselectively controlled (*b*, *c*) aza-Michael addition reactions for asymmetric synthesis of C1-chiral THIQs



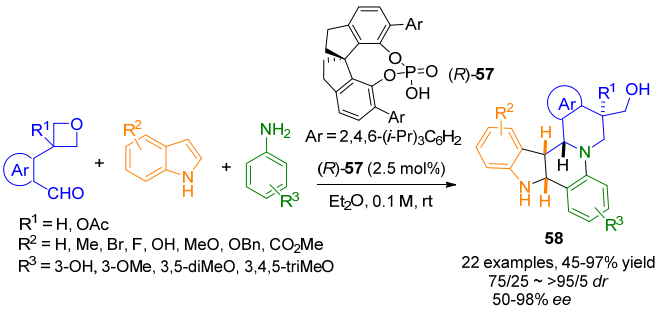
Scheme 19. Catalytic asymmetric hydroaminatioin with organolithium reagent.

substoichiometric amount of bisoxazoline ligand **L6**. However, no further substrate scope studies were provided.

2.4.4 Asymmetric hetero Diels-Alder reaction. A recent report by Sun and Zhu on the asymmetric three component aza-hetero Diels-Alder reaction between indole and *in situ* generated *N*-aryl imines represents a very efficient construction of polycyclic compounds **58** (Scheme 20).[51] In initial experiments aryl aldehydes *without* directing groups gave a mixture of various products. Intriguingly, with azetidine as directing group the reaction not only preceded with high efficiency but delivered the azetidine ring opened product **58** with perfect enantio- and diastereoselectivity when spirochiral phosphoric acid (*R*)-**57** was used as catalyst. This remarkable transformation forms four bonds and four stereogenic centers in one step and the product skeleton is found in a few natural products and bioactive moelcules. Selected compounds exhibited good antitumor effects against A549 and HeLa cell lines.

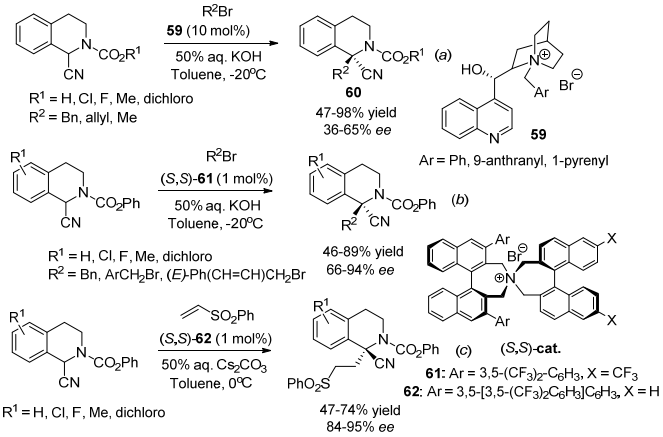
2.5 Miscellaneous reactions

2.5.1 Direct alkylation. Highly enantioselective catalytic processes for asymmetric synthesis of 1,1-disubstituted THIQs are much less documented compared to those for THIQs bearing tertiary C1 chiral centers. Direct asymmetric alkylation of C1-substituted THIQs provides a straightforward synthesis of these compounds. Rozwadowska *et. al.* documented the first example of phase transfer catalytic alkylation of C1-CN substituted THIQ (the Ressert compounds) in 2006.[52] Under the catalysis of chiral quaternary



Scheme 20. Asymmetric synthesis of THIQ-containing polycycles *via* three component aza-hetero Diels-Alder reaction

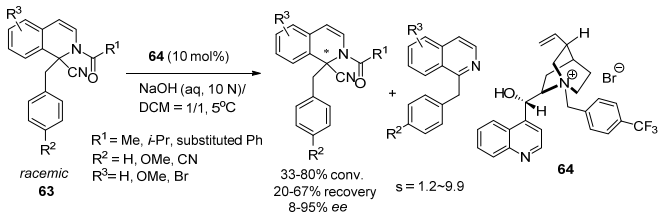
ammonium salts **59** derived from cinchona alkaloids, moderate enantioselection was achieved in the alkylation product **60** (Scheme 21, *a*). In 2011 Maruoka and coworkers achieved high enantioselection of this reaction and an analogous Michael addition reaction using chiral quaternary ammonium salt catalysts (*S*,*S*)-**61** (Scheme 21, *b* & *c*).[53] Notably, the Michael addition gave opposite sense of enantioselection with a bulkier catalyst (*S*,*S*)-**62**.



Scheme 21. Alkylation of Reissert compounds *via* asymmetric phase transfer catalysis

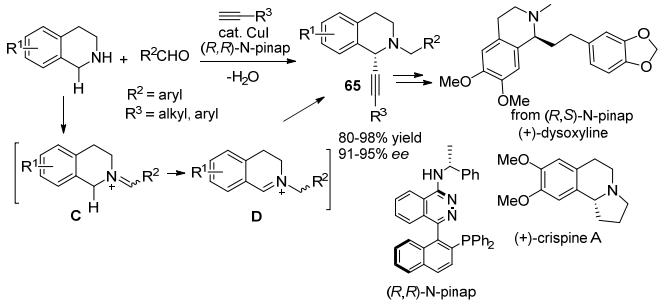
2.5.2 Asymmetric destruction. During their studies toward asymmetric alkylation of Reissert compounds, Jørgensen and coworkers observed the unexpected asymmetric decomposition of

Reissert compounds to 1-substituted isoquinoline, which was named "asymmetric destruction" (Scheme 22).[54] The reaction, a formal kinetic resolution of the hydrolysis of the starting 1,1-disubstituted THIQ **63**, was catalyzed by chiral quarternary ammonium salt **64** as phase-transfer catalyst and exhibited moderate enantioselectivities with selectivity factors ranging from 1.2~9.9.



Scheme 22. Phase transfer catalyzed "asymmetric destruction" of 1,1-disubstituted DHIQ compounds.

2.5.3 Others. Ma[55] and Yu[56] independently disclosed C1-alkynylation of THIQs *via* three component reaction of N-H THIQ, aldehyde and alkynes (Scheme 23). The product **65** was originally isolated as a side product in the corresponding A^3 reaction, according to Ma and coworkers. Addition of catalytic PPh_3 along with copper catalyst reversed the regioselectivity whereby **65** could be obtained as the major product, while Yu *et. al.* found this regioselectivity tuning could be realized by simply switching the catalyst from CuBr to CuI. With CuI/(*R*,*R*)-N-pinap catalytic system Ma *et.al.* were able to develop a catalytic asymmetric process which afforded optically enriched C1-alkynylated products with high enantioselectivities for both alkyl and aryl substituted alkynes. As a unique alternative strategy wherein the aldehyde serves as *N*-alkylating reagent and imminium precursor, this methodology was utilized by Ma and coworkers in the concise synthesis of natural products (+)-dysoxyline and (+)-crispine A very recently.[57]

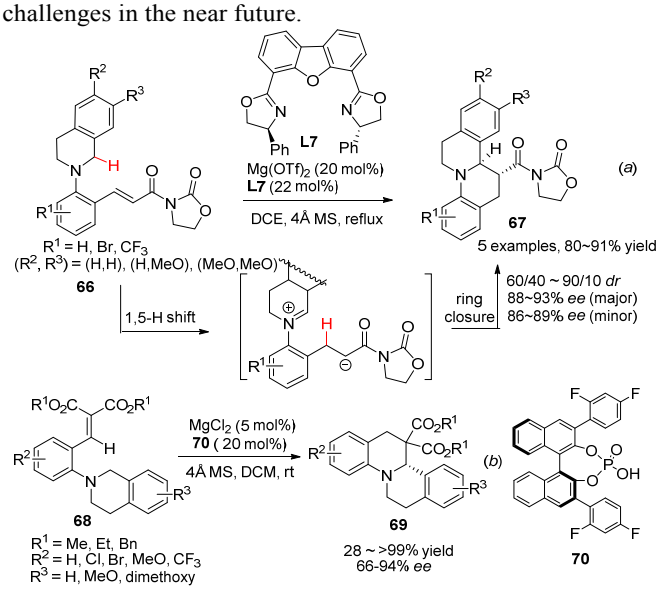


Scheme 23. Formation of *N*-alkylated iminium ion from N−H THIQ with aldehyde.

The redox neutrality feature of intramolecular redox reaction makes it an efficient greener alternative for the asymmetric construction of some nitrogen containing heterocycles.[20] Catalytic enantioselective variant of this reaction was realized by Siedel and coworkers in 2009.[58] The sequential 1,5-hydride transfer/Michael addition reaction of substrates **66** with a well-designed acyl oxazolidinone moiety as chelating acceptor group afforded the annulation products **67** with high enantioselection and moderate diastereoselection (Schem 24, *a*). The reaction is tolerant of electron rich aromatic ring containing substrates on THIQ moiety, but electron withdrawing substituents on *N*-aryl moiety (R^1) could be tolerated. A similar hydride transfer reaction was realized by Luo and coworkers with a "binary acid catalysis" strategy. One of the α-C−H bond of the tethered amine moiety in **68** undergoes 1,5-hydride shift and the annulation follows to deliver products **69** with high selectivities (Scheme 24, *b*).[59] Not surprisingly, dramatically compromised reactivity and enantioselection were observed when R^2 was methoxy group. DFT calculations indicated of a transition state involving coordination of phosphoric acid **70** to magnesium Lewis acid, creating a chiral environment favoring one of the two diastereotopic hydrogens to migrate.

3. Conclusion and perspective

The past ten years have witnessed great advances in the catalytic asymmetric synthesis of C1-chiral THIQs in the context of continuing development of organocatalysis and transiton-metal catalysis as well as the renaissance of photoredox catalysis. Novel asymmetric strategies were realized via distinct activation modes or annulation approaches. The rapidly developing non-stereoselective reactions also offer more platforms for the design of catalytic asymmetric variants. Despite of these exciting advances, formidable challenges remain unsolved, among which are highly efficient construction of enantioenriched C1-aryl THIQs and 1,1-disubstituted THIQs, whose highly enantioselective synthetic methods remain scarce despite of their prevalence in a good number of natural products. Moreover, examples to prepare enantioenriched THIQs with electron-deficient aryl moiety or electron-deficient heterocycles at the core THIQ scaffold are far less documented, although such analogues were found to exhibit higher bioactivities than the parent structure in some cases.[60] Nevertheless, the rapid development in this field continues to provide impetus for advancement in molecular medicine and asymmetric catalysis. It is our hope that this paper will attract attention from synthetic organic chemists toward the solvation of the above mentioned challenges in the near future.



Scheme 24. Construction of C1-chiral THIQ *via* Lewis acid promoted 1,5-hydride transfer/annulation process

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Notes and references

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