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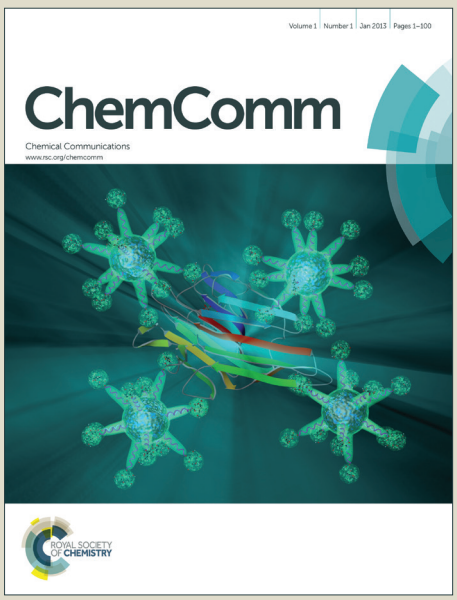

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FEATURE ARTICLE

Simple sulfur-olefins as new promising chiral ligands for asymmetric catalysis

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Since 2003, the discovery of chiral dienes as steering ligands in asymmetric process has opened the field of chiral chelating olefin catalysis. However, despite the impressive advances, the development of readily accessible and catalytically promising chiral olefins has been much less successful. In very recent years, chiral sulfur-containing olefins have emerged as a new exciting class of hybrid ligands for asymmetric catalysis. This article summarizes our efforts in developing extremely simple chiral sulfur-olefins as ligands for a variety of transition-metal-catalyzed asymmetric transformations, and the recent progress by other groups in the design and use of sulfinamide- or sulfoxide-based olefins in asymmetric catalysis.

1. Introduction

The use of olefins as ligands in organometallic chemistry has a long and continuing history,[1] starting in 1827,[2] when the first platinum-ethylene complex Zeise's salt ($K[PtCl_3(C_2H_4)]$) was discovered. During the last century, in addition to many coordination studies, olefin complexes involving late-transition metals such as Rh, Ir, Pt, Pd or Ni are mostly employed as catalyst precursors in catalysis.[3] Because of the relatively weak metal-olefin coordination bonding, metal-bound olefins often exhibit low stabilities and dissociate in the course of catalytic cycles. For this reason, the corresponding preparation of chiral olefin-metal complexes as catalysts for enantioselective asymmetric transformations did not gain much attention until the early 2000's. A breakthrough was the discoveries by Hayashi[4] and Carreira[5] in 2003-2004 that chiral bicyclo[2.2.1]heptadiene and bicyclo[2.2.2]octadiene were very efficient ligands to give excellent results in Rh-catalyzed asymmetric conjugate addition of boronic acids to enones and Ir-catalyzed kinetic resolution of allylic carbonates, respectively, thereby opening up an important and exciting new research area in asymmetric catalysis.

In the past ten years, design and use of chiral chelating olefins as steering ligands in asymmetric catalysis have become an active and vibrant area, there has been considerable progress particularly in the development of chiral bicyclic dienes and the application of their metal complexes.[6] In these studies, it is often observed that chiral dienes only with the proper molecular geometry are superior ligands in terms of both catalytic activity and enantioselectivity. In other words, despite excellent performance shown in asymmetric catalysis, efficient and expedient access to various dienes bearing a specially rigid chiral backbone is relatively difficult, many of them requiring complex multi-step syntheses or HPLC resolution by expensive preparative chiral columns. On the other hand, the development of pnictogen-based olefin ligands such as chiral phosphane-olefins or amine-olefins has proved another new promising class of ligands[6c,f] since the pioneering work of Grützmacher.[7] Notably, compared to chiral dienes, the combination of olefin with phosphorus or nitrogen in a single ligand framework largely improved the coordination ability to transition-metals. Considering the ligand architectures, however, like most chiral

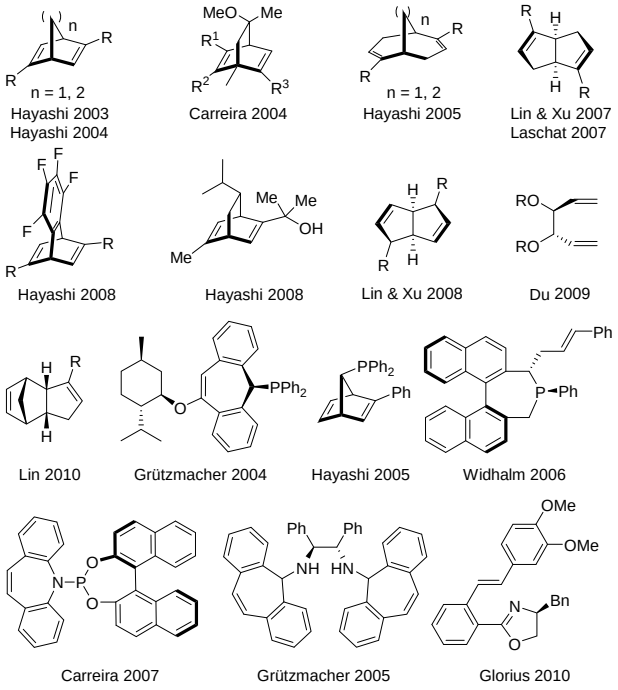


Fig. 1 Some representative chiral diene and P/N-olefin ligands.

dienes, they also generally possess a complicated scaffold having carbon chirality, which in many cases is again not synthetically easily accessible. Figure 1 gives a profile of several representative chiral dienes[4,5,8] and P/N-olefins[7,9] reported in the literatures.

2. Development of sulfur-based simple olefins as new chiral ligands

Inspired by the initial work of chiral dienes,[4,5] we became interested in the discovery of new chiral olefin ligands with simpler chemical architecture that are more easily accessible. Since 2007, we have documented the design and synthesis of a new type of C_2-symmetric chiral diene ligands bearing a simple bicyclic [3.3.0] backbone and their successful applications in asymmetric catalysis.[6e,8c,8g,10] In addition, our group have been involved in the chemistry of *N*-*tert*-butanesulfinyl imines[11] for asymmetric synthesis of various important chiral amines.[12] During the studies, it was found that the *N*-sulfinyl group often serves as a nice chiral directing group in the reaction. In considering the good coordination ability of sulfur as well as the success of using chiral sulfur ligands[13] in asymmetric catalysis, we became intrigued by the possibility of combining olefin and *N*-*tert*-butanesulfinamide elements into one ligand molecule to design an unprecedented type of sulfur-olefin hybrid class ligand. Compared to the known chiral dienes and pnictogen-based olefin ligands with the chirality being installed in the carbon backbone, it is reasoned that structurally proper sulfur-olefins, upon coordination to transition-metals, might also be able to form stable complexes, thereby allowing them to function as new efficient chiral ligands, in which the reaction stereocontrol through neighbouring stereogenic sulfur might be expected (Figure 2).

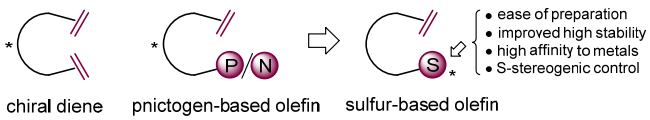


Fig. 2 Chiral chelating olefin ligand design.

Following these design considerations and with the structure profile in mind, we then found that easily accessed *N*-sulfinyl homoallylic amines **2** (R^2 = H or OBz)[12d,14] could indeed act as a good candidate of sulfur-based olefin class ligand in rhodium-catalyzed asymmetric 1,4-Addition of arylboronic acids to α,β-unsaturated cyclic carbonyl compounds. Further investigations with this S-olefin idea led us to the discovery that extremely simple thus readily available *N*-cinnamyl sulfinamide **4** could exert both excellent catalytic activity and enantioselectivity in these asymmetric arylation reactions.[15] Moreover, our studies revealed that chiral sulfoxide-olefins **3** can also be useful ligand in catalysis.[16]

Concurrent with our studies of the sulfur-based olefin catalysis, other research groups of Knochel,[17] Du,[18] Liao[19] and Wan[20] also conducted studies of rhodium-catalyzed asymmetric 1,4-addition using conceptually similar ligand (**1**, **5-8**) system. Within the last three years, a series of chiral sulfur-containing olefins has been successfully developed. Figure 3 summarizes the representative chiral sulfur-olefin ligands (SOLs). These studies clearly indicate that chiral sulfur-olefins have emerged as a significantly new and interesting class of ligands. This feature article describes the recent progress on exploring sulfur-containing hybrid olefins for enantioselective catalytic processes, with a focus on the development of simple but promising sulfinamide-olefin ligands.

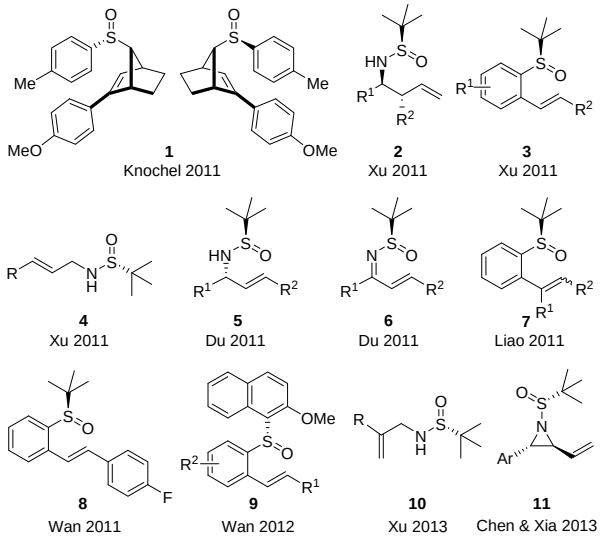


Fig. 3 Representative chiral sulfur-olefin ligands (SOLs).

3. Application of chiral sulfur-olefin ligands in asymmetric catalysis

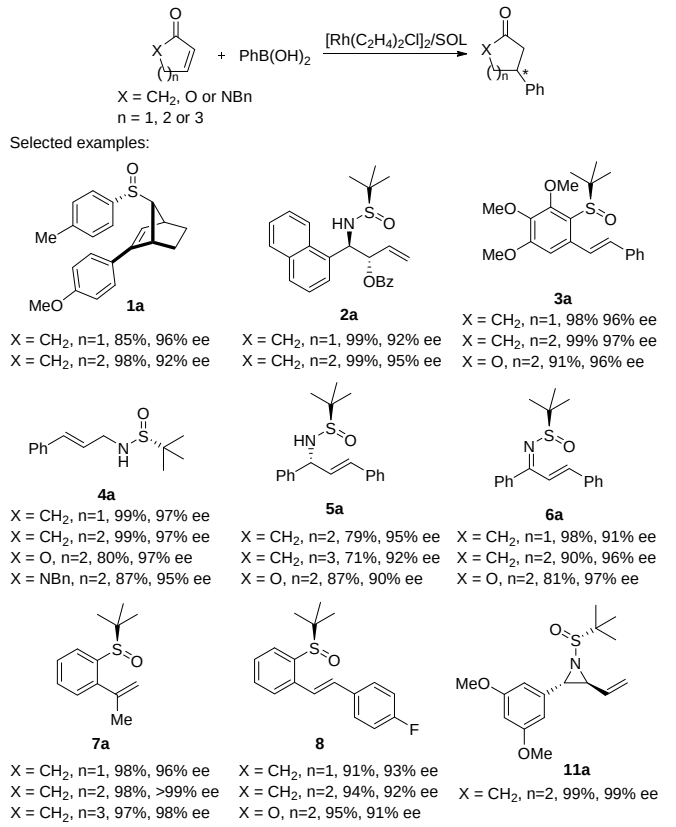
3.1 1,4-Addition of arylboronic acids to α,β-unsaturated carbonyl compounds.

Asymmetric conjugate addition of organoboronic acids to electron deficient olefins has been established as one of the most powerful and convenient tools for enantioselective synthesis of β-substituted functionalized compounds.[21] Over the past few years, a diverse range of chiral ligands has been developed. The first successful application of chiral sulfur-olefins as steering ligands for asymmetric catalysis was rhodium-catalyzed conjugate addition of arylboronic acids to α,β-unsaturated carbonyl compounds.[14-20,22-27]

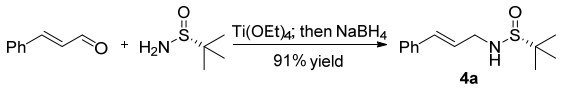
In 2011, we discovered that simple and readily available chiral sulfinamide- or sulfoxide-olefins can display great catalytic activities and enantioselectivities in rhodium-catalyzed asymmetric 1,4-addition reactions. In the meantime, other research groups of Knochel,[17] Du,[18] Liao[19] and Wan[20] also found that structurally appropriate sulfur-containing olefins (**1**, **5-8**) are capable of rhodium catalysis for 1,4-addition. For example, by using easily accessible chiral sulfur-olefins as ligands (**1a-7a**, **8** and **11a**), a variety of α,β-unsaturated cyclic carbonyl compounds could be subjected to the reactions smoothly with various arylboronic acids under mild conditions,

and gave the desired products in high yields with excellent enantioselectivities (Scheme 1).[14-20,22-26]

It is particularly worthy of note that extremely simple *N*-cinnamyl sulfinamide **4a** exhibited excellent catalytic activity and enantioselectivity, leading to addition products uniformly in high yield and stereoselection (94-98% ee).[15] The ligand only incorporates a single chiral center at the sulfur on a sulfinamide moiety, which could be very easily synthesized by a one-pot operation from commercially available cinnamaldehyde and chiral *N*-*tert*-butanesulfinamide (Scheme 2).



Scheme 1 Rh/SOL-catalyzed asymmetric 1,4-addition of phenylboronic acid to α,β-unsaturated cyclic carbonyl compounds.



Scheme 2. Synthesis of SOL**4a**.

The observed selectivity for 1,4-addition was rationalized by a preferred transition state model, involving a specific geometry in which the aryl substituent is positioned *trans* to the olefin ligand and the *tert*-butyl moiety is staggered. *si*-Face-selective coordination of 2-cyclohexenone with rhodium give favourably the (*S*)-configuration product (Figure 4).

Interestingly, with sulfoxide-olefin ligands **7a-d** bearing double bond geometry or substitution difference, a reversal of enantioselectivity (up to 99% ee for (*R*)-product and 98% ee for (*S*)-product) was observed by Liao and co-workers (Scheme 3).[19,23] The result was presumably attributed to the steric repulsion between substituent group attached to the double bond of ligand and the carbonyl moiety of the enone in the transition state.

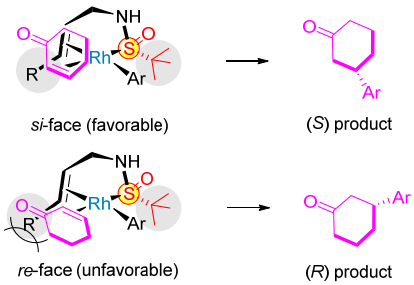
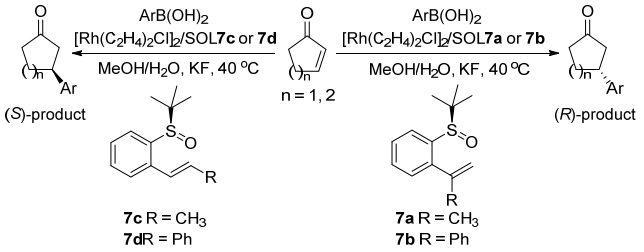


Fig.4 Proposed reaction transition state model.



Scheme 3 Rh/SOL-catalyzed asymmetric 1,4-addition to α,β-unsaturated ketones.

To investigate the formation of Rh/SOL complex, we carried out NMR spectroscopy study by treatment of *N*-cinnamyl sulfinamide ligand **4a** with $[RhCl(C_2H_4)_2]_2$ (0.5 equiv) in $CDCl_3$ at room temperature.[15] In both ^1H and ^{13}C NMR spectra, large chemical shifts of olefin protons/carbons and tetrasubstituted *tert*-butyl protons/carbon were observed due to the formation of dimeric rhodium complex, which suggests coordination of rhodium to both olefin and sulfinyl sulfur had taken place. In the meantime, X-ray structure studies by Du[18] and Liao[19] research groups also indicated that the transition metal Rh is bound to the sulfur atom as well as to the olefinic bond (Figure 5). These studies also clearly indicate that sulfur-olefins can form stable complexes with metal rhodium. Thus, unprecedented chiral sulfur–olefins have proved as a new class of ligands for asymmetric synthesis.

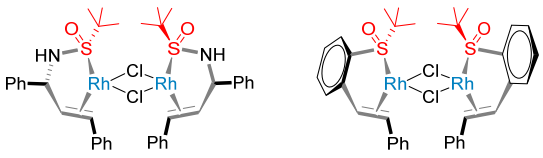
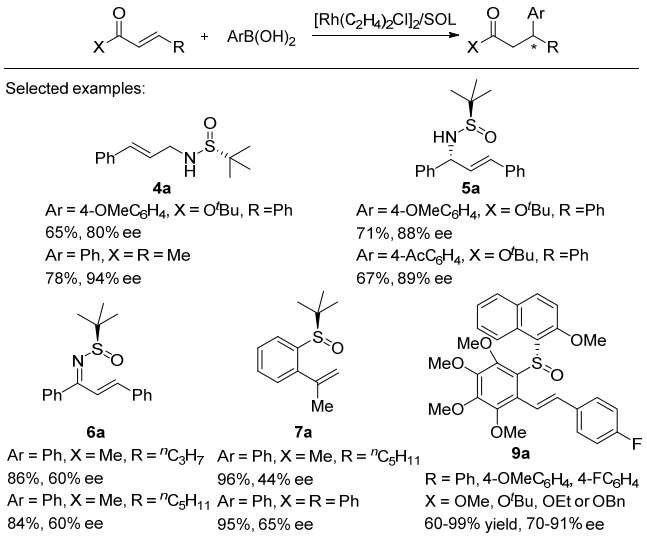


Fig.5 Structure of Rh/SOL complex.

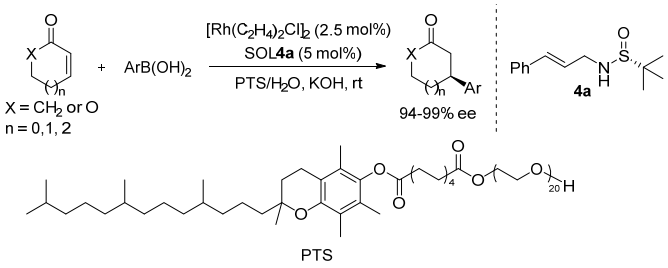
The same catalytic system was further applied to more challenging α,β-unsaturated acyclic enones.[15,18-19,22,24,27] Compared to cyclic substrates, lower yields and enantioselectivities were generally obtained. Notably, in the case of (*E*)-pent-3-en-2-one, the best result of 94% ee was

observed in the presence of chiral *N*-cinnamyl sulfinamide ligand **4a**.[24] The poor enantioselectivity may be attributed to the competitive binding between the acyclic enones and sulfur-olefin ligand toward the rhodium metal center (Scheme 4).



Scheme 4 Rh/SOL-catalyzed asymmetric 1,4-addition to α,β-unsaturated acyclic enones.

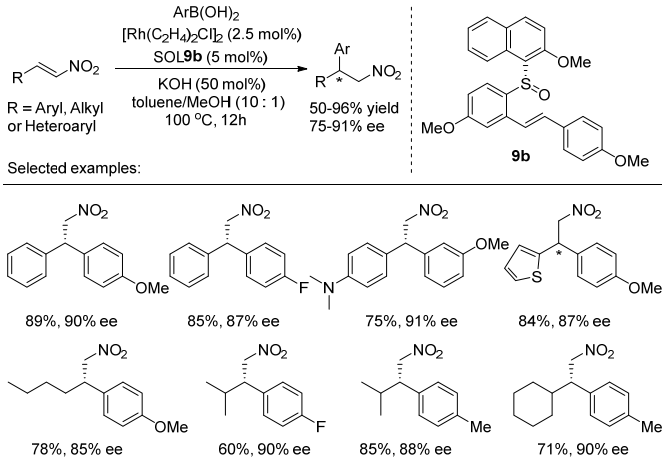
Extension of the chiral Rh/**4a** catalyst (5 mol%) in aqueous media was also achieved successfully by Khiar, Fernández and coworkers to provide the corresponding products in very high yield (up to 100%) and stereocontrol (up to 99% ee) (Scheme 5).[25]



Scheme 5 Rh/SOL**4a**-catalyzed asymmetric 1, 4-addition in aqueous media.

3.2 1,4-Addition of arylboronic acids to nitroalkenes

Despite much progress has been made in the addition to α,β-unsaturated carbonyl compounds, far fewer studies reported the efficient asymmetric addition of organoboronic acids to nitroalkenes that lack α-substitutents due to the difficulty in the control of reaction stereoselectivity. We previously demonstrated that chiral bicyclo[3.3.0] dienes were superior ligands and achieved the first highly enantioselective addition of rhodium-catalyzed arylboronic acids to α-unsubstituted nitroalkenes.[10b] Other type of chiral ligands that capable of effective catalysis in this transformation is very rare, only recently have sulfoxide−phosphine ligand been developed.[28] In 2012, Wan and co-workers reported that chiral sulfoxide-olefin ligands can also be utilized in rhodium-catalyzed asymmetric addition of organoboron compounds to nitroalkenes.[29] Among them, 2-methoxy-1-naphthyl sulfoxide-olefin ligand **9b** was found to exhibit high enantioselectivity in this transformation. Under the optimized conditions, a range of arylboronic acids reacted with aromatic nitroalkenes and furnished the corresponding addition products in moderate to high yields (50−96%) with relatively good enantioselectivites (82-91% ee). Additionally, Rh/SOL**9b** can effectively catalyze the reaction with challenging aliphatic nitroalkenes to give the product with equally high enantioselectivity (85-90% ee) (Scheme 6).



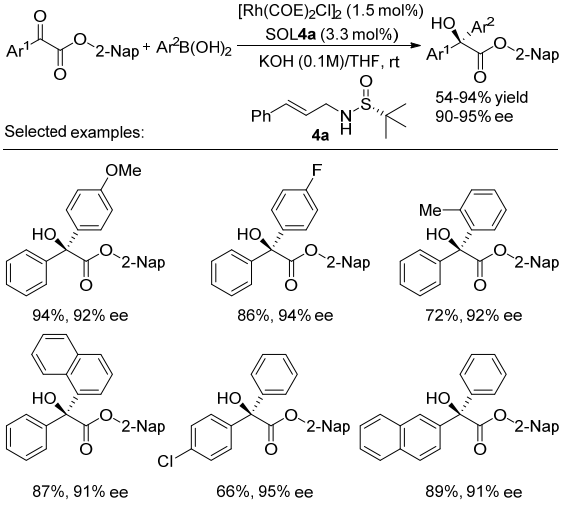
Scheme 6 Rh/SOL**9b**-catalyzed asymmetric 1,4-addition to nitroalkenes.

3.3 1,2-Addition of arylboronic acids to α-ketoesters and α-diketones.

Rh-catalyzed asymmetric 1,2-addition of arylboronic acids to carbon-oxygen double bonds is a highly desired transformation for straightforward synthesis of enantioenriched alcohols. In 2008, Zhou reported the first asymmetric addition of arylboronic acids to α-ketoesters under rhodium catalysis.[30] Chiral spirophosphites were found to be effective ligands, however, enantioselectivities were unsatisfactory for addition to aryl α-ketoesters (mostly 70-88% ee).

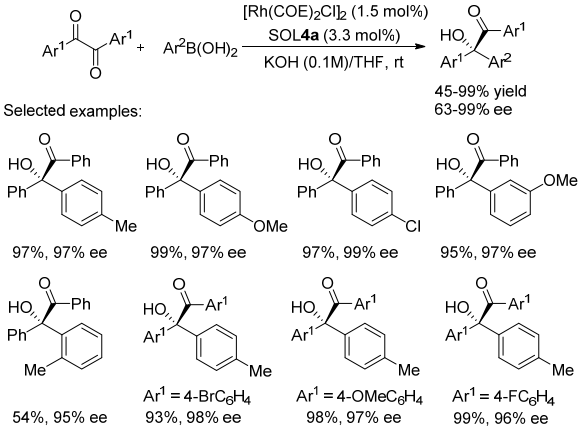
Encouraged by the early success on 1,4-addition using sulfur-olefins, we became interested in such a transformation in 2011 immediately after we discovered that simple sulfur-olefins could serve as unique chiral ligands. Fortunately, carefully screening studies led us to the discovery that chiral *N*-cinnamyl sulfinamide **4a** was able to catalyze the reaction of arylboronic acids to aryl α-ketoesters with good enantioselection.[31] The use of other olefin ligand such as chiral bicyclo[3.3.0] diene leads to very low enantioselectivity (9% ee). Under the optimized conditions, a range of aryl α-ketoesters underwent successful arylation at room temperature to furnish the corresponding tertiary α-hydroxyesters in moderate to high yields (54-94%) with excellent enantioselectivites (90-95% ee). Notably, it was found that the electronic and steric properties of the aromatic ring of either the α-ketoesters or arylboronic acids exhibit apparently little influence on the addition reaction. Both

sterically encumbered 2-naphthyl 2-naphthylglyoxylate substrate and arylboronic acid reagents, such as *ortho*-substituted aryl boronic acids or 1-naphthylboronic acid, could be successfully employed to give the desired adducts with high level of enantioselectivity (90-94% ee) (Scheme 7).



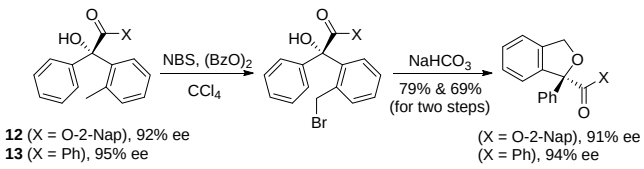
Scheme 7 Rh/SOL**4a**-catalyzed asymmetric 1,2-addition to aryl α-ketoesters.

Other than using aryl α-ketoesters, we also found that more interesting α-diketones could be suitable substrates. The use of same catalytic system allowed the highly enantioselective 1,2-addition of arylboronic acids to proceed smoothly, affording a series of tertiary α-hydroxyketone derivatives in very high yields and enantioselectivities (54-99%, 95-99% ee) (Scheme 8). Similarly, the 1,2-addition reaction of α-diketones seems insensitive to the steric effects of arylboronic acids. It is worth noting that this is the first successful example of catalytic asymmetric arylation of α-diketones.



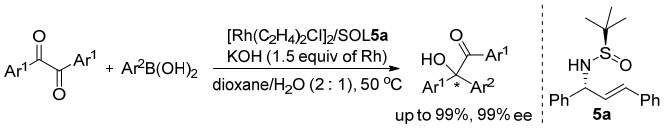
Scheme 8 Rh/SOL**4a**-catalyzed asymmetric 1,2-addition to α-diketone.

Remarkably, as depicted in Scheme 9, the resulting 1,2-addition products such as **12** and **13** can be utilized as key intermediates to easily construct fully-substituted-carbon-containing, chiral 1,3-dihydroisobenzofuran (phthalan) framework, which is key unit of numerous pharmacologically valuable compounds, as exemplified by the antidepressant drug citalopram.[32]

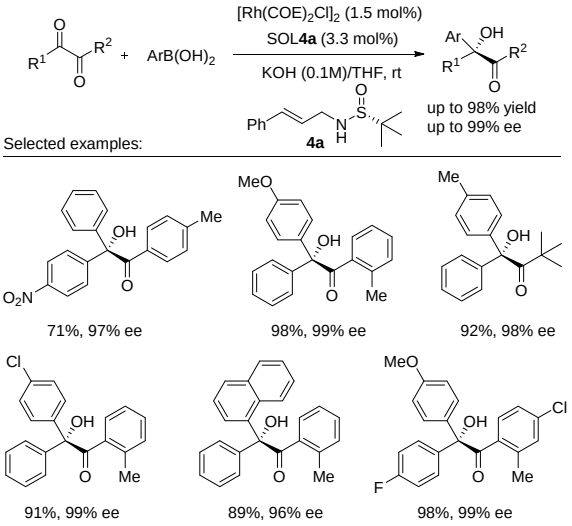


Scheme 9 Synthesis of chiral 1,3-dihydroisobenzofuran derivatives.

Soon after our publication, Du and co-workers also reported the asymmetric 1,2-addition of arylboronic acids to symmetrical aryl α-diketones using another chiral sulfinamide-olefins ligand **5a** in aqueous KOH/dioxane at 50 °C.[33] In some cases, it was found the reactions can proceed smoothly in the presence of 0.05 mol% of $[Rh(C_2H_4)_2Cl]_2$, giving the optically active tertiary α-hydroxyketone products in high yield with up to 99% ee (Scheme 10). As also revealed by us,[34] cyclic α-diketones with two carbonyl *cis*-positioned such as phenanthrene-9,10-dione were not suitable substrates for such rhodium catalysis.[33] With isatin as substrate, a moderate enantioselectivity (76% ee) was observed.



Scheme 10 Rh/SOL**5a**-catalyzed asymmetric 1,2-addition to symmetrical aryl α-diketone.

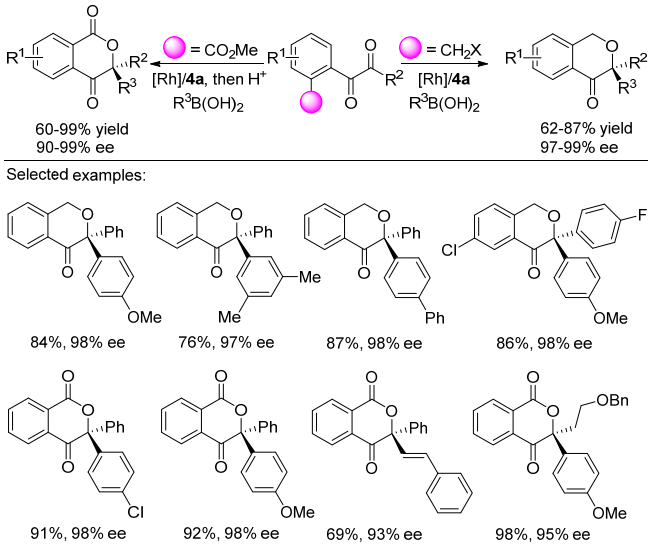


Scheme 11 Rh/SOL**4a**-catalyzed asymmetric 1,2-addition to unsymmetrical α-diketones.

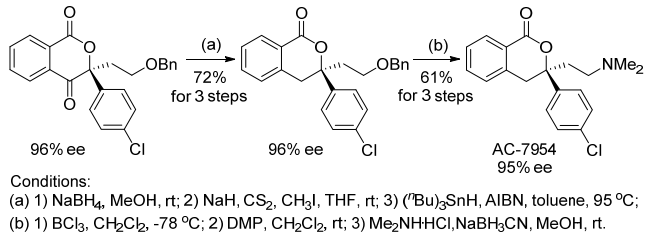
In parallel with our studies of the enantioselective addition of symmetrical α-diketones, we started to explore the catalytic ability of chiral sulfur-olefin ligand **4** in asymmetric addition to unsymmetrical α-diketones. The development of an efficient and highly regioselective as well as enantioselective addition

represents a demanding subject. Thus we consider that the potential of a highly regio- and enantioselective 1,2-addition could be only expected when unsymmetrical α-diketones that have large differences in the steric and electronic properties of each ketone moiety are employed. In general, a regioselectivity favoring addition to the less hindered or more electron deficient carbonyl group should be observed. In order to investigate these considerations, a variety of unsymmetrical benzil derivatives with large electronic or sterically hindered differences between the two carbonyl groups were synthesized and employed in Rh/**4a**-catalyzed 1,2-addition reaction. As revealed in Scheme 11, in all cases, the reactions proceeded very well and gave exclusive adducts in high yields with excellent regio- and enantioselectivities.[35]

Subsequently, by designing α-diketone substrates with a bromomethyl, chloromethyl or ester substituent (COOMe) at the *ortho* position of one ketone phenyl ring, the rhodium-catalyzed highly regio- and enantioselective 1,2-addition of arylboronic acids using an extremely simple chiral *N*-sulfinyl cinnamylamine ligand **4a** was utilized for the tandem one-pot synthesis of optically active 3-tetrasubstituted isochroman derivatives in high yields with excellent ees (Scheme 12). Isochromans can be found in a wide range of naturally occurring products and biologically active compounds; they are usually difficult to access through asymmetric catalysis.

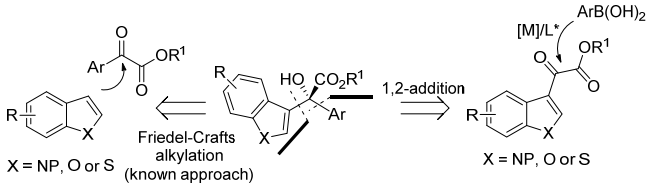


Scheme 12 One-pot synthesis of optically active 3-tetrasubstituted isochroman derivatives.

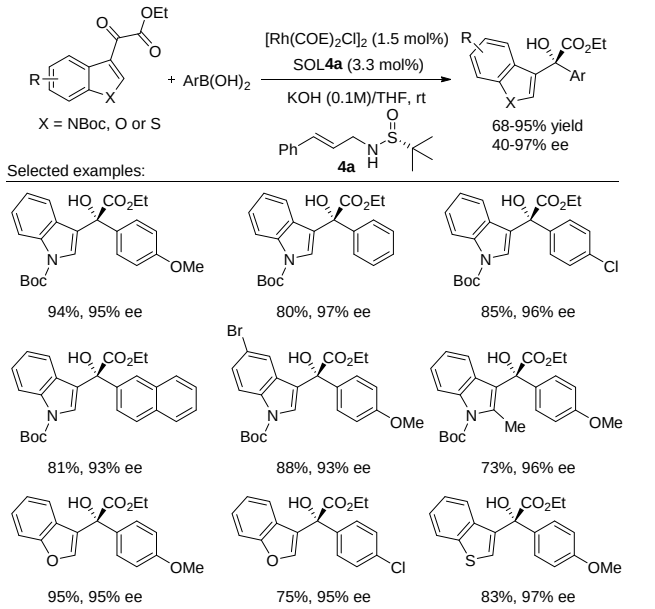


Scheme 13 The asymmetric synthesis of AC-7954.

It is noteworthy that the potential synthetic value of the above methodology was demonstrated in the application of AC-7954[36] synthesis. By taking advantage of the Rh/**4a**-catalyzed asymmetric cascade arylation/cyclization, the first asymmetric synthesis of the non-peptide urotensin II receptor agonist AC-7954 was successfully achieved (Scheme 13).[35] Thus, a greatly valuable enantioselective approach to the generation of a wide range of isochroman-based urotensin-II agonists was developed.



Scheme 14 Synthetic strategies to heteroaryl α-hydroxy esters.



Scheme 15 Rh/SOL**4a**-catalyzed asymmetric 1,2-addition to heteroaryl α-ketoesters.

For the preparation of optically active heteroaromatic α-hydroxy carbonyl compounds, asymmetric Friedel-Crafts alkylation reaction has been known as a powerful tool, however, a drawback of this approach is that feasibility of the reaction and selectivity of the product highly depend on the electronic nature of the substrates (Scheme 14). To circumvent this problem, we developed the first example of direct 1,2-addition approach.[37] When 3 mol% of Rh/SOL**4a** complex was used as a catalyst, the reaction proceeded efficiently without dependence on the electronic nature of the substrates, and afforded the corresponding products in high yield with up to 97% ee under mild conditions. It is noted that sterically encumbered α-ketoester with a methyl substituent at the 2-position of indole pyrrole ring, 3-benzofuranglyoxylates as well as 3-benzothiopheneglyoxylates are also effective reaction

substrates, giving adducts with equally excellent enantioselectivities (95-97% ee) (Scheme 15).

Given our success with highly enantioselective carbonyl addition using chiral sulfinamide-olefin ligands, we became intrigued by the possibility of achieving asymmetric 1,2-addition of sterically very hindered aryl α-ketoesters containing an *ortho*-functionality to generate optically active α-aryl-α-hydroxy ester intermediates, which could undergo further intramolecular cyclization to generate various valuable chiral heterocycles such as tetrasubstituted 3-hydroxyoxindoles, 1,3-dihydroisobenzofurans and 3-isochromanones (Figure 6).

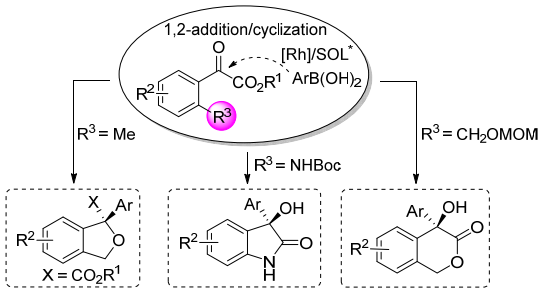
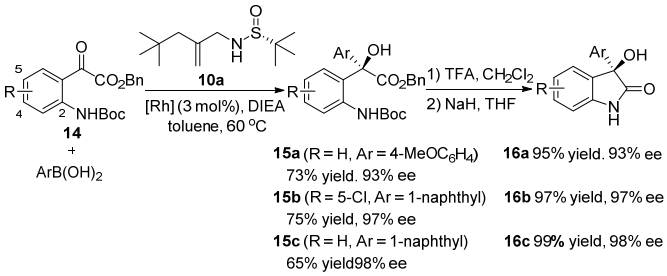


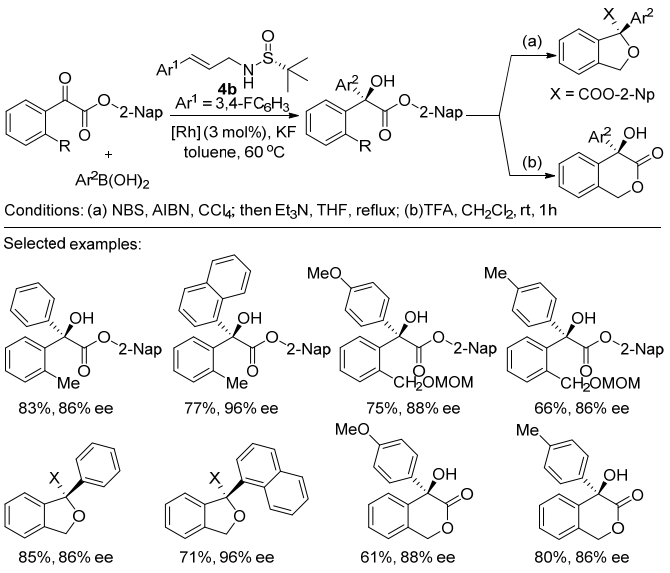
Fig.6 1,2-Addition/cyclization of *ortho*-substituted aryl α-ketoesters.

To this end, we investigated the catalytic properties of a range of chiral sulfur-olefins in the reaction of *ortho*-NHBoc-substituted methyl phenylglyoxylate **14** with *p*-anisylboronic acid. As expected, branched sulfinamide-olefin **10a** afforded product with highest enantioselectivity (84% ee). Attempts to improve enantioselectivity revealed that a combination of *N*-Boc protected amino and benzyl ester in DIEA/toluene was optimal. Under those conditions, the reactions proceeded smoothly to generate the desired adducts in good yields with high levels of stereocontrol (87%-98% ee). Notably, when sterically congested 1-naphthylboronic acid was employed, we observed all extremely high enantioselectivities (97%-98% ee). A subsequent synthetic transformation provided efficient access to pharmaceutically interesting 3-aryl-3-hydroxyoxindole derivatives (Scheme 16).[38]

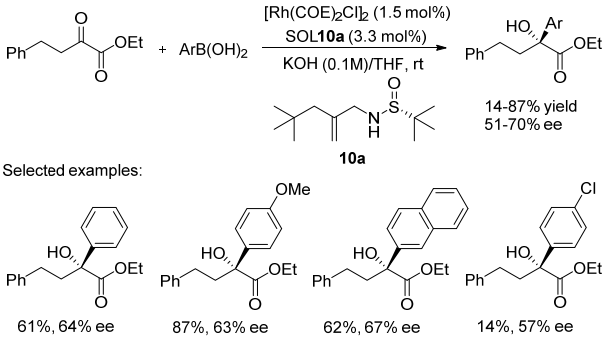


Scheme 16 Rh/SOL**10a**-catalyzed asymmeric 1,2-addition/cyclization.

With the same strategy, we next turned to 1,2-addition reaction of other aryl α-ketoester substrates. Surprisingly, the previously optimal ligand **10a** displayed very low catalytic activity under standard conditions. Further improvements in enantioselectivity were achieved by switching to the linear sulfinamide-olefin ligand **4b** and changing DIEA to KF (Scheme 17). Accordingly, the facile construction of otherwise-difficult-to-access chiral tetrasubstituted-carbon-containing 1,3-dihydroisobenzofurans and 3-isochromanones was readily accomplished.



Scheme17 Rh/SOL**4b**-catalyzed asymmeric 1,2-addition/cyclization.

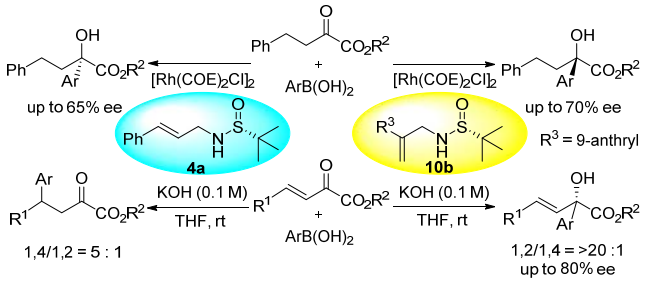


Scheme 18 Rh/SOL**10a**-catalyzed asymmetric 1,2-addition to aliphatic α-ketoesters.

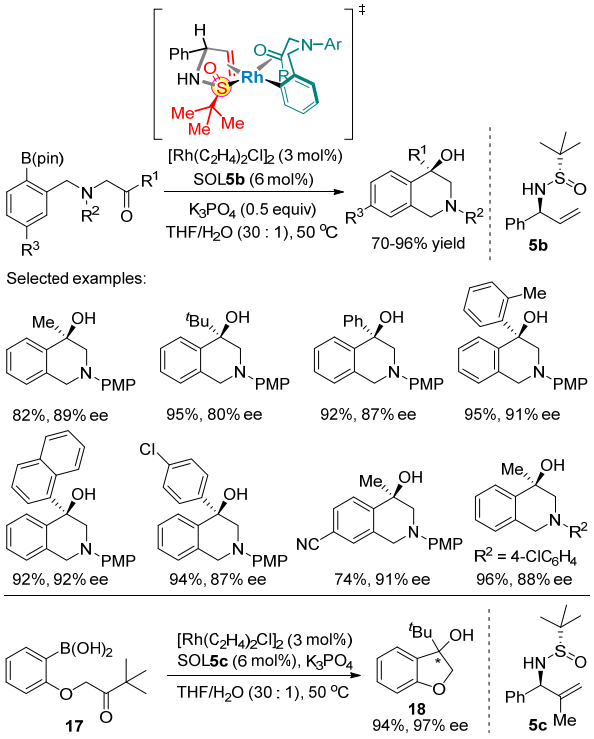
The superior catalytic properties demonstrated by chiral sulfinamide-olefin ligands in the above-mentioned enantioselective arylation prompted us to examine their performance in the rhodium-catalyzed asymmetric addition of arylboronic acids to more challenging α-H-containing aliphatic α-ketoesters. Unlike aryl α-ketoesters, aliphatic α-ketoesters with the existence of α-H can form enolate esters upon deprotonation under basic reaction conditions. For this reason, the undesired self-Aldol condensation could be competitive and the expected chelation control for 1,2-addition might be problematic. After careful experiments, we recently found that the reaction of arylboronic acids to ethyl 2-oxo-4-phenylbutanoate can be carried out using branched sulfinamide-olefin **10a** as ligand, giving the desired chiral tertiary α-hydroxy esters in moderate to good yields (57-87%) and enantioselectivities (51-70% ee). Nevertheless, those with

electron-withdrawing groups were exceptions with poor yield of the addition reaction (14-34%) (Scheme 18).

Interestingly, a reversal of stereocontrol was observed through changing the position of substituent (branched and linear) on the ligand olefin moiety. When methyl styrylglyoxylate was employed as substrate, the screening of catalysts also illustrated the dramatic influence of the structure of the ligand on the reaction regioselectivity. It was found that a simple variation from linear to branched sulfinamide-olefin ligands could switch the regioselectivity from 1,4- to 1,2-addition (Scheme 19).[39] Unfortunately, the reaction stereocontrol is still far from satisfactory at this stage.



Scheme 19 Rh/SOL-catalyzed asymmetric 1,2/1,4-addition to α-ketoesters.

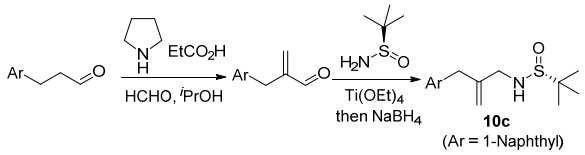


Scheme 20 Rh/SOL-catalyzed intramolecular asymmetric 1,2-addition.

Very recently, the efficacy of chiral sulfur-olefin ligand is also demonstrated by Lam and co-workers in Rh-catalyzed intramolecular 1,2-addition of arylboron onto less reactive ketones.[40] In an initial investigation, cyclization of arylpinacolboronic ester tethered methyl ketone substrate was conducted to evaluate the effect of different chiral ligands including bisphosphines (such as BINAP and SEGPHOS), chiral dienes, TADDOL-derived phosphoramidite and sulfinamide-olefin in the presence of 5 or 10 mol% of rhodium. Although the reaction proceeds smoothly in all cases, sulfinamide-olefin ligand **5b** turns out to be the best, giving 84% ee. These results, again, suggest the unique chiral environment of sulfur-olefin ligand in asymmetric catalysis. Ligand **5b** was applied successfully in the cyclization reaction of a range of alkyl as well as aryl ketones to provide various five-, and six-membered aza-, oxa-, and carbocycles with selectivities of up to 92% ee (Scheme 20). Interestingly, when substrate **17** containing an phenylboronic acid tethered to a *tert*-butyl ketone via an oxygen linkage was examined, a new isopropenyl-substituted sulfinamide ligand **5c** gave dihydrobenzofuranol **18** in best 94% yield and 97% ee (Scheme 20).

3.4 1,2-Addition of arylboronic acids to imines.

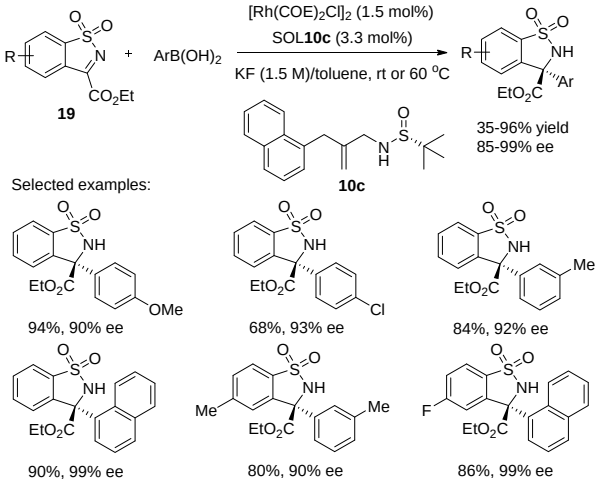
Inspired by the success of enantioselective addition of arylboron reagents to C=C and C=O double bonds using simple chiral sulfur-olefin ligands, we became interested in their application in the asymmetric 1,2-addition to C=N double bonds to construct pharmacologically attractive chiral amines. Sultams and sulfamidates are cyclic amines bearing sulfonamide functionality in the ring, they have been recognized as an intriguing class of synthetic targets. Although transition-metal-catalyzed asymmetric reduction of the corresponding cyclic *N*-sulfonyl ketimines represents an efficient approach for the enantioselective synthesis of benzosultams or benzosulfamidates, this is not the case for those containing an α-tetrasubstituted stereogenic center in amine moiety. On the other hand, catalytic asymmetric addition of organometallic reagents to cyclic *N*-sulfonyl ketimines can be a direct route, but only have two examples of using chiral Rh-diene complex catalysts been reported.[41-42]



Scheme 21 Synthesis of SOL**10c**.

Our first objective was to access highly optically active 3-carboxy-substituted benzosultams that contain a unique α-amino acid framework. Despite the importance, catalytic enantioselective synthesis of such molecules are unprecedented.[43] In an initial study, we determined that $[Rh(COE)_2Cl]_2$/**4a** catalyzed the reaction of cyclic *N*-sulfonyl α-iminoester **19** with *p*-anisylboronic acid smoothly to give the expected adduct 3-aryl-3-carboxy benzosultam **3a** in 96% yield with 50% ee in aqueous KF (1.5 M)/toluene at room temperature. This result suggested that simple sulfur-olefin can indeed promote this arylation reaction. Further elaboration on the ligand structure indicated that easily prepared sulfinamide-

based branched olefin **10c** was elegant ligand (Scheme 21).[44] The optimized catalytic system worked very well for the reactions between a wide variety of cyclic *N*-sulfonyl α-iminoesters and arylboronic acids with diverse steric and electronic properties, giving the corresponding addition products mostly in high yields (up to 96%) and with excellent enantioselectivities (85-99% ee) (Scheme 22).[44]



Scheme 22 Rh/SOL**10c**-catalyzed asymmetric arylation of cyclic *N*-sulfonyl α-iminoester.

On the basis of the observed stereoselectivity, an empirical transition state model[45] is proposed. As shown in Figure 7, the arylrhodium species has a preferred conformation with the aryl group positioned *trans* to the olefin ligand and the *tert*-butyl moiety staggered. To avoid the steric repulsion between the sulfonyl moiety with the bulky R substituent attached to the double bond, rhodium coordination to the cyclic *N*-sulfonyl α-iminoester is favored in TS-2. Therefore, carborhodation from the *Si* face of the C=N bond takes place to give the corresponding (*R*)-products (Figure 7).

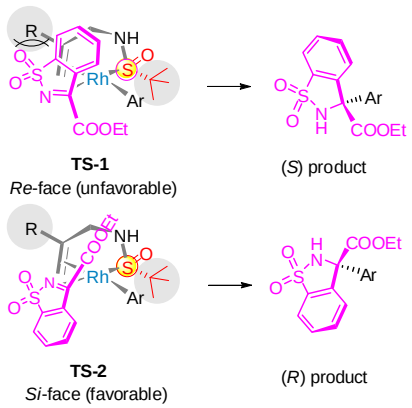
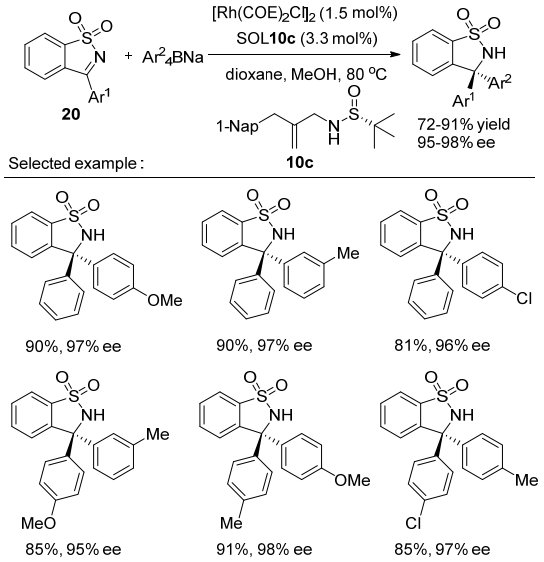
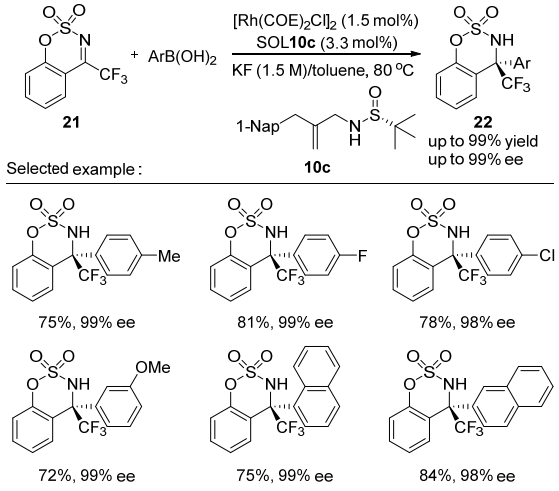


Fig. 7 Proposed transition state model.

Recently, Nishimura and Hayashi investigated Rh/diene-catalyzed highly enantioselective addition of arylboroxines to cyclic *N*-sulfonyl ketimines **20**. To explore the possible applicability of our catalytic system for constructing benzosultams bearing an α-triaryl-substituted stereogenic center, we also carried out a study. As illustrated in Scheme 23, the reaction of various cyclic *N*-sulfonyl ketimines **20** with sodium tetraarylborate was successfully promoted by only 3 mol% of Rh-SOL**10c** complex at 80 °C in dioxane/MeOH. In all cases, excellent enantioselectivities (95-98% ee) that are comparable to those reported using 5 mol% of Rh-diene complex[41] were observed.[44]



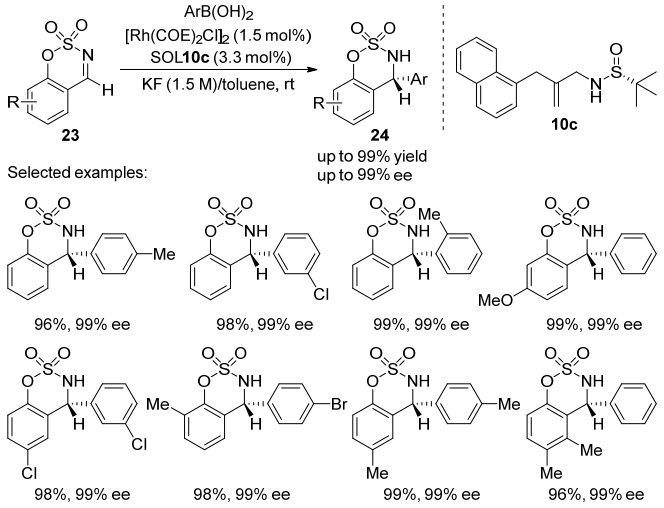
Scheme 23 Rh/SOL**10c**-catalyzed asymmetric arylation of cyclic *N*-sulfonyl ketimines.



Scheme 24 Rh/SOL**10c**-catalyzed asymmetric arylation of cyclic imines **21**.

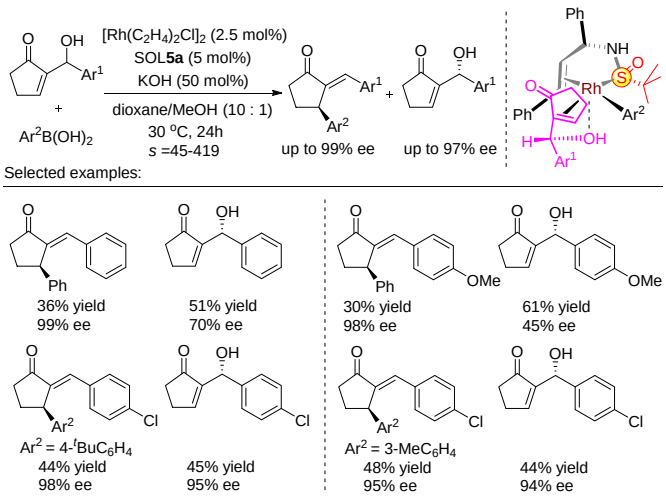
Having established that branched sulfinamide-olefin **10c** is a superior ligand for C=N addition, we subsequently investigated the asymmetric arylation of benzo-fused six-membered cyclic imine **21** to yield particularly interesting CF_3-containing tetrasubstituted cyclic sulfamidates **22**. Gratifyingly, the catalytic system works brilliantly for the reactions with a sterically and electronically diverse range of arylboronic acids,

providing the desired benzosulfamidates in good yields with all extremely high enantioselectivities (98-99% ee) (Scheme 24).[44] Also particularly noteworthy, when a series of cyclic aldimines **23** with either electron-donating or electron-withdrawing groups (R) on each aromatic carbon were employed, the addition proceeds efficiently at room temperature to give the resulting adducts in excellent yields and with a very narrow rang of high enantioselectivity (98-99% ee) (Scheme 25).[44,46] This process represents the most efficient and convenient route to chiral cyclic sulfamidates **24**.



Scheme 25 Rh/SOL**10c**-catalyzed asymmetric arylation of cyclic aldimines **23**.

3.5 Kinetic resolution of hindered MBH adducts

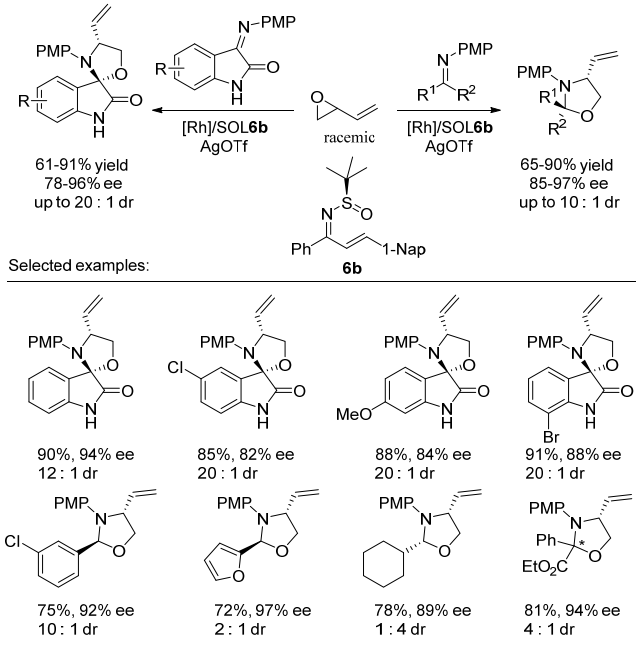


Scheme 26 Rh/SOL**5a**-catalyzed asymmetric 1,4-addition/β-hydroxyelimination.

In 2011, Du and co-workers demonstrated that chiral sulfinamide-olefins in particular **5a** could serve as efficient ligand to promote Rh-catalyzed 1,4-addition/β-hydroxyelimination reactions of arylboronic acids to hindered Morita-Baylis–Hillman (MBH) adducts. The process is highly enantioselective and gives functionalized chiral alkenes in high yields with up to 99% ee.[47] It is noted that a kinetic resolution are found for the first time in this transformation with a high s-factor (up to 419). This phenomenon was explained by the different coordination model between the hydroxyl group of MBH adduct and rhodium center (Scheme 26).

3.6 Formal [3+2] cycloaddition of imines with vinyl epoxide

The catalytic asymmetric [3+2] cycloaddition process is effective for the construction of five membered ring compounds. In 2011, Jarvo and co-workers developed a rhodium-catalyzed stereospecific reaction of enantioenriched vinyl epoxide with aryl imines for asymmetric synthesis of 1,3-oxazolidines. Recognizing that $Rh(COD)_2OTf$ are used as catalyst but phosphine ligands such as BINAP would inhibit the reaction, Du and co-workers smartly initiated a study using chiral sulfur-olefins as ligands. The catalytic activity of a variety of easily available olefin ligands bearing sulfinamide and sulfinylimine moiety were evaluated in the cycloaddition of isatin imine with 1.2 equivalent of racemic butadiene monoxide. Indeed, the reaction was found to be greatly accerated by sulfur-olefin ligand. The sulfinylimine-olefin **6b** demonstrates its good ability as a chiral ligand in this transformation to give up to 68% ee and 50:1 diastereoselectivity. Further reaction condition optimization led to the generation of enantioenriched spirooxindole oxazolidines or 1,3-oxazolidines in good yields with moderate to excellent stereoselectivities (3:1~20:1 dr, 78-98% ee) (Scheme 27).[48] According to the stereochemical outcome of the reaction, it was concluded that the absolute configuration of products is dependent on that of chiral ligand.



Scheme 27 Rh/SOL**6b**-catalyzed asymmetric [3+2] cycloaddition reaction.

4 Conclusion and outlook

Since 2011, chiral sulfur-containing hybrid olefins have been successfully employed as new promising ligands in a series of rhodium-catalyed asymmetric reactions. This article gives an overview of the design and development of simple chiral sulfur-olefin ligands for enantioselective catalysis by our research group as well as related work by others. These novel sulfur-olefin ligands exhibit noticeable and unique catalytic properties (activity and selectivity) in asymmetric process as compared to other conventional chiral ligands. In particular, they are greatly useful to promote organoboron reagent addition to specific C=O and C=N double bonds for highly enantioselective construction of otherwise-difficult-to-access fully-substituted carbon stereocenters. While limited examples of enantioselective arylation of ketimines using chiral diene complexes exist, there appear to be a distinct advantage of the sulfur-olefin ligand system that they can generally display an exceptional performance in challenging 1,2-addition reactions. In view of these noteworthy achievements, they have become nowadays an important class of chiral chelating olefin ligands in asymmetric catalysis. Compared to the known chiral dienes and pnictogen-based olefin ligands possessing sophisticated scaffolds with the chirality being introduced in the carbon backbone, chiral sulfur-based olefin ligands are rather remarkable for their easy and practical synthesis with the use of stereogenic sulfinamide/sulfoxide as a simple chiral directing group. Undoubtedly, this extraordinary structural simplicity feature will offer significant synthetic and economic benefits for asymmetric catalysis on industrial scale.

In general, the use of simple sulfur-olefin ligands in asymmetric transformations is still in its infancy. Although impressive progress has been made, challenges remain in the mechanistic understanding of the catalytic role of ligands and the development of a wide range of different asymmetric transformations using various transition metals besides rhodium (for example, palladium and iridium). Nevertheless, the current success of chiral sulfur-olefin catalysis provides an exciting opportunity for future exploration. It can be expected that this new type of sulfur-containing olefin ligand as well as its design principles will find wide applications in many enantioselective reactions.

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Ming-Hua Xu was born in Zhejiang, China. He obtained his Ph.D. from Shanghai Institute of Organic Chemistry (SIOC), Chinese Academy of Sciences in 1999. Following postdoctoral research at the University of Virginia and Georgetown University Medical Center, he joined the faculty at SIOC as an associate professor in 2003. He has been a professor at Shanghai Institute of Materia Medica, Chinese Academy of Sciences since 2005. His research interests mainly involve asymmetric synthesis and drug discovery.

Notes and references

1 (*a*) G. Frenking and N. Frohlich, *Chem. Rev.* 2000, **100**, 717; (*b*) R. H. Crabtree, *The Organometallic Chemistry of the Transition Metals*, Wiley, Hoboken, New Jersey, 2005, Fourth Edition, Chapter 5; (*c*) D. Astruc, *Organometallic Chemistry and Catalysis*, Springer-Verlag, 2007, Chapter 10.
2 W.C. Zeise, *Poggendorffs Ann. Phys.* 1827, **9**, 632.
3 *Comprehensive Organometallic Chemistry III, ed. R. H. Crabtree and D. M. P. Mingos*, Elsevier, 2007.
4 T. Hayashi, K. Ueyama, N. Tokunaga and K. Yoshida, *J. Am. Chem. Soc.*, 2003, **125**, 11508.
5 C. Fischer, C. Defieber, T. Suzuki and E. M. Carreira, *J. Am. Chem. Soc.*, 2004, **126**, 1628.
6 For reviews see: (*a*) F. Glorius, *Angew. Chem., Int. Ed.*, 2004, **43**, 3364; (*b*) J. B.Johnson and T. Rovis, *Angew. Chem., Int. Ed.* 2008, **47**, 4482; (*c*) C. Defieber, H. Grützmacher and E. M. Carreira, *Angew. Chem., Int. Ed.*, 2008, **47**, 4482; (*d*) R. Shintani and T. Hayashi, *Aldrichim. Acta*, 2009, **42**, 31; (*e*) C.-G. Feng, M.-H. Xu and G.-Q. Lin, *Synlett*, 2011, 1345; (*f*) X. Feng and H. Du, *Asian J. Org. Chem.*, 2012, **1**, 204.
7 (*a*) P. Maire, S. Deblon, F. Breher, J. Geier, C. Böhler, H. Rüegger, H. Schönberg and H. Grützmacher, *Chem. –Eur. J.*, 2004, **10**, 4198; (*b*) E. Piras, F. Läng, H. Rüegger, D. Stein, M. Wörle and H. Grützmacher, *Chem.–Eur. J.*, 2006, **12**, 5849.
8 For early representative examples of chiral dienes, see: (*a*) N. Tokunaga, Y. Otomaru, K. Okamoto, K. Ueyama, R. Shintani and T. Hayashi, *J. Am. Chem. Soc.*, 2004, **126**, 13584; (*b*) Y. Otomaru, N. Tokunaga, R. Shintani and T. Hayashi, *Org. Lett.*, 2005, **7**, 307; (*c*) Z.-Q. Wang, C.-G. Feng, M.-H. Xu and G.-Q. Lin, *J. Am. Chem. Soc.*, 2007, **129**, 5336; (*d*) S. Helbig, S. Sauer, N. Cramer, S. Laschat, A. Baro and W. Frey, *Adv. Synth. Catal.*, 2007, **349**, 2331; (*e*) T. Nishimura, M. Nagaosa and T. Hayashi, *Chem. Lett.*, 2008, **37**, 860; (*f*) K. Okamoto, T. Hayashi and V. H. Rawal, *Org. Lett.*, 2008, **10**, 4387; (*g*) C.-G. Feng, Z.-Q. Wang, C. Shao, M.-H. Xu and G.-Q. Lin, *Org. Lett.*, 2008, **10**, 4101; (*h*)

X. Hu, M. Zhang, Z. Cao and H, Du, *Org. Lett.*, 2009, **11**, 4744; (*i*) C. Shao, H.-J. Yu, N.-Y. Wu, C.-G. Feng and G.-Q. Lin, *Org. Lett.*, 2010, **12**, 3820.
9 For early representative examples of P/N-Olefin, see: (*a*) R. Shintani, W.-L. Duan, T. Nagano, A. Okada and T. Hayashi, *Angew. Chem., Int. Ed.*, 2005, **44**, 4611; (*b*) P. Kasák, V. B. Arion and M. Widhalm, *Tetrahedron: Asymmetry*, 2006, **17**, 3084; (*c*) P. Maire, F. Breher, H. Schöberg and H. Grützmacher, *Organometallics*, 2005, **24**, 3207; (*d*) B. T. Hahn, F. Tewes, R. Frölich and F. Glorius, *Angew. Chem., Int. Ed.*, 2010, **49**, 1143.
10 (*a*) C.-G. Feng, Z.-Q. Wang, P. Tian, M.-H. Xu and G.-Q. Lin, *Chem.–Asian J.*, 2008, **3**, 1511; (*b*) Z.-Q. Wang, C.-G. Feng, S.-S. Zhang, M.-H. Xu and G.-Q. Lin, *Angew. Chem., Int. Ed.*, 2010, **49**, 5780; (*c*) L.Wang, Z.-Q. Wang, M.-H. Xu and G.-Q. Lin, *Synthesis*, 2010, 3263; (*d*) H.-Y. Yang and M.-H. Xu, *Chem. Commun.*, 2010, **46**, 9223; (*e*) S.-S. Zhang, Z.-Q. Wang, M.-H. Xu and G.-Q. Lin, *Org. Lett.* 2010, **12**, 5546; (*f*) H.-Y. Yang and M.-H. Xu, *Chin. J. Chem.* 2013, **31**, 119.
11 For reviews on the chemistry of *N*-*tert*-butanesulfinamide, see: (*a*) F. Ferreira, C. Botuha, F. Chemla and A. Pérez-Luna, *Chem. Soc. Rev.*, 2009, **38**, 1162; (*b*) M. T. Robak, M. A. Herbage and J. A. Ellman, *Chem. Rev.*, 2010, **110**, 3600.
12 (*a*) G.-Q. Lin, M.-H. Xu, Y.-W. Zhong and X.-W. Sun, *Acc. Chem. Res.*, 2008, **41**, 831, and references cited therein; (*b*) X.-W. Sun, M. Liu, M.-H. Xu and G.-Q. Lin, *Org. Lett.*, 2008, **10**, 1259; (*c*) A. Shen, M. Liu, Z.-S. Jia, M.-H. Xu and G.-Q. Lin, *Org. Lett.*, 2010, **12**, 5154; (*d*) M. Liu, A. Shen, X.-W. Sun, F. Deng, M.-H. Xu and G.-Q. Lin, *Chem. Commun.*, 2010, **46**, 8460; (*e*) D.-M. Ji and M.-H. Xu, *Chem. Commun.*, 2010, **46**, 1550; (*f*) S.-S. Jin and M.-H. Xu, *Adv. Synth. Catal.*, 2010, **352**, 3136; (*g*) Y. Li, D.-M. Ji and M.-H. Xu, *Org. Biomol. Chem.*, 2011, **9**, 8452; (*h*) Y. Li and M.-H. Xu, *Org. Lett.*, 2012, **14**, 2062; (*i*) Yi, Li and M.-H, Xu, *Asian J. Org. Chem.*, 2013, **2**, 50. (*j*) D. Chen and M.-H. Xu, *Chem. Commun.*, 2013, **49**, 1327.
13 (*a*) *Chiral Sulphur Ligands: Asymmetric Catalysis*; *ed*. H. Pellissier, Royal Society of Chemistry: Cambridge, U.K., 2009; (*b*) M. Mellah, A. Voituriez and E. Schulz, *Chem. Rev.* 2007, **107**, 5133.
14 S.-S. Jin, H. Wang and M.-H. Xu, *Chem. Commun.*, 2011, **47**, 7230.
15 S.-S. Jin, H. Wang, T.-S. Zhu and M.-H. Xu, *Org. Biomol. Chem.*, 2012, **10**, 1764.
16 W.-Y. Qi, T.-S. Zhu and M.-H. Xu, *Org. Lett.*, 2011, **13**, 3410.
17 T. Thaler, L.-N. Guo, A. K. Steib, M. Raducan, K. Karaghiosoff, P. Mayer and P. Knochel, *Org. Lett.*, 2011, **13**, 3182.
18 X. Feng, Y. Wang, B. Wei, J. Yang and H. Du, *Org. Lett.*, 2011, **13**, 3300.
19 G. Chen, J. Gui, L. Li ang J. Liao, *Angew. Chem., Int. Ed.*, 2011, **50**, 7681.
20 F. Xue, X. Li and B. Wan, *J. Org. Chem.*, 2011, **76**, 7256.
21 For review, see: T. Hayashi and K. Yamasaki, *Chem. Rev.*, 2003, **103**, 2829, and references cited therein.
22 X. Feng, B. Wei, J, Yang and H. Du, *Org. Biomol. Chem.*, 2011, **9**, 5927.
23 G. Chen, J. Gui, P. Cao and J. Liao, *Tetrahedron*, 2012, **68**, 3220.
24 N. Khiar, Á. Salvador, A. Chelouan, A. Alcudia and I. Fernández, *Org. Biomol. Chem.*, 2012, **10**, 2366.
25 N. Khiar, V. Valdivia, Á. Salvador, A. Chelouan, A. Alcudia and I. Fernández, *Adv. Synth. Catal.*, 2013, **355**, 1303.
26 Q. Chen, C. Chen, F. Guo and W. Xia, *Chem. Commun.*, 2013, **49**, 6433.
27 F, Xue, D. Wang, X. Li and B. Wan, *Org. Biomol. Chem.*, 2013, **11**, 7893.
28 F. Lang, G. Chen, L. Li, J. Xing, F. Han, L, Cun and J. Liao, *Chem. Eur. J.*, 2011, **17**, 5242.
29 F. Xue, D. Wang, X. Li and B. Wan, *J. Org. Chem.*, 2012, **77**, 3071.
30 H.-F. Duan, J.-H. Xie, X.-C. Qiao, L.-X. Wang and Q.-L. Zhou, *Angew. Chem., Int. Ed.*, 2008, **47**, 4351.
31 T.-S. Zhu, S.-S. Jin and M.-H. Xu, *Angew. Chem., Int. Ed.*, 2012, **51**, 780.
32 (*a*) J. N. N. Eildal, J. Andersen, A. S. Kristensen, A. M. Jøgensen, B. Bang-Andersen, M. Jøgensen and K. Strøgaard, *J. Med. Chem.*, 2008, **51**, 3045; (*b*) P. Zhang, G. Cyriac, T. Kopajtic, Y. Zhao, J. A. Javitch, J. L. Katz and A. H. Newman, *J. Med. Chem.*, 2010, **53**, 6112.
33 X. Feng, Y. Nie, J. Yang and H. Du, *Org. Lett.*, 2012, **14**, 624.
34 T.-S. Zhu, Ph.D. Thesis, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, 2012.
35 T.-S. Zhu, J.-P. Chen and M.-H. Xu, *Chem. Eur. J.*, 2013, **19**, 865.
36 (*a*) G. E. Croston, R. Olsson, E. A. Currier, E. S. Burstein, D. Weiner, N. Nash, D. Severance, S. G. Allenmark, L. Thunberg, J.-N. Ma, N. Mohell, B. O'dowd, M. R. Brann and U. Hacksell, *J. Med. Chem.*, 2002, **45**, 4950; (*b*) F. Lehmann, E. A. Currier, R. Olsson, U. Hacksell and K. Luthman, *Bioorg. Med. Chem.*, 2005, **13**, 3057.
37 H. Wang, T.-S Zhu and M.-H. Xu, *Org. Biomol. Chem.*, 2012, **10**, 9158.
38 Y. Li, D.-X. Zhu and M.-H. Xu, *Chem. Commun.*, 2013, **49**, 11659.
39 T.-S. Zhu and M.-H. Xu, *Chin. J. Chem.*, 2013, **31**, 321.
40 D. W. Low, G. Pattison, M. D. Wieczysty, G. H. Churchill and H. W. Lam, *Org. Lett.*, 2012, **14**, 2548.
41 T. Nishimura, A. Noishiki, G. C. Tsui and T. Hayashi, *J. Am. Chem. Soc.*, 2012, **134**, 5056.
42 Y.-F. Luo, A. J. Carnell and H. W. Lam, *Angew. Chem., Int. Ed.*, 2012, **51**. 6762.
43 K. H. Ahn, H.-H. Baek, S. J. Lee and C.-W. Cho, *J. Org. Chem.*, 2000, **65**, 7690.
44 H. Wang, T. Jiang and M.-H. Xu, *J. Am. Chem. Soc.*, 2013, **135**, 971.
45 (*a*) T. Hayashi, K. Ueyama, N. Tokunaga and K. Yoshida, *J. Am. Chem. Soc.*, 2003, **125**, 11508; (*b*) K. Fagnou and M. Lautens, *Chem. Rev.*, 2003, **103**, 169.
46 H. Wang and M.-H. Xu, *Synthesis*, 2013, **45**, 2125.
47 Y. Wang, X. Feng and H. Du, *Org. Lett.*, 2011, **13**, 4954.
48 Z. Liu, X. Feng and H. Du, *Org. Lett.*, 2012, **14**, 3154.