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Transition-Metal-Free Hydrogen Autotransfer: Diastereoselective N-Alkylation of Amines with Racemic Alcohols

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Abstract: A practical method for the synthesis of α -chiral amines via alkylation of amines with alcohols in the absence of any transition metal catalysts has been developed. Under the co-catalysis of a ketone and NaOH, racemic secondary alcohols reacted with Ellman's chiral *tert*-butanesulfinamide via a hydrogen autotransfer process to afford chiral amines with high diastereoselectivities (up to > 99:1). Broad substrate scope and up to 10-gram scale production of chiral amines were demonstrated. The method could be applied to the synthesis of chiral deuterium-labelled amines with high deuterium incorporation and optical purity, including examples of chiral deuterated drugs. The configuration of amine products is found to be determined solely by the configuration of the chiral *tert*-butanesulfinamide regardless of that of alcohols, which is corroborated by DFT calculations. Further mechanistic studies showed that the reaction is initiated by the ketone catalyst and involves a transition state similar to that proposed for the Meerwein-Ponndorf-Verley (MPV) reduction and importantly, it is the interaction of the sodium cation of the base with both the nitrogen and oxygen atoms of the sulfinamide moiety that makes feasible, and determines the diastereoselectivity of, the reaction.

Introduction

Chiral amines, particularly α -chiral primary amines, are arguably the most important intermediates used in the synthesis of pharmaceuticals, agrochemicals and specialty chemicals.^[1] Indeed, many drug molecules contain α -chiral amine moieties (Figure 1). A clean method for accessing such primary amines would be asymmetric hydrogenation of imino species.^[1v, 1w, 2] However, this remains challenging in terms of substrate scope and catalyst efficiency, with only a few literature reports being seen,^[3] documenting the preparation of α -chiral primary amines with high enantioselectivity via catalytic hydrogenation or transfer hydrogenation. Industrially, α -chiral amines have been produced via resolution with chiral acids^[4] and biocatalytic transformation,^[2e, 5] and there are also a few examples of

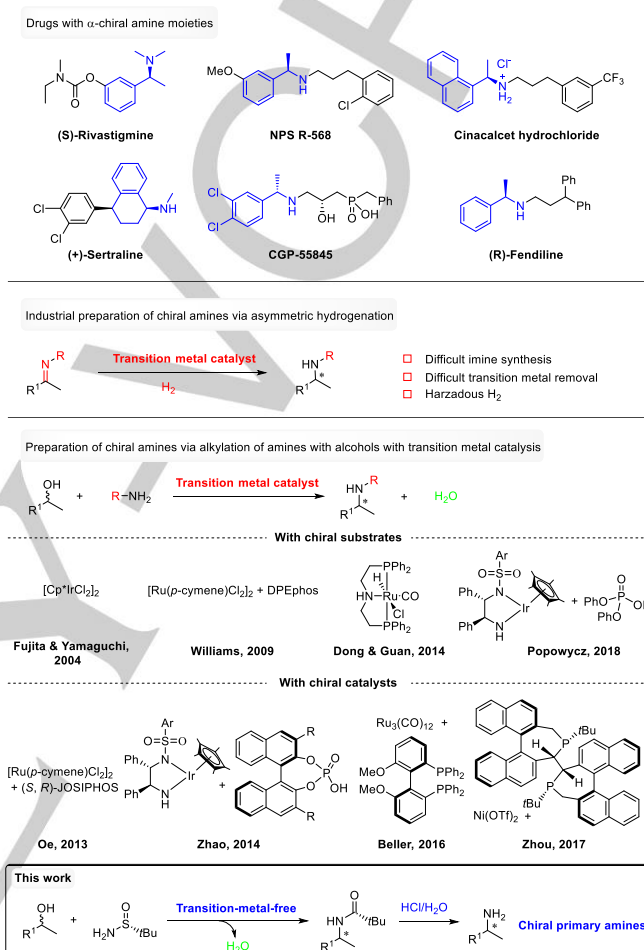


Figure 1. Drugs with α -chiral amine moieties and routes for the synthesis of α -chiral amines.

asymmetric hydrogenation of C=N bonds to afford α -chiral secondary amines.^[1v, 1x, 2a-d, 6] An excellent example is seen in the industrial production of the herbicide (S)-metolachlor via the asymmetric hydrogenation of an imine with an iridium catalyst at 80 bar H_2 , on a >10000 tonnes/year scale.^[7] A disadvantage of the hydrogenation method is the need for the usually-labile imine precursors and high hydrogen pressure; the latter may not suit routine fine chemical and pharmaceutical synthesis (Figure 1).

The direct asymmetric alkylation of amines with alcohols (or amination of alcohols with amines) via a "borrowing hydrogen" (or hydrogen autotransfer) strategy^[8] is an attractive alternative to access chiral amines. In 2004, Fujita, Yamaguchi and co-workers reported the first diastereoselective amination of alcohols with chiral amine substrates catalyzed by [Cp*IrCl₂]₂ (Figure 1),^[9] which was later applied by Trudell and co-workers in the synthesis of a natural product.^[10] Williams and co-workers also used a chiral amine substrate in a Ru catalyzed amination of alcohols with retention of chirality in the product, albeit with no

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new chiral center generated.^[11] In 2013, Oe and co-workers reported the first asymmetric alkylation of achiral amines with racemic alcohols with a chiral Ru catalyst, affording moderate yields (<70%).^[12] A major breakthrough was made by Zhao and co-workers in 2014, who showed that chiral amines of up to >99% ee can be formed by reacting achiral amines with racemic alcohols using a chiral Ir catalyst in conjunction with a chiral phosphoric acid (Figure 1).^[13] This metal-Bronsted acid dual-catalyst system has subsequently been exploited in various asymmetric *N*-alkylation reactions.^[14] In a further development, Dong, Guan and their co-worker reported that racemic alcohols can be aminated highly diastereoselectively with Ellman's chiral sulfinamide, using an achiral ruthenium catalyst with no need for additional chiral additives (Figure 1).^[15]

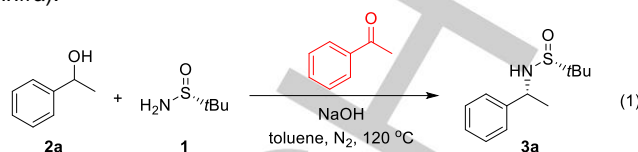
Mechanistically, the "borrowing hydrogen" strategy generally involves dehydrogenation of the alcohol by a metal catalyst to give a ketone and a metal hydride. This is followed by enantioselective/diastereoselective reduction of the resulting imine with the hydride. Circumventing the need for imines and reductants and with water as the only by product, the method has since been exploited for the synthesis of a range of chiral amines by the groups of Beller,^[16] Zhou,^[17] and Popowycz^[18] (Figure 1). Whilst featuring high stereoselectivity, the borrowing-hydrogen strategies reported so far necessitate the use of transition metal catalysts, special chiral ligands or additives, which could hamper its practical application in large-scale pharmaceutical manufacturing.

Herein, we present a transition metal-free asymmetric alkylation of amines with racemic alcohols for the preparation of α -chiral amines (Figure 1).^[19] Under the co-catalysis of a ketone and NaOH, racemic secondary alcohols reacted with Ellman's chiral sulfinamide,^[20] affording α -chiral amines with high diastereoselectivities (up to > 99:1 dr), which can be readily converted into chiral primary amines following simple acidolysis.

Results and Discussion

1. Identification of a metal-free asymmetric amination protocol. In continuing our study of metal-catalyzed borrowing hydrogen reactions,^[21] we thought that it would be interesting to replace the Ru complex of Dong, Guan and coworkers^[15] with cheaper Fe-based catalysts. Additional benefit would derive from the use of Ellman's sulfinamide, which allows for easy access to chiral primary amines with wide industrial and academic applications.^[3] During the study, we serendipitously found that in the presence of a catalytic amount of acetophenone and a base, racemic 2-phenylethanol **2a** was aminated with (*R*)-(+)-*tert*-butanesulfinamide **1** in toluene, affording the chiral amine product **3a** with surprisingly good diastereoselectivity (Eq. 1, and Table S1 in SI). For example, **3a** was obtained with 70% NMR yield and >95:5 dr in the presence of acetophenone (40 mol%) and NaOH (50 mol%) (Table S1, entry 1). Screening of the reaction conditions revealed that both the ketone and base are essential (Table S1, entries 2-4); however, the amount of ketone could be decreased to 15 mol% without affecting the yield and selectivity of the reaction (Table S1, entries 5-7). This ketone-catalyzed amination appears to be reminiscent of the aldehyde-catalyzed *achiral* alkylation

reactions reported by Xu^[22], Kang^[22b] and coworkers, in which a catalytic amount of an aldehyde initiates the reaction with the catalysis sustained by aldehyde subsequently generated (*vide infra*).



Somewhat intriguingly, the reaction rate was found to be strongly affected by the choice of base, and in particular by the cation of the inorganic base, with Na⁺ being most promoting (Table S1, entries 8-11. Also see Table S5 for more details). Using NaOH of 99.99% purity (Sigma-Aldrich), which contains very low amounts of Ru, Rh, Ir, Pd and Fe (all <1 mg/kg) and Ni (<5 mg/kg) as measured by ICP-MS analysis, in conjunction with a new reaction tube and stir bar, the alkylation proceeded equally well (Table S1, entry 12), suggesting that the reaction is not catalyzed by trace transition metals and may not involve the borrowing hydrogen process aforementioned. Instead, the base may act as a catalyst for the transformation. Alkali metal cations catalyzed-transfer hydrogenation and related reactions have been reported previously; however, the role of the metal ions has been rarely studied mechanistically.^[23] Solvents appear also important, with the apolar, non-protic toluene affording the highest conversion (See Table S7 in SI for details). We also noticed that the reaction is sensitive to air and water (See Table S9 in SI for details). Thus, the substrates and solvents need to be dried for small scale reactions and a Dean-Stark apparatus is required for large scale ones (*vide infra*).

2. Scope of the amination. The substrate scope of this transition metal-free system was then examined with various alcohols with their corresponding ketones as the initial "catalyst" (15 mol%). As is shown in Figure 2, under the conditions established, the sulfinamide **3a** was obtained in 72% isolated yield and 99:1 dr as measured with HPLC. Both electron-withdrawing and -donating substituents at the *para* position on the phenyl ring of 1-phenylethanol were tolerated (Figure 2, **3b-3j**). Worth noting are the thioethers **2i** and **3i**, which could exert a poisoning effect if a metal catalyst were used. However, substrates bearing very electron-withdrawing substituents were less active, as exemplified by the *para*-CF₃-substituted **2e**, its product **3e** being obtained in a lower yield, and by the *para*-CN or NO₂-substituted 1-phenylethanols, which were essentially inactive in the reaction. This reduced activity stems probably from their poor ability in participating in hydride transfer (*vide infra*). 1-Phenylethanols bearing *meta*-substituents reacted equally well, with the sulfinamides isolated in 64-84% yield and >97:3 dr (**3k-3q**). Note that the yield of **3n** is considerably higher than that of **3e**; the latter bears a more electron-withdrawing CF₃ moiety (σ_p 0.54 vs σ_m 0.43). Moderate yields were obtained for the electron-rich as well as electron-deficient disubstituted 1-phenylethanols (**3r** vs **3s**), with good diastereoselectivities observed in all cases. The varied yields obtained are probably a reflection of the intertwining electronic effect of the substituents concerned at the *meta* vs *para*-positions of the phenyl ring. However, 1-phenylethanols with *ortho* substitution and 1-

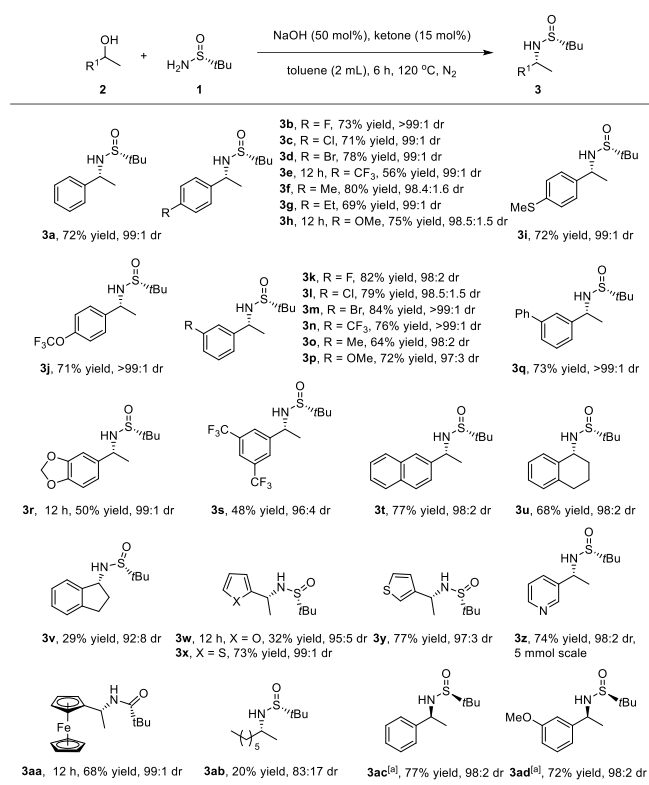


Figure 2. Scope of substrates. Unless otherwise noted, see entry 6 of Table S1 for reaction conditions. Yields of **3** were isolated yield after silica gel chromatography, and dr of **3** was determined by HPLC analysis. [a] (S)-(-)-*tert*-butanesulfinamide **1a** was used.

phenylpropan-1-ol showed only negligible activity, indicating that steric effect dominates the amination of such alcohols, which is similar to the metal-catalyzed reaction reported by Dong, Guan and co-workers.^[15]

Other aryl alcohols were also examined. 1-(Naphthalen-2-yl) ethanol is a viable substrate for the reaction (**3t**). Cyclic alcohols, such as 1-tetralol and 1-indanol also reacted, albeit with lower yield and dr for 1-indanol (**3u** vs **3v**). Whilst a low yield was observed for the oxygen-containing heterocyclic alcohol (**3w**), the thiophene alcohols afforded a high yield and dr (**3x** and **3y**). The chiral amine **3z** with a pyridine ring was obtained with good yield (74%) and dr (98 : 2) at a large scale of 5 mmol, which is a high-value synthetic intermediate (> ¥2000 rmb/g for the free amine)^[24] (see SI for detailed conditions). Pleasingly, the ferrocene moiety is tolerated, with **3aa** obtained in 68% yield and 99:1 dr, which could be used for the synthesis of chiral ligands.^[25] To access the configurationally-opposite amine products, all that is required is to replace the (*R*)-(+)-*tert*-butanesulfinamide with its (*S*)-analogue, as exemplified by **3ac** and **3ad**. A shortfall of the protocol is that it does not appear to be suitable for aliphatic alcohols, as indicated by the poor yield and diastereoselectivity obtained for octan-2-ol (**3ab**), possibly due to the much-reduced differentiation between the two alkyl groups. The metal-catalyzed amination mentioned above afford better yields^[15] and selectivity,^[13] however.

During our mechanistic studies (*vide infra*), it was found that the deuterium atom at the α -position of 1-phenylethanol remains in the chiral amine product. Chiral deuterated amines have

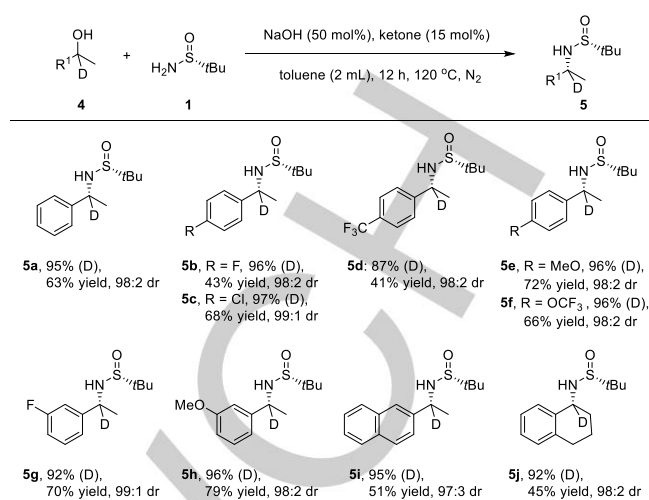


Figure 3. Scope of chiral deuterated amines. Reaction conditions: **1** (0.25 mmol), **4** (0.75 mmol), NaOH (50 mol%), and ketone (15 mol%) in solvent (2 mL) under N₂ at 120 °C for 12 h, isolated yield. Deuterium ratios were determined by ¹H NMR analysis, and drs were determined by HPLC analysis.

important pharmaceutical applications, but are difficult to prepare.^[26] Thus, we exploited the amination in question for the preparation of deuterium-labelled chiral amines. As shown in Figure 3, highly deuterated sulfinamides alongside excellent diastereoselectivities were achieved for the substrates examined (Figure 3, **5a-5j**). Since the racemic, deuterium-labelled alcohols can be readily prepared via reduction of the corresponding ketones with NaBD₄, this protocol provides an operationally-simple, transition metal-free route for the synthesis of chiral deuterium-labelled amines, which should be of particular appeal to pharmaceutical synthesis. Note that a significantly longer reaction time is required for the amination of these alcohols (Figures 2 vs 3), indicating that the turnover limiting step of the amination may involve cleavage of the α -C-H bond of the alcohol.

The practical utility of the method was further examined in larger scale reactions (Figure 4). Using a Dean-Stark apparatus to remove the by-product water, the amination could be scaled up to 10-gram scale, in the presence of only 25 mol% of NaOH at 135 °C bath temperature. Under this condition, **3f** was obtained with 68% isolated yield and 98:2 dr. The dr of **3f** could be improved to >99:1 by column chromatography. To showcase the easy access to chiral free primary amines with the protocol, the so-isolated **3f** was treated with hydrochloric acid, affording the amine **6** with >99:1 er (Figure 4).

A better procedure was later found, which is simpler and gives better yield to the free amine. During the amination, we observed that the yield of the sulfinamide product would decrease after prolonging the reaction time, as illustrated with the amination of **2t** with **1** (Figure 4, Eq. 2; also see Table S9 in the SI). Careful examination of the resulting products revealed that the amine product **3t** decomposed into **3t'** under the reaction conditions (*cf* Figure 2); but the total isolated yield of the products was high, reaching 88%. This result prompted us to propose a one-pot alkylation/hydrolysis process to access the free amines. Delightfully, when the amination of **2f** was carried out this manner, the free amine **6** was obtained in 77% yield and 98:2 er (Figure 4, Eq. 3).

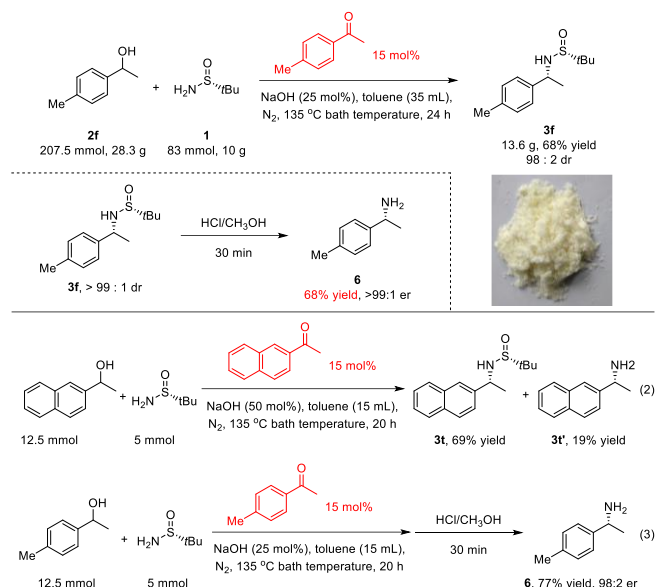


Figure 4. Gram scale reaction and one-pot alkylation/hydrolysis process. See SI for experimental details.

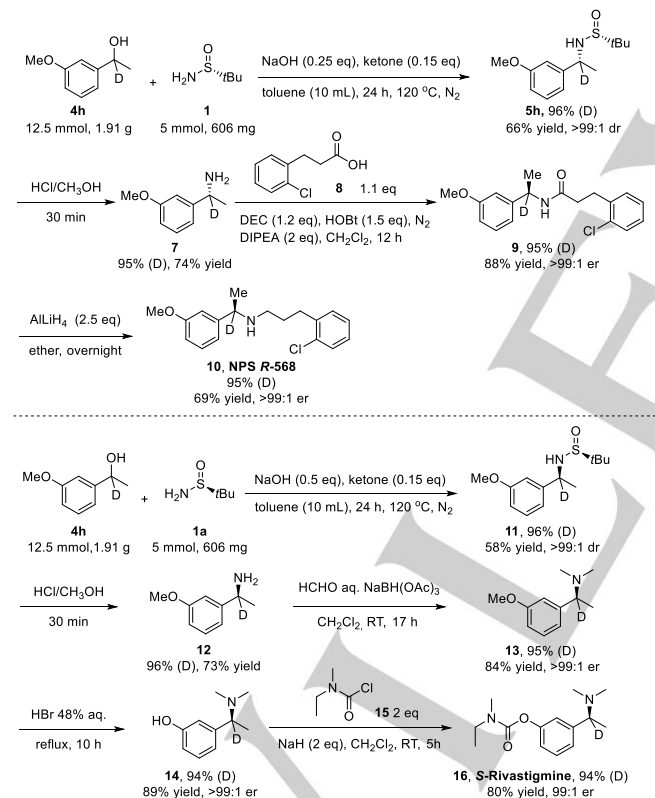


Figure 5. Stereoselective synthesis of deuterated NPS R-568 and deuterated (S)-Rivastigmine.

The practical utility of the method is also highlighted by the synthesis of deuterium-labelled drug molecules. Taking advantage of the easy availability of both enantiomers of Ellman's sulfonamide, the deuterium-labelled NPS R-568 (**10**) for treating hyperparathyroidism^[27] and (S)-Rivastigmine (**16**) for treating Alzheimer's disease^[28] were synthesized, with this newly

developed protocol as the key step (Figure 5).^[29] The coupling of **4h** (96% deuterium labelled) with **1** led to the expected chiral amine **5h** in 66% yield with >99:1 dr and full deuterium retention after column chromatography purification. Subsequent removal of the *tert*-butylsulfinyl group afforded (*R*)-**7** in 74% yield, which was reacted with **8** to yield the corresponding amide **9** in 88% yield with > 99:1 er. Finally, compound **9** was reduced to afford NPS R-568 **10** in 69% isolated yield with >99:1 er and 95% deuterium incorporation.

Starting with (S)-(+)-*tert*-butanesulfonamide **1a**, the (S)-enantiomer **12** was obtained via the same procedure as that for **7**. *N*-Methylation of **12** afforded **13** in 84% yield with >99:1 er and 95% deuterium incorporation. Cleavage of the O-methyl group followed by ester formation gave the deuterated (S)-rivastigmine **16** in 80% yield with 99:1 er and 94% deuterium incorporation (Figure 5).

3. Experimental probing of the reaction mechanism.

While the scope of the protocol was studied, the mechanism of the asymmetric amination was also considered. The high deuterium ratios observed in the amine products presented above are supportive of the assertion that the amination in question does not involve transition metal catalysis, which would promote easy H/D exchange. As both the ketone and the base are indispensable for the reaction, we thought that the reaction might proceed via a mechanism similar to that proposed for the aldehyde-catalyzed achiral amination of alcohols mentioned above.^[22] Thus, taking the amination of 2-phenylethanol **2a** with (*R*)-(+)-*tert*-butanesulfonamide **1** as an example, the initially-introduced catalytic ketone would react reversibly with **1** to form an imine *R*-**17**, the reduction of which by the sodium salt of the racemic **2a** would then afford the diastereomerically pure **3a** while releasing one new ketone molecule and the base used in forming the alkoxide from **2a** (Figure 6). The resulting ketone would start a new cycle of amination, thus ensuring that only catalytic ketone is necessary to initiate the reaction. This can be viewed as a hydrogen autotransfer process,^[22d] but involving no hydrogen borrowing.

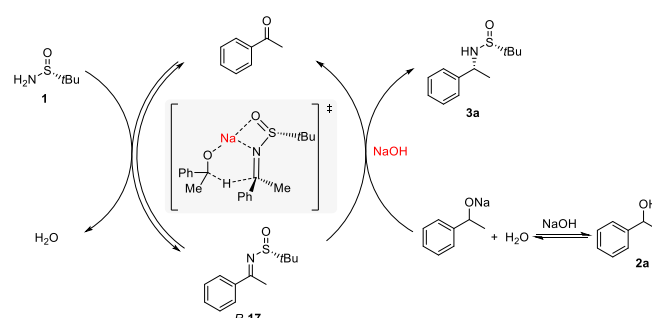


Figure 6. Proposed mechanism for the ketone-catalyzed *N*-alkylation.

A highly interesting question is how the hydrogen is transferred between the alcohol and the imine and hence how the diastereoselectivity of the reaction is determined. Considering the well-known MPV mechanism for carbonyl reduction with alcohols^[30] and the proposed mechanisms for nucleophilic addition to sulfinimines,^[1b, 20e] the hydrogen transfer in question may occur via a transition state as depicted in Figure

6, involving the Lewis acidic sodium cation bridging the alkoxide and sulfinimine while the hydrogen of the former being transferred. However, few mechanistic studies of such transition metal-free reactions have been reported and in particular, little is known of the mechanism of the hydrogen transfer step therein.^[22, 31]

Subsequently, we carried out a series of experiments and DFT calculations, in the hope to gain insight into the mechanism of the asymmetric amination. Toward this end, the imine **R-17** was first synthesized. Under the conditions established but in a short reaction time of 1 h, **R-17** was indeed reduced by **2a**, affording the amine **3a** in 64% yield, thus supporting the intermediary of an imine in the amination (Eq. S1 in Section 8 of SI). Replacing **2a** with the deuterium-labelled **4a** resulted in a significantly lower yield of **5a**. This is suggestive of the turnover rate of the amination being limited by the step of hydrogen transfer, which involves C-H cleavage. A kinetic isotope effect is indeed seen in the overall amination reaction (Figures 2 vs 3, and Eq. S2 in Section 8 of SI), although it is less pronounced as indicated in Eq. S1.^[32]

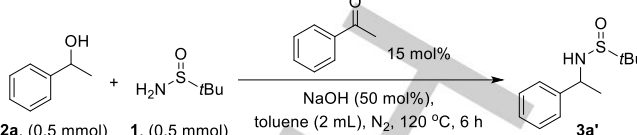
If the reduction proceeds via the MPV type mechanism, the cation of the base would be expected to influence the reaction rate and/or selectivity. Indeed, Table S1 shows (Table S1, entries 6 and 8-11) that sodium is the best cation for the reaction under comparable conditions. The effect of the sodium cation on the reaction is further seen in the amination when a crown ether is present. Thus, as shown in Figure S1, with the introduction of increasing amount of the crown ether 15-crown-5, which has a high affinity for Na⁺,^[33] the amination of **2a** with **1** slowed down progressively. *This indicates strongly that the sodium cation is involved in the rate-limiting step of the overall reaction, presumably in an MPV transition state as shown in Figure 6.*

Further insight into the diastereoselectivity-determining step of hydrogen transfer was gained by examining the effect of the configuration of the alcohol on the amination. As shown in Table 1, reacting the racemic **2a** with an equal amount of **R-1** and **S-1**, respectively, afforded a similar yield of amine, but with opposite configuration (Table 1, entries 1 and 2). Note that the er of the unreacted **2a** was approximately equal, indicating that **1** does not preferentially aminate one of the enantiomers of **2a**, leading, consequently, to no kinetic resolution of the alcohol. More interestingly, the same product (**R,R**)-**3a** was obtained when either **R-2a** or **S-2a** was reacted with **R-1** (Table 1, entries 3 and 4). Similar observations were made when the enantiomerically pure alcohols were aminated with **S-1** (Table 1, entries 5 and 6).

The most significant conclusion that could be drawn from the above results is that *the configuration of the amine product is determined by the configuration of the sulfinamide 1, regardless of that of the alcohol.* A possible explanation is that both **R-2a** and **S-2a** could react with the imine intermediate generated from either **R-1** or **S-1**, with only slight difference in rates. This proposition finds support in DFT calculations (*vide infra*).

4. Computational study of the hydride transfer step. To probe the feasibility and the structure of a MPV type transition state, DFT calculations were carried out on the step of hydrogen transfer shown in Figure 6. Note that in addition to the **R/S** configurational isomerism on the sulfoxide moiety, the imine substrate **17** can exist as a *trans* and *cis* isomer, and calculations showed that the absolute free energy of the *cis*

Table 1. The effect of the configuration of alcohol and amine substrates on the selectivity of the amination.



Entry ^[a]	Config. of 2a	Config. of 1	er of unreacted 2a (R:S) ^[b]	Config. of 3a ^[c]
1	rac	<i>R</i>	53:47	<i>R,R</i>
2	rac	<i>S</i>	54:46	<i>S,S</i>
3	<i>R</i>	<i>R</i>	97:3	<i>R,R</i>
4	<i>S</i>	<i>R</i>	7:93	<i>R,R</i>
5	<i>R</i>	<i>S</i>	95:5	<i>S,S</i>
6	<i>S</i>	<i>S</i>	7:93	<i>S,S</i>

[a] Reaction conditions: **1** (0.5 mmol), **2a** (0.5 mmol), base (50 mol%), and ketone (15 mol%), toluene (2 mL), under N₂ at 120 °C for 6 h. [b] Determined by HPLC analysis. [c] Absolute configuration determined by comparison with literature.

isomer of **17** is 3.5 kcal/mol higher than the *trans* isomer. It is obvious that the *trans* isomer is more stable, which is consistent with the experimental results that only the *trans* imine was observed for the isolated imine **R-17**. For this reason, our discussion is focused on reactions of this imine.

Figure 7 shows the free energy profile of the hydrogenation of the imine *trans* **R-17** (denoted as **R-17**) with the sodium alkoxide formed from **2a** to give the amido adduct **19**, hydrolysis of which affords the chiral amine. The hydrogenation is exergonic, as may be expected. There are four possible pathways when **R-17** interacts with the alkoxide, considering that the alkoxide exists in the form of *R*- and *S*-alkoxide, each of which can approach the imine on its *re* or *si* face. As can be seen, when the *S*-alkoxide reacts with **R-17** on its *si* face (denoted as the *R-S-si* route), an intermediate adduct *R-S-si-18* is formed exergonically, in which the Na ion is coordinated by both the O and N atoms of the imine. Similarly, the reaction of the *R*-alkoxide yields *R-R-si-18*. The reactions on the *re* face give rise to *R-S-re-18* and *R-R-re-18*. With the Na interacting only with the nitrogen atom, these two adducts are less stable by 7.6 and 7.2 kcal/mol than *R-S-si-18* and *R-R-si-18*, respectively. On going from **18** to the amide **19**, the hydridic hydrogen of the alkoxide is transferred to the carbon atom of the imine moiety via the transition state **TS18-19**. The free energy barrier of the hydride transfer step is lower along the *R-R-si* and *R-S-si* pathways, at 5.6 and 4.7 kcal/mol, respectively. In contrast, the reactions along the *R-R-re* and *R-S-re* pathways are of considerably higher barrier, at 9.6 and 9.4 kcal/mol, respectively, and would lead to an amine with reversed configuration at the α carbon. Thus, with either the *R* or *S* alkoxide, the hydrogen addition occurs on the *si* face of the *R*-sulfinimine **17**, affording the same *R,R*-amido adduct **19**.

A closer look into the various possible species during the hydride transfer is shown in Figure S2. We actually explored twelve possible reaction pathways for the attack of the alkoxide

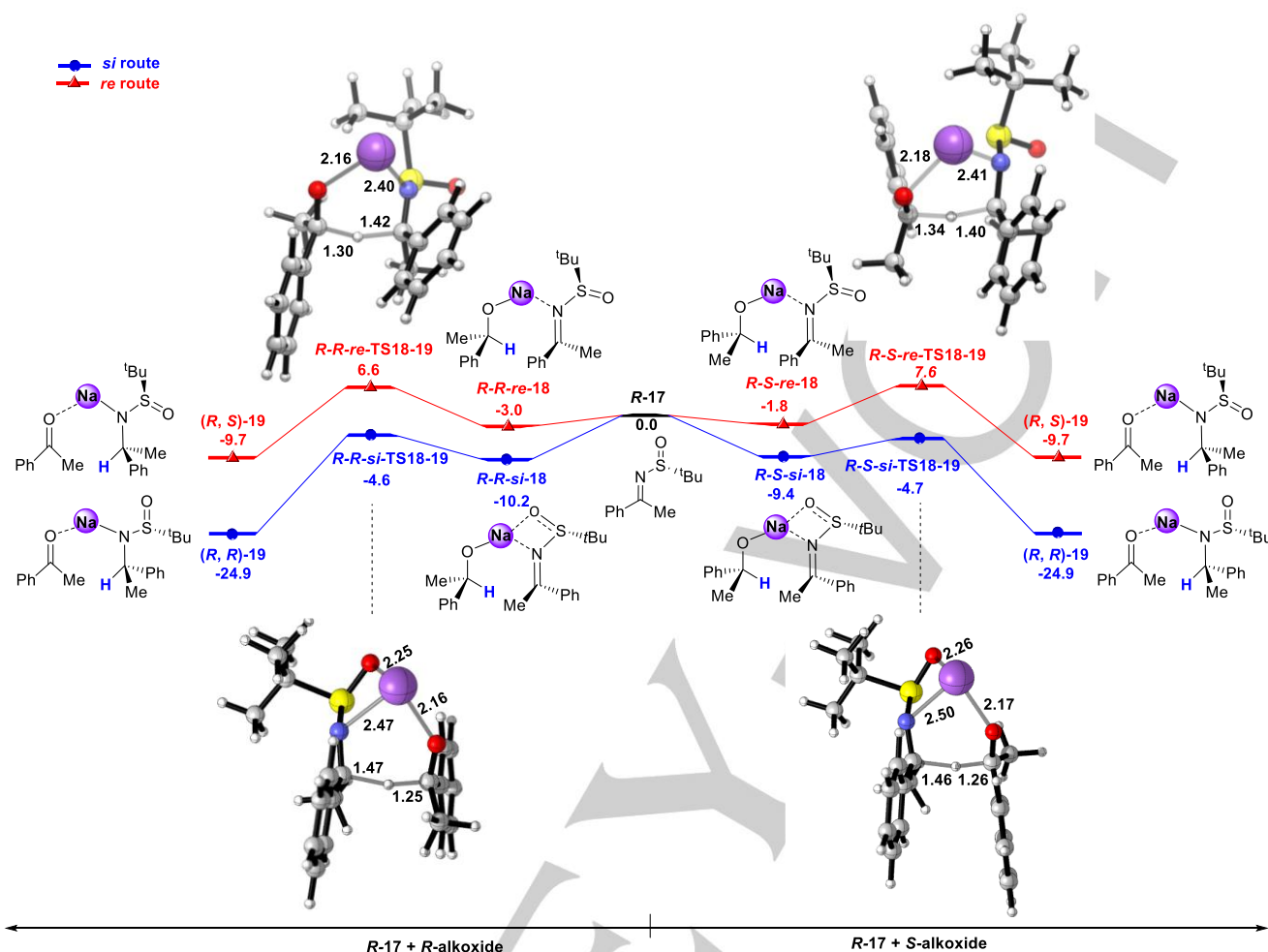


Figure 7. Computed structures and free Gibbs energies of transition states and intermediates in the hydrogenation of imine *R*-17 with the sodium alkoxide formed from **2a**. All energies are denoted in kcal/mol, and interatomic distances are shown in angstroms.

at the *R*-17, including those of relatively low energies described above (see Section 9 in SI for more details). Three reaction modes were identified, which could lead to productive transition states. Mode 1, displaying a [6+4] ring structure, corresponds to the attack at *R*-17 along the *R*-*R*-*si* and *R*-*S*-*si* pathways, while mode 2, featuring an eight-membered ring, is only found in the *R*-*S*-*si* route involving no chelating interaction with the Na^+ . Similarly, mode 3, with a six-membered ring structure, corresponds to the *R*-*R*-*re* and *R*-*S*-*re* pathways for *R*-17 and features no chelating interaction with the Na^+ . The figure shows that only when both the $\text{Na}^6\text{-N}^4$ and $\text{Na}^6\text{-O}^5$ distances fall within a bonding distance can the energy barrier of the hydride transfer be lowered considerably. Furthermore, the C^2 atom in mode 1 carries more positive charge compared with that in mode 2 and 3 (See Figure S3 in SI), which should facilitate the hydride transfer.

Important insight into the key step of the amination can be gleaned from the calculations. Thus, the differences in relative energy by over 11 kcal/mol between the four transition states of hydride transfer (Figure 7) suggest that for the imine *R*-17, hydride transfer occurs on its *si* face to afford a *R*,*R*-product, and this is the case regardless of the configuration of the

attacking alkoxide, both of which are consistent with the experimental observations (Table 1). By analogy, the imine *S*-17 will furnish the *S*,*S*-amine regardless of the attacking alkoxide (See Figure S4 in SI). Clearly, it is the configuration of the starting sulfonamide **1** that determines that of the amine product in the amination under question, and this is made possible by the Lewis acidic Na^+ cation being able to bond with both the *N* and *O* atoms of the sulfinimine moiety along the low-energy pathway. It is also obvious that the hydride transfer step is the chirality-determining step.

Similar observations concerning the cations of bases were also made for base-catalyzed reduction of ketones via the MPV mechanism.^[23e] However, the reason for the cation effect remains unclear. We thus further compared the transition states of the rate-limiting hydride transfer step involving different cations computationally. As shown in Figure S5 (See SI), on replacing the Na atom with hydrogen in the structure of **18**, the free energy barrier of the hydride transfer from the *S*-alkoxide to *R*-17 rises to 34.0 kcal/mol along the *R*-*S*-*si* pathway, corroborating the experimental observation that without using a base, the amination is infeasible under the conditions employed. The instability of the transition state must at least partly stem

from the hydrogen being unable to interact with the nitrogen of **R-17**. Similarly, replacing the Na with a Li atom in **18** also raises the energy barrier, albeit much less significantly, to 7.4 kcal/mol. This is again in line with the observation that a sodium-containing base gives faster amination. Note that whilst like Na, Li bonds with both the nitrogen and oxygen atoms, the C² atom in **R-S-si-TS18-19-Na** carries more positive charge than in **R-S-si-TS18-19-Li**, and in the case of **R-S-si-TS18-19-H**, the C² atom is even slightly negatively charged, suggesting the C=N bond in **R-S-si-TS18-19-Na** to be most electrophilic and thus more reactive toward the hydride donor. Cation bonding with the O or N atoms or both has often been invoked in the transition state of nucleophilic addition to sulfinimines.^[34] However, it appears to us that there has been no reported study of whether or how the cation may affect the reaction thus far.

Conclusion

We have developed a practical, convenient, and transition-metal-free method for the synthesis of α -chiral amines via alkylation of amines with alcohols. Using cheap, readily available racemic alcohols and Ellman's chiral sulfinamide, this highly diastereoselective protocol is easy to operate and scale-up, while avoiding transition-metal contamination, thus providing an attractive route for the synthesis of α -chiral primary amines for the pharmaceutical industry. Chiral deuterium-labelled amines, including chiral deuterated drugs, could be readily synthesized with high deuterium incorporation and optical purity. Mechanistic studies including DFT calculations showed that this hydrogen autotransfer reaction is initiated by a ketone catalyst and the cation of the base plays a critical role in the hydride transfer step, bonding with both the nitrogen and oxygen atoms of the intermediate sulfinimine in the transition state. Of further interest is the finding that the configuration of amine products is determined solely by the configuration of the chiral *tert*-butanesulfinamide regardless of that of the alcohols, which is rationalized by DFT calculations.

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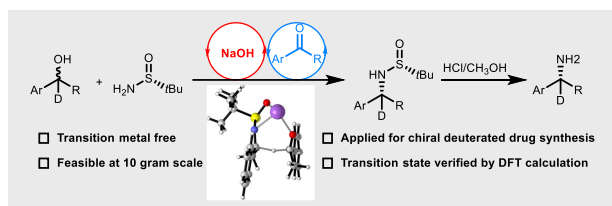
Keywords: chiral amine • alcohol • *tert*-butanesulfinamide • alkylation • deuterium drug

- [1] a) S. Kobayashi, H. Ishitani, *Chem. Rev.* **1999**, *99*, 1069-1094; b) J. A. Ellman, T. D. Owens, T. P. Tang, *Acc. Chem. Res.* **2002**, *35*, 984-995; c) S. Gomez, J. A. Peters, T. Maschmeyer, *Adv. Synth. Catal.* **2002**, *344*, 1037-1057; d) M. Besson, C. Pinel, *Top. Catal.* **2003**, *25*, 43-61; e) H.-U. Blaser, C. Malan, B. Pugin, F. Spindler, H. Steiner, M. Studer, *Adv. Synth. Catal.* **2003**, *345*, 103-151; f) J. A. Ellman, *Pure Appl. Chem.* **2003**, *75*, 39-46; g) P. Kukula, R. Prins, *Top. Catal.* **2003**, *25*, 29-42; h) G. K. Friestad, *Eur. J. Org. Chem.* **2005**, *2005*, 3157-3172; i) V. I. Tararov, A. Börner, *Synlett* **2005**, *2005*, 203-211; j) A. F. Abdel-Magid, S. J. Mehrman, *Org. Proc. Res. Dev.* **2006**, *10*, 971-1031; k) D. Morton, R. A. Stockman, *Tetrahedron* **2006**, *62*, 8869-8905; l) P. V. Ramachandran, T. E. Burghardt, *Pure Appl. Chem.* **2006**, *78*, 1397-1406; m) G. K. Friestad, A. K. Mathies, *Tetrahedron* **2007**, *63*, 2541-2569; n) J.-C. Kizirian, *Chem. Rev.* **2007**, *108*, 140-205; o) A. J. Minnaard, B. L. Feringa, L. Lefort, J. G. de Vries, *Acc. Chem. Res.* **2007**, *40*, 1267-1277; p) M. Petrini, E. Torregiani, *Synthesis* **2007**, *2007*, 159-186; q) E. Skucas, M.-Y. Ngai, V. Komanduri, M. J. Krische, *Acc. Chem. Res.* **2007**, *40*, 1394-1401; r) S.-L. You, *Chem. Asian J.* **2007**, *2*, 820-827; s) H. U. Blaser, S. Felix, *Enantioselective Hydrogenation of C=N Functions and Enamines*, Wiley-VCH **2008**; t) T. E. Müller, K. C. Hultsch, M. Yus, F. Foubelo, M. Tada, *Chem. Rev.* **2008**, *108*, 3795-3892; u) R. P. Tripathi, S. S. Verma, J. Pandey, V. K. Tiwari, *Curr. Org. Chem.* **2008**, *12*, 1093-1115; v) T. C. Nugent, M. El-Shazly, *Adv. Synth. Catal.* **2010**, *352*, 753-819; w) C. Wang, B. Villa-Marcos, J. Xiao, *Chem. Commun.* **2011**, *47*, 9773-9785; x) J.-H. Xie, S.-F. Zhu, Q.-L. Zhou, *Chem. Soc. Rev.* **2012**, *41*, 4126-4139.
- [2] a) H.-U. Blaser, C. Malan, B. Pugin, F. Spindler, H. Steiner, M. Studer, *Adv. Synth. Catal.* **2003**, *345*, 103-151; b) N. Fleury-Brégeot, V. de la Fuente, S. Castillón, C. Claver, *Chemcatchem* **2010**, *2*, 1346-1371; c) J.-H. Xie, S.-F. Zhu, Q.-L. Zhou, *Chem. Rev.* **2011**, *111*, 1713-1760; d) W. Li, X. Zhang, in *Stereoselective Formation of Amines* (Eds.: W. Li, X. Zhang), Springer Berlin Heidelberg, Berlin, Heidelberg, **2014**, pp. 103-144; e) C. Wang, J. Xiao, in *Stereoselective Formation of Amines* (Eds.: W. Li, X. Zhang), Springer Berlin Heidelberg, Berlin, Heidelberg, **2014**, pp. 261-282.
- [3] a) R. Kadyrov, T. H. Riermeier, *Angew. Chem. Int. Ed.* **2003**, *42*, 5472-5474; b) G. Hou, F. Gosselin, W. Li, J. C. McWilliams, Y. Sun, M. Weisel, P. D. O'Shea, C.-Y. Chen, I. W. Davies, X. Zhang, *J. Am. Chem. Soc.* **2009**, *131*, 9882-9883; c) D. Steinhuebel, Y. Sun, K. Matsumura, N. Sayo, T. Saito, *J. Am. Chem. Soc.* **2009**, *131*, 11316-11317; d) G. Hou, W. Li, M. Ma, X. Zhang, X. Zhang, *J. Am. Chem. Soc.* **2010**, *132*, 12844-12846; e) G. Hou, R. Tao, Y. Sun, X. Zhang, F. Gosselin, *J. Am. Chem. Soc.* **2010**, *132*, 2124-2125; f) Q. Zhao, J. Wen, R. Tan, K. Huang, P. Metola, R. Wang, E. V. Anslyn, X. Zhang, *Angew. Chem. Int. Ed.* **2014**, *53*, 8467-8470; g) J. Gallardo-Donaire, M. Hermesen, J. Wysocki, M. Ernst, F. Rominger, O. Trapp, A. S. K. Hashmi, A. Schäfer, P. Comba, T. Schaub, *J. Am. Chem. Soc.* **2018**, *140*, 355-361; h) X. Tan, S. Gao, W. Zeng, S. Xin, Q. Yin, X. Zhang, *J. Am. Chem. Soc.* **2018**, *140*, 2024-2027.
- [4] a) T. Vries, H. Wynberg, E. van Echten, J. Koek, W. ten Hoeve, R. M. Kellogg, Q. B. Broxterman, A. Minnaard, B. Kaptein, S. van der Sluis, L. Hulshof, J. Kooistra, *Angew. Chem. Int. Ed.* **1998**, *37*, 2349-2354; b) M. Breuer, K. Ditrach, T. Habicher, B. Hauer, M. Keßeler, R. Stürmer, T. Zelinski, *Angew. Chem. Int. Ed.* **2004**, *43*, 788-824.
- [5] a) S. M. A. De Wildeman, T. Sonke, H. E. Schoemaker, O. May, *Acc. Chem. Res.* **2007**, *40*, 1260-1266; b) M. Höhne, U. T. Bornscheuer, *Chemcatchem* **2009**, *1*, 42-51; c) C. K. Savile, J. M. Janey, E. C. Mundorff, J. C. Moore, S. Tam, W. R. Jarvis, J. C. Colbeck, A. Krebber, F. J. Fleitz, J. Brands, P. N. Devine, G. W. Huisman, G. J. Hughes, *Science* **2010**, *329*, 305-309; d) A. A. Desai, *Angew. Chem. Int. Ed.* **2011**, *50*, 1974-1976; e) M. Hall, A. S. Bommarius, *Chem. Rev.* **2011**, *111*, 4088-4110; f) F. Hollmann, I. W. C. E. Arends, D. Holtmann, *Green Chem.* **2011**, *13*, 2285-2314; g) E. Ricca, B. Brucher, J. H. Schrittwieser, *Adv. Synth. Catal.* **2011**, *353*, 2239-2262; h) F. Guo, P. Berglund, *Green Chem.* **2017**, *19*, 333-360; i) I. Slabu, J. L. Galman, R. C. Lloyd, N. J. Turner, *ACS Catal.* **2017**, *7*, 8263-8284; j) S. A. Kelly, S. Pohle, S. Wharry, S. Mix, C. C. R. Allen, T. S. Moody, B. F. Gilmore, *Chem. Rev.* **2018**, *118*, 349-367; k) J. H. Schrittwieser, S. Velikogne, M. Hall, W. Kroutil, *Chem. Rev.* **2018**, *118*, 270-348.
- [6] a) W. Tang, X. Zhang, *Chem. Rev.* **2003**, *103*, 3029-3070; b) A. Fabrello, A. Bachelier, M. Urrutigoity, P. Kalck, *Coord. Chem. Rev.* **2010**, *254*, 273-287; c) A. Bartoszewicz, N. Ahlsten, B. Martin-Matute, *Chem. Eur. J.* **2013**, *19*, 7274-7302; d) Q.-A. Chen, Z.-S. Ye, Y. Duan, Y.-G. Zhou, *Chem. Soc. Rev.* **2013**, *42*, 497-511; e) P. Etayo, A. Vidal-Ferran, *Chem. Soc. Rev.* **2013**, *42*, 728-754; f) K. H. Hopmann, A.

- Bayer, *Coord. Chem. Rev.* **2014**, 268, 59-82; g) D. Dario, G. A. Carmela, *Curr. Org. Chem.* **2016**, 20, 2552-2590; h) P.-G. Echeverria, T. Ayad, P. Phansavath, V. Ratovelomanana-Vidal, *Synthesis* **2016**, 48, 2523-2539; i) *Asymmetric Catalysis on Industrial Scale: Challenges, Approaches and Solutions* (Eds.: H. U. Blaser, H. J. Federsell), 2nd ed., Wiley-VCH, Weinheim, **2010**.
- [7] H. U. Blaser, H. P. Buser, K. Loers, R. Hanreich, H. P. Jalett, E. Jelsch, B. Pugin, H. D. Schneider, F. Spindler, A. Wagmann, *Chimia* **1999**, 53, 275-280.
- [8] a) M. H. S. A. Hamid, P. A. Slatford, J. M. J. Williams, *Adv. Synth. Catal.* **2007**, 349, 1555-1575; b) G. Guillena, D. J. Ramón, M. Yus, *Chem. Rev.* **2009**, 110, 1611-1641; c) T. D. Nixon, M. K. Whittlesey, J. M. J. Williams, *Dalton Trans.* **2009**, 753-762; d) G. E. Dobereiner, R. H. Crabtree, *Chem. Rev.* **2010**, 110, 681-703; e) A. J. A. Watson, J. M. J. Williams, *Science* **2010**, 329, 635-636; f) J. Choi, A. H. R. MacArthur, M. Brookhart, A. S. Goldman, *Chem. Rev.* **2011**, 111, 1761-1779; g) A. C. Marr, *Catal. Sci. Technol.* **2012**, 2, 279-287; h) C. Gunanathan, D. Milstein, *Science* **2013**, 341, 1229712; i) S. Pan, T. Shibata, *ACS Catal.* **2013**, 3, 704-712; j) Y. Obara, *ACS Catal.* **2014**, 4, 3972-3981; k) A. Nandakumar, S. P. Midya, V. G. Landge, E. Balaraman, *Angew. Chem. Int. Ed.* **2015**, 54, 11022-11034; l) S. Werkmeister, J. Neumann, K. Junge, M. Beller, *Chem. Eur. J.* **2015**, 21, 12226-12250; m) Q. Yang, Q. Wang, Z. Yu, *Chem. Soc. Rev.* **2015**, 44, 2305-2329; n) Y. Nakamura, A. E. Putra, Y. Oe, T. Ohta, *J. Syn. Org. Chem. Jpn.* **2016**, 74, 1182-1193; o) R. H. Crabtree, *Chem. Rev.* **2017**, 117, 9228-9246; p) C. Wang, J. Xiao, *Chem. Commun.* **2017**, 53, 3399-3411.
- [9] K.-i. Fujita, T. Fujii, R. Yamaguchi, *Org. Lett.* **2004**, 6, 3525-3528.
- [10] L. Miao, S. C. DiMaggio, H. Shu, M. L. Trudell, *Org. Lett.* **2009**, 11, 1579-1582.
- [11] M. H. S. A. Hamid, C. L. Allen, G. W. Lamb, A. C. Maxwell, H. C. Maytum, A. J. A. Watson, J. M. J. Williams, *J. Am. Chem. Soc.* **2009**, 131, 1766-1774.
- [12] A. Eka Putra, Y. Oe, T. Ohta, *Eur. J. Org. Chem.* **2013**, 2013, 6146-6151.
- [13] Y. Zhang, C.-S. Lim, D. S. B. Sim, H.-J. Pan, Y. Zhao, *Angew. Chem. Int. Ed.* **2014**, 53, 1399-1403.
- [14] a) Z.-Q. Rong, Y. Zhang, R. H. B. Chua, H.-J. Pan, Y. Zhao, *J. Am. Chem. Soc.* **2015**, 137, 4944-4947; b) C. S. Lim, T. T. Quach, Y. Zhao, *Angew. Chem. Int. Ed.* **2017**, 56, 7176-7180; c) L.-C. Yang, Y.-N. Wang, Y. Zhang, Y. Zhao, *ACS Catal.* **2017**, 7, 93-97; d) S. Tribedi, Christopher M. Hadad, R. B. Sunoj, *Chem Sci.* **2018**, 9, 6126-6133.
- [15] N. J. Oldenhuis, V. M. Dong, Z. Guan, *J. Am. Chem. Soc.* **2014**, 136, 12548-12551.
- [16] M. Peña-López, H. Neumann, M. Beller, *Angew. Chem. Int. Ed.* **2016**, 55, 7826-7830.
- [17] P. Yang, C. Zhang, Y. Ma, C. Zhang, A. Li, B. Tang, J. S. Zhou, *Angew. Chem. Int. Ed.* **2017**, 56, 14702-14706.
- [18] M. Jacolot, S. Moebis-Sanchez, F. Popowycz, *J. Org. Chem.* **2018**, 83, 9456-9463.
- [19] M. Chen, Y. Han, D. Ma, Y. Wang, Z. Lai, J. Sun, *Chin. J. Chem.* **2018**, 36, 587-593. This is an elegant example of organocatalytic *N*-alkylation with alcohols via S_N1 mechanism.
- [20] a) G. Liu, D. A. Cogan, J. A. Ellman, *J. Am. Chem. Soc.* **1997**, 119, 9913-9914; b) D. A. Cogan, G. Liu, K. Kim, B. J. Backes, J. A. Ellman, *J. Am. Chem. Soc.* **1998**, 120, 8011-8019; c) D. J. Weix, J. A. Ellman, *Org. Lett.* **2003**, 5, 1317-1320; d) M. Wakayama, J. A. Ellman, *J. Org. Chem.* **2009**, 74, 2646-2650; e) M. T. Robak, M. A. Herbage, J. A. Ellman, *Chem. Rev.* **2010**, 110, 3600-3740.
- [21] a) Q. Zou, C. Wang, J. Smith, D. Xue, J. Xiao, *Chem. Eur. J.* **2015**, 21, 9656-9661; b) J. Cheng, M. Zhu, C. Wang, J. Li, X. Jiang, Y. Wei, W. Tang, D. Xue, J. Xiao, *Chem. Sci.* **2016**, 7, 4428-4434; c) X. Jiang, W. Tang, D. Xue, J. Xiao, C. Wang, *ACS Catal.* **2017**, 7, 1831-1835; d) J. Li, Y. Liu, W. Tang, D. Xue, C. Li, J. Xiao, C. Wang, *Chem. Eur. J.* **2017**, 23, 14445-14449; e) W. Ma, S. Cui, H. Sun, W. Tang, D. Xue, C. Li, J. Fan, J. Xiao, C. Wang, *Chem. Eur. J.* **2018**, 24, 13118-13123.
- [22] a) Q. Xu, Q. Li, X. Zhu, J. Chen, *Adv. Synth. Catal.* **2013**, 355, 73-80; b) Q.-Q. Li, Z.-F. Xiao, C.-Z. Yao, H.-X. Zheng, Y.-B. Kang, *Org. Lett.* **2015**, 17, 5328-5331; c) X. Li, S. Li, Q. Li, X. Dong, Y. Li, X. Yu, Q. Xu, *Tetrahedron* **2016**, 72, 264-272; d) X. Ma, C. Su, Q. Xu, *Top. Curr. Chem.* **2016**, 374, 27.
- [23] a) W. v. E. Doering, T. C. Aschner, *J. Am. Chem. Soc.* **1953**, 75, 393-397; b) R. L. Chowdhury, J. E. Backvall, *J. Chem. Soc. Chem. Commun.* **1991**, 1063-1064; c) J. R. Miecznikowski, R. H. Crabtree, *Organometallics* **2004**, 23, 629-631; d) J. Ekström, J. Wettergren, H. Adolfsson, *Adv. Synth. Catal.* **2007**, 349, 1609-1613; e) A. Ouali, J.-P. Majoral, A.-M. Caminade, M. Taillefer, *ChemCatChem* **2009**, 1, 504-509; f) V. Polshettiwar, R. S. Vama, *Green Chem.* **2009**, 11, 1313-1316; g) L. J. Allen, R. H. Crabtree, *Green Chem.* **2010**, 12, 1362-1364; h) R. Radhakrishnan, D. M. Do, S. Jaenicke, Y. Sasson, G.-K. Chuah, *ACS Catal.* **2011**, 1, 1631-1636; i) Y.-F. Liang, X.-F. Zhou, S.-Y. Tang, Y.-B. Huang, Y.-S. Feng, H.-J. Xu, *RSC Adv.* **2013**, 3, 7739-7742; j) J. Ballester, A.-M. Caminade, J.-P. Majoral, M. Taillefer, A. Ouali, *Catal. Commun.* **2014**, 47, 58-62; k) D. Wang, C. Deraedt, J. Ruiz, D. Astruc, *J. Mol. Catal. A: Chem.* **2015**, 400, 14-21; l) H. Bauer, M. Alonso, C. Färber, H. Elsen, J. Pahl, A. Causero, G. Ballmann, F. De Proft, S. Harder, *Nat. Catal.* **2018**, 1, 40-47; m) M. Xu, A. R. Jupp, Z.-W. Qu, D. W. Stephan, *Angew. Chem. Int. Ed.* **2018**, 57, 11050-11054; n) D. C. Elliott, A. Marti, P. Mauleón, A. Pfaltz, *Chem. Eur. J.* **2019**, 25, 1918-1922.
- [24] The price for the hydrochloride salt of **3z** is 8536 rmb/g from J & K Scientific.
- [25] a) T. J. Colacot, *Chem. Rev.* **2003**, 103, 3101-3118; b) R. Gómez Arrayás, A. Adrio, J. C. Carretero, *Angew. Chem. Int. Ed.* **2006**, 45, 7674-7715.
- [26] a) L. Neubert, D. Michalik, S. Bähn, S. Imm, H. Neumann, J. Atzrodt, V. Derdau, W. Holla, M. Beller, *J. Am. Chem. Soc.* **2012**, 134, 12239-12244; b) T. Sakamoto, K. Mori, T. Akiyama, *Org. Lett.* **2012**, 14, 3312-3315; c) W. Bai, K.-H. Lee, S. K. S. Tse, K. W. Chan, Z. Lin, G. Jia, *Organometallics* **2015**, 34, 3686-3698; d) C. Taglang, L. M. Martínez-Prieto, I. del Rosal, L. Maron, R. Poteau, K. Philippot, B. Chaudret, S. Perato, A. Sam Lone, C. Puente, C. Dugave, B. Rousseau, G. Pieters, *Angew. Chem. Int. Ed.* **2015**, 54, 10474-10477; e) L. V. A. Hale, N. K. Szymczak, *J. Am. Chem. Soc.* **2016**, 138, 13489-13492; f) Y. Y. Loh, K. Nagao, A. J. Hoover, D. Hesk, N. R. Rivera, S. L. Colletti, I. W. Davies, D. W. C. MacMillan, *Science* **2017**, 358, 1182-1187; g) W. N. Palmer, P. J. Chirik, *ACS Catal.* **2017**, 7, 5674-5678; h) M. Valero, R. Weck, S. Güssregen, J. Atzrodt, V. Derdau, *Angew. Chem. Int. Ed.* **2018**, 57, 8159-8163; i) H. Yang, P. G. Dormer, N. R. Rivera, A. J. Hoover, *Angew. Chem. Int. Ed.* **2018**, 57, 1883-1887.
- [27] R. Rao, M. P. Shewalkar, R. Nandipati, J. S. Yadav, M. Khagga, D. B. Shinde, *Synth. Commun.* **2012**, 42, 589-598.
- [28] a) C. M. Spencer, S. Noble, *Drugs & Aging* **1998**, 13, 391-411; b) P.-C. Yan, G.-L. Zhu, J.-H. Xie, X.-D. Zhang, Q.-L. Zhou, Y.-Q. Li, W.-H. Shen, D.-Q. Che, *Org. Proc. Res. Dev.* **2013**, 17, 307-312.
- [29] a) V. N. Wakchaure, P. S. J. Kaib, M. Leutzsch, B. List, *Angew. Chem. Int. Ed.* **2015**, 54, 11852-11856; b) A. Chelouan, R. Recio, L. G. Borrego, E. Álvarez, N. Khair, I. Fernández, *Org. Lett.* **2016**, 18, 3258-3261.
- [30] a) C. F. de Graauw, J. A. Peters, H. van Bakkum, J. Huskens, *Synthesis* **1994**, 1994, 1007-1017; b) K. Nishide, M. Node, *Chirality* **2002**, 14, 759-767; c) J. S. Cha, *Org. Proc. Res. Dev.* **2006**, 10, 1032-1053.
- [31] Q. Xu, J. Chen, H. Tian, X. Yuan, S. Li, C. Zhou, J. Liu, *Angew. Chem. Int. Ed.* **2014**, 53, 225-229.
- [32] This weakened effect may be due to a preequilibrium between the ketone/amine and imine, preceding the turnover limiting reduction of the imine by the alkoxide.
- [33] T. Yasuyuki, K. Koji, I. Yoshihisa, H. Tadao, *Bull. Chem. Soc. Jpn.* **1988**, 61, 627-632.
- [34] T. P. Tang, J. A. Ellman, *J. Org. Chem.* **1999**, 64, 12-13.

Entry for the Table of Contents

RESEARCH ARTICLE



An asymmetric hydrogen autotransfer reaction has been found, which allows for the practical synthesis of α -chiral amines via alkylation of amines with alcohols. Under the co-catalysis of a ketone and NaOH, racemic secondary alcohols reacted with Ellman's chiral *tert*-butanesulfinamide, affording chiral amines with high diastereoselectivities (up to > 99:1 dr).

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Wang*

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**Transition-Metal-Free Hydrogen
Autotransfer: Diastereoselective *N*-
Alkylation of Amines with Racemic
Alcohols**