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Asymmetric Stepwise Reductive Amination of Sulfonamides, Sulfamates and a Phosphinamide via Nickel Catalysis

Xiaohu Zhao, Haiyan Xu, Xiaolei Huang and Jianrong Steve Zhou*

Abstract: asymmetric reductive amination of poorly nucleophilic sulfonamides is realized in the presence of nickel catalysts and titanium alkoxide. A wide range of enolizable ketones, including some dialkyl and biaryl ones, were converted to sulfonamides in excellent enantiomeric excess. Cyclization of sulfamates and intermolecular reductive amination of a diarylphosphinamide were also successful. Formic acid was used as a safe and economic surrogate of high-pressure hydrogen gas.

Chiral alkylamines are commonly structural elements in modern medicines and their enentioselective synthesis has attracted significant research interest.[1] Sulfonamides, in particular, are common pharmacophores and are considered to be useful isosteres of carboxylic acids and carboxamides in drug discovery.[2] In fact, the sulfonamide family of antibiotics are the first family of antibiotics that were used systematically.[3] Sulfonamides are also present in many other medicines, such as antiviral, anticancer and antiinflammatory agents.[4] Moreover, chiral sulfonamides containing α-stereogenic centers have also emerged recently in medicine, for example, ramatroban, a drug for the treatment of coronary artery disease and asthma[5] and MK-7246, a drug candidate targeting respiratory diseases.[6] Other chiral sulfonamide drugs target cancers,[7] Type II diabetes[8] and Alzheimer's disease[9] (Figure 1).

Compared to asymmetric hydrogenation of pre-formed ketimines and enamines using rare noble metal catalysts[10] and abundant 3d metal catalysts,[11] reductive amination of ketones and amines avoids the isolation and purification of ketimines, some of which are unstable during purification and storage.[12] To date, most late metal-catalyzed[13] or organocatalytic[14] methods for asymmetric reductive amination are limited to arylamines and acylhydrazines, which undergo facile condensation with ketones to form ketimines in the presence of acid catalysts and molecular sieves. For instance, in 2016 we reported nickel-catalyzed asymmetric reductive amination using arylamines and benzhydrazide.[15] Reductive amination using amines of attenuated nucleophilicity, such as sulfonamides and phosphinamides, still remains a challenge, especially when enolizable ketones are used.[16] Thus, in existing Rh- and Pd-catalyzed asymmetric hydrogenation, for example, *N*-sulfonyl ketimine needed to be prepared first, by condensing ketones with more nucleophilic sulfinamides followed by oxidation.[17] In a typical example, Zhang *et al.* reported that 1 mol% palladium/TangPhos catalyzed hydrogenation of pre-formed *N*-tosyl ketimines, although 75 bar of hydrogen pressure was required.[17a] Similarly, simple condensation of diarylphosphinamides and ketones has remained difficult.[18] In asymmetric hydrogenation,[11c,17b] borohydride reduction[19] and hydrosilylation of these ketimines,[20] they were prepared beforehand via a moderately-yielding condensation of oximes and chlorodiarylphosphines.[21] Notably, high pressure of hydrogen gas (40-75 bar) was needed in hydrogenation of the two types of ketimines.

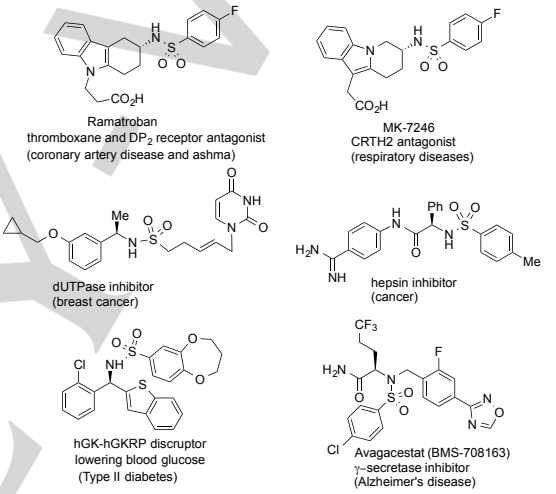
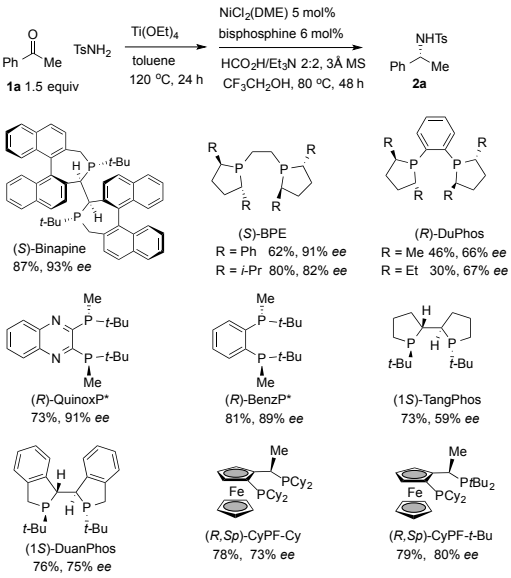


Figure 1. Chiral sulfonamides in medicines



Scheme 1. The effect of chiral bisphosphines on reductive amination of acetophenone and *p*-tosylamine.

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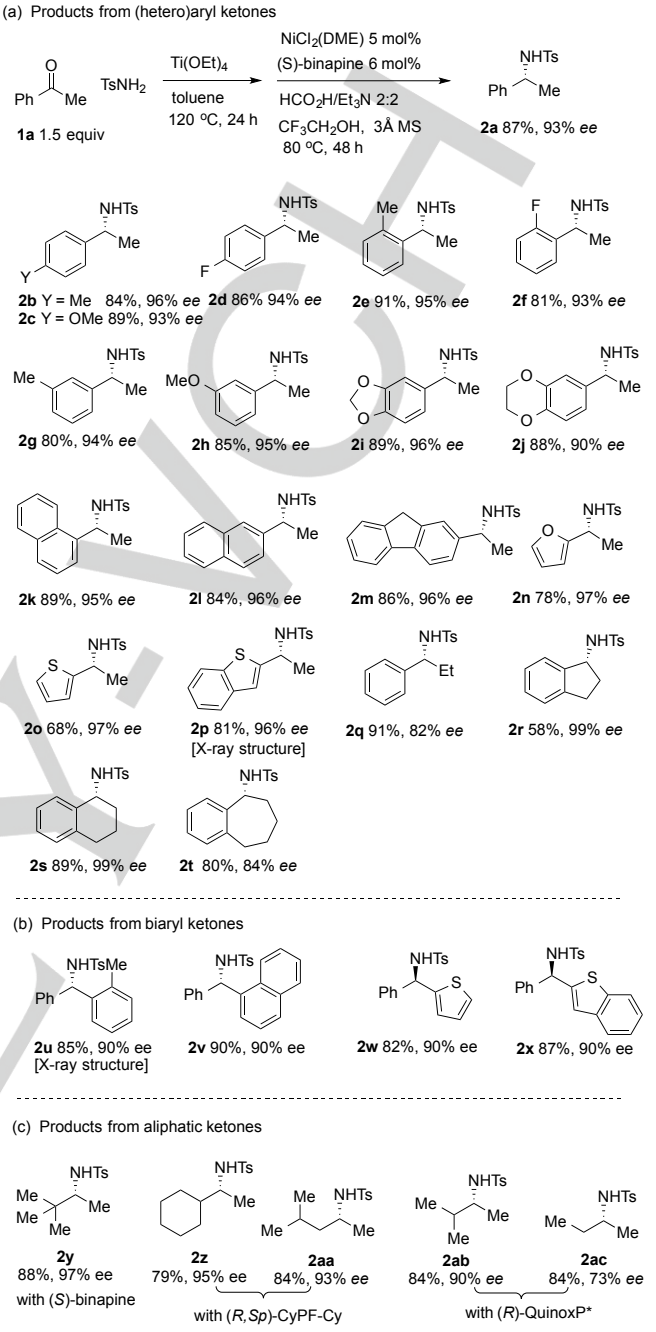
Initially, we attempted nickel-catalyzed reductive amination of acetophenone **1a** and *p*-tosylamine using formic acid under various condensation conditions (Scheme 1). Often we observed facile ketone reduction, self-aldol condensation of acetophenone to form an enone. The latter also underwent nonselective reduction in the reaction mixture. Eventually, we attempted the condensation using titanium ethoxide in refluxing toluene,[16] which led to the desired ketimine in good yield. Subsequent treatment of the *N*-sulfonyl ketimine[17] with a nickel catalyst ligated with binapine,[22] formic acid and triethylamine afforded sulfonamide **2a** in 93% yield and 93% *ee*. Notably, when this model reaction was conducted without prior formation of the ketimine, **2a** was still obtained in 87% yield in the presence of $Ti(OEt)_4$. A detailed catalyst screening revealed that several other chiral bisphosphines also provided >90% ee for this hydrogenation, including Ph-BPE, QuinoxP* and BenzP* (see Scheme 1). We also tested catalytic performance of [(*S*)-binapine]$NiCl_2$ complex, which was similar to the catalyst cocktail described in Scheme 1. When 1, 2 and 5 mol% nickel complex was used, the yield of **2a** was 43, 65 and 82% after 48 h, respectively.

With the optimal conditions using the nickel/binapine catalyst in hand, we explored the scope of ketones in reaction of *p*-tosylamine (Scheme 2a). Aryl ketones with different electronic properties (**2b-j**) and heteroaryl ketones (**2n-p**) gave the desired products in good yields and >95% ee values. Interestingly, both cyclic 1-indanone and 1-tetralone provided products (**2r-s**) in almost perfect ees. In the reaction of indanone, a moderate yield of **2r** resulted, owing to facile aldol condensation of 1-indanone. Unfortunately, titanium ethoxide failed to promote condensation of highly electron-deficient 1,1,1-trifluoroacetophenone with tosylamine.

Excitingly, we found that some biaryl ketones furnished the corresponding tosylamines (**2u-2x**) in excellent *ee* values (Scheme 2b).[23] On the ketimines, to our delight, the nickel/binapine catalyst successfully differentiated a phenyl ring and a larger *o*-tolyl or 1-naphthyl group (**2u-2v**). Furthermore, the same catalyst also discriminated a phenyl ring versus thiophene and benzothiophene (**2w-2x**). The absolute configuration of product **2u** was determined by X-ray diffractional analysis.[24]

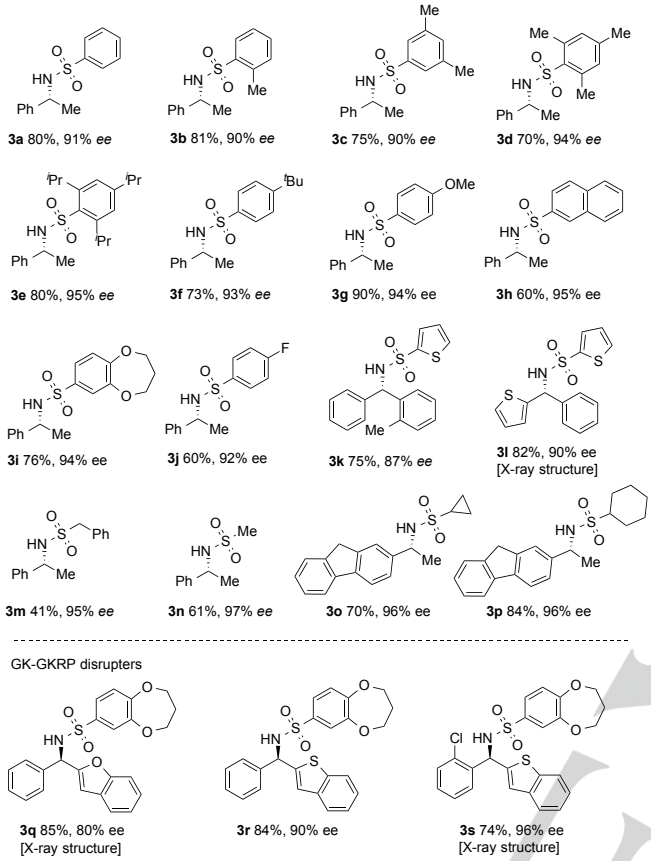
In reactions of common aliphatic ketones (Scheme 2c), we found that nickel catalysts can successfully provide >90% ee, when a suitable bisphosphine was used judiciously. Thus, methyl ketones bearing *t*-butyl, cyclohexyl, *sec*-butyl and isopropyl groups (**2y-2ab**) were hydrogenated in excellent ee by nickel catalysts of binapine, Josiphos CyPF-Cy and QuinoxP*, respectively. However, asymmetric reductive amination of ethyl methyl ketone (**2ac**) still remained a significant challenge as expected (73% ee).



Scheme 2. Reductive amination of different types of ketones with *p*-tosylamine.

We then investigated the scope of sulfonamides using the nickel/binapine catalyst under conditions described in Scheme 2. The results are summarized in Scheme 3. The sulfonamides tolerated large ortho groups on aryl rings (**3d-e**) and strongly electron-donating groups (**3g** and **3i**). However, many arenesulfonamides with highly electron-deficient arenes failed to condense with acetophenone, except that 4-fluorobenzenesulfonamide still reacted and gave the desired amine (**3j**) in 60% yield. Notably, thiophene (**3k-l**), a cyclopropyl ring (**3o**) and aliphatic groups (**3m, 3n** and **3p**) can be present on sulfonamides. In cases that afforded desired products (**3m-n**) in moderate yields, self-aldol

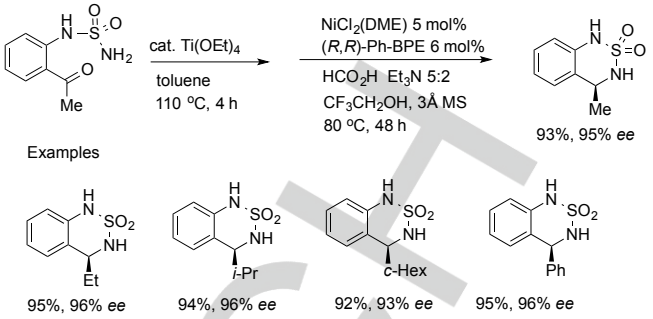
condensation of acetophenone accounted for most of the remaining material. Unfortunately, the reaction of bulky *t*-butylsulfonamide with acetophenone resulted in only 10% yield of the target product.



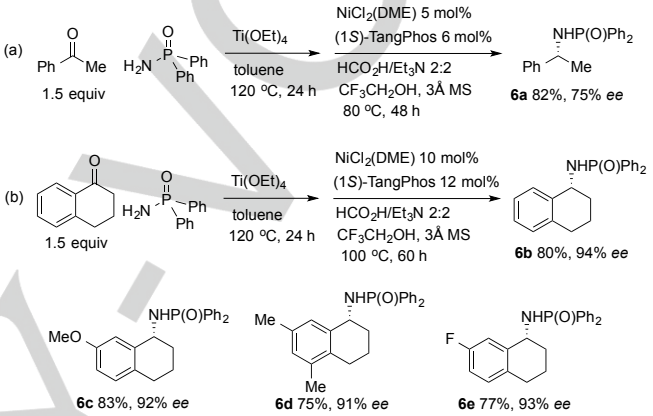
Scheme 3. Asymmetric reductive amination of other sulfonamides (**3a-p**) and synthesis of drug candidates (**3q-s**).

Furthermore, the nickel catalysis was successfully applied to asymmetric synthesis of biarylmethylamines (**3q-s**), which were identified to be promising candidates for the treatment of Type II diabetes.[8] In particular, **3s** is a disruptor of human glucokinase and its regulatory protein at nanomolar concentrations. In the two examples containing benzothiophene rings, over 90% ee was achieved. We have ascertained the absolute stereochemistry of **3q** and **3s** with single crystal X-ray diffraction.[24]

We also attempted intermolecular reductive amination of ketones and sulfamates, but unfortunately sulfamates were unstable towards titanium alkoxides and *p*-tosylic acid. Luckily, we found that intramolecular condensation of sulfamate **4a** was readily catalyzed by *p*-tosylic acid, which allowed us to prepare cyclized product **5a** in one pot (Scheme 4). Alternatively, 10 mol% of $Ti(OEt)_4$ can be used for the condensation to give almost identical results. From catalyst screening, the nickel catalyst of Ph-BPE delivered **5a** in excellent yield and 95% ee. The absolute configuration of **5a** was established by single-crystal X-ray diffraction.[24] This stepwise procedure was readily applied to asymmetric synthesis of other benzofused sulfamates.[25]



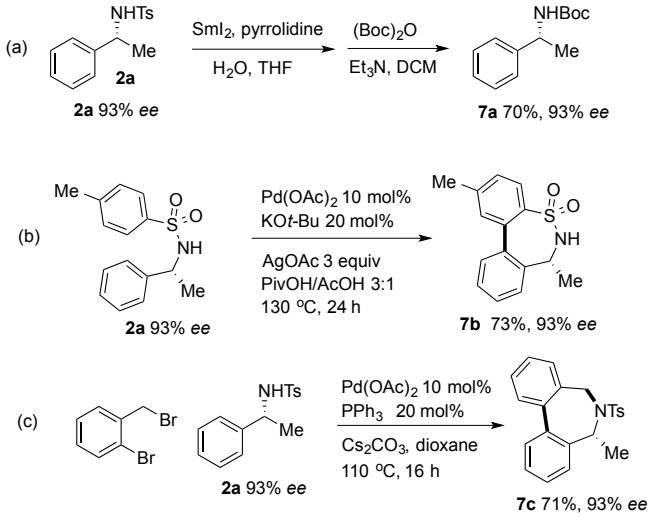
Scheme 4. Asymmetric synthesis of benzosulfamates.



Scheme 5. Asymmetric reductive amination of ketones and diphenylphosphinamide.

Gratifyingly, we discovered that stepwise reductive amination with titanium ethoxide can be successfully extended to diphenylphosphinamide without any problem. For example, a nickel/TangPhos catalyst afforded product **6a** in 82% yield and 75% ee (Scheme 5a), while the nickel/binapine catalyst only afforded the product in 30% ee. To our delight, reductive amination of substituted 1-tetralones afforded desired products **6b**-**e** in greater than 90% ee, even though a longer reaction time was needed (Scheme 5b). Of note, a similar reaction with indanone, however, led mainly to self-aldol condensation.

The chiral *N*-tosylamines from the reductive amination were readily transformed to other chiral building blocks (Scheme 6). For example, the *N*-tosyl group of benzylamine **2a** was easily converted into an *N*-Boc group (**7a**) after the treatment of SmI_2.[26] Moreover, biaryl sultam **7b** was also synthesized under an oxidative coupling condition with AgOAc.[27] In a third example, **2a** efficiently coupled with *o*-bromobenzyl bromide in one pot to provide dibenzoazepine **7c**.[28] No loss of enantiomeric purity was detected in all the transformations herein. For biaryl **7b-c**, only a single atropoisomer was detected in solution by proton NMR spectroscopy.



Scheme 6. Product transformation.

In conclusion, we developed a nickel-catalyzed asymmetric reductive amination of sulfonamides for the first time. A diverse set of ketones, including some biaryl ketones and aliphatic ketones, reacted to afford chiral sulfonamides in excellent ees. A similar stepwise procedure also proved successful in asymmetric cyclization of sulfamates and intermolecular reductive amination of a diarylphosphinamide. Formic acid was used as safe, easy-to-handle source of hydrogen, which helped avoid the use and handling of high-pressure hydrogen gas, a safety hazard.

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Conflict of interest

The authors declare no conflict of interest

Keywords: chiral alkylamines • nickel catalysis • reductive amination • transfer hydrogenation • sulfonamides

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COMMUNICATION

Reductive Amination

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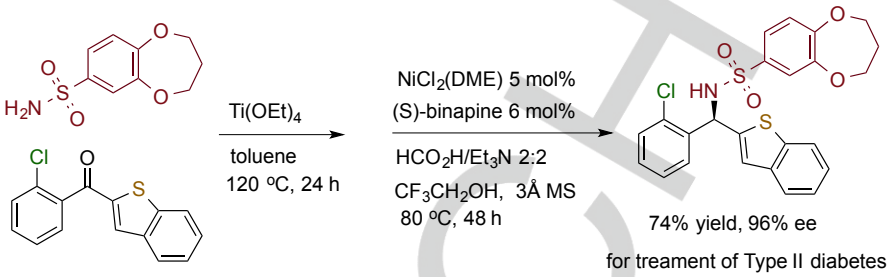
Asymmetric Stepwise Reductive Amination of Sulfonamides, Sulfamates and a Phosphinamide via Nickel Catalysis



Intermolecular reductive amination of amines with attenuated nucleophilicity, including sulfonamides, sulfamates and a phosphinamide, proceeds without the need of isolating ketimines. Formic acid is used as a safe and easy-to-handle hydrogen source.