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Nickel-Catalyzed Asymmetric Transfer Hydrogenation and α-Selective Deuteration of *N*-Sulfonyl Imines with Alcohols: Access to α-Deuterated Chiral Amines

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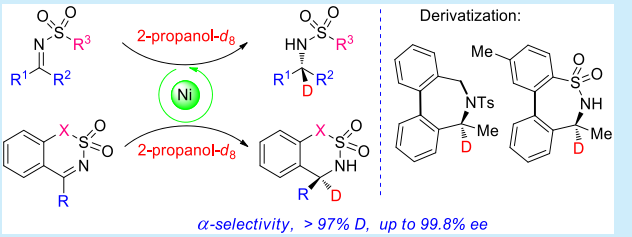
ABSTRACT: A nickel-catalyzed enantioselective transfer hydrogenation and deuteration of *N*-sulfonyl imines was developed. Excellent α-selectivity and high deuterium content were achieved by using inexpensive 2-propanol-d_8 as a deuterium source. As a highlight, no deuteration of β-C−H and the remote C−H of *N*-sulfonyl amines occurred, which is hard to achieve using other imines or by hydrogen isotope exchange with D_2O. Mechanism studies indicated a stepwise pathway through the [Ni−D] intermediate.



Sulfonamides are common pharmacophores and have been used as antibiotics in clinic for nearly 50 years.[1] In recent years, many bioactive molecules that contain chiral sulfonamide subunits have been developed (Figure 1).[2] The *N*-sulfonyl group can be removed to afford chiral amines,[3] which are easily transformed to chiral pharmaceuticals and bioactive compounds. Although excellent enantioselectivities have been obtained for the asymmetric hydrogenation[4] and transfer hydrogenation[5] of *N*-sulfonyl imines using rare noble-metal (Rh, Ru, Ir, and Pd) catalysts, there are very few examples in which 3d earth-abundant transition-metal (Mn, Fe, Co, Ni, and Cu) catalysts have shown satisfactory reactivity and enantioselectivity. Morris and coworkers developed an iron(II)-based complex containing PNNP ligand for the transfer hydrogenation of *N*-(*p*-tolylsulphonyl)ketimine with *i*-PrOH and *t*-BuOK, obtaining 26% conversion and 94% enantiomeric excess (ee).[6] Zhou and coworkers reported a high enantioselective stepwise reductive amination of ketones with various sulfonamides using 5 mol % nickel catalyst and formic acid.[7] More recently, Zhang and coauthors realized a nickel-catalyzed asymmetric hydrogenation of *N*-*t*Bu-sulfonyl imines with the highest activity (S/C up to 10 500) and excellent enantioselectivity.[8] However, high-pressure H_2 gas (30−50 bar) was used in their method. Despite of these three remarkable examples, the hydrogenation of *N*-sulfonyl imines using a cheap 3d transition-metal catalyst under milder reaction conditions is still desirable.

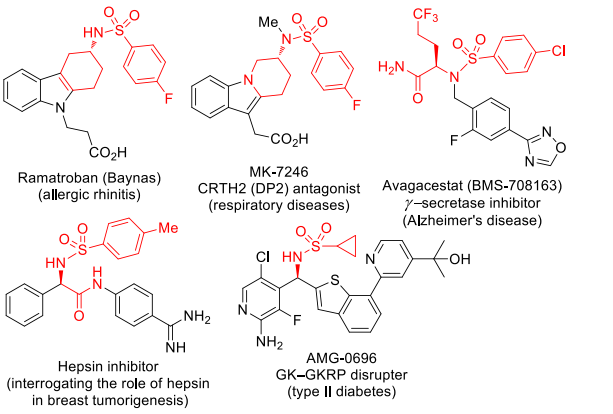


Figure 1. Examples of bioactive molecules containing chiral sulfonamides.

In the past decade, deuterium replacement at the metabolically active site of pharmaceuticals has been recognized as a potential path to improve the metabolic stability or pharmacokinetic profiles.[9] In particular, deuterating a stereogenic center will stabilize the undesired stereoisomer interconversion (as illustrated with the notorious drug thalidomide). Since the first deuterated drug, deutetrabenazine (Austedo), got approval by the U.S. FDA,[10] the interest in deuterated drugs has greatly increased the demand for effective methods to install deuterium atoms at the precise positions of molecules. Several examples of postsynthetic regioselectivity deuteration by hydrogen isotope exchange (HIE) or halogen−deuterium exchange have been reported;[11] however, the enantioselective installation of deuterium is not well established.[12]

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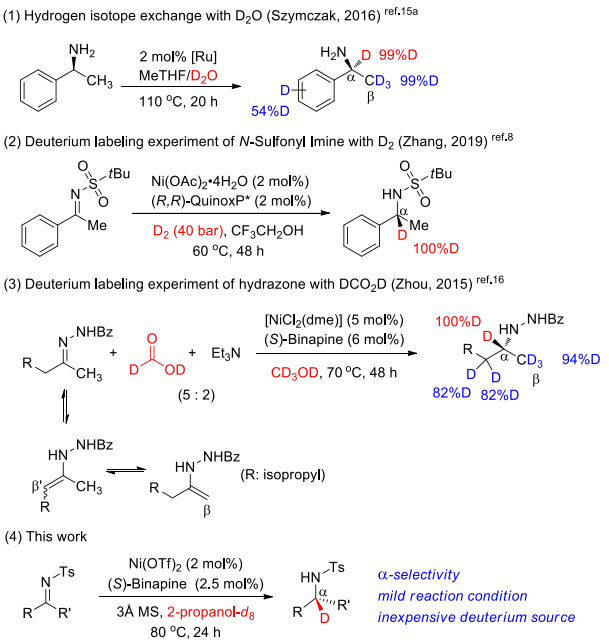
Chiral amines are one of the most frequently occurring structures in pharmaceuticals.[13] Therefore, the α-deuteration of chiral amines is in great demand. A cheap and easy-to-operate deuterium source is crucial for asymmetric deuteration.[14] Hydrogen isotope exchange with D_2O usually encounters low regioselectivity (Scheme 1a).[15] D_2 is expensive

Scheme 1. Strategies for α-Deuteration of Chiral Amines



and explosive and is often used in a high-pressure autoclave (Scheme 1b).[8] The asymmetric transfer deuteration of ketimine with deuterated formic acid (DCO_2D) usually gives products in which both the α- and β-C−H are deuterated via the fast imine−enamine tautomerization (Scheme 1c).[16] In this direction, deuterated alcohols (methanol, ethanol, or 2-propanol) are perfect candidates for deuterium sources due to their easy accessibility, simple manipulation, neutral pH, and low toxicity.[17] Herein we report an efficient nickel-catalyzed transfer hydrogenation of *N*-sulfonyl ketimines using alcohols as the hydrogen source. Moreover, by utilizing 2-propanol-d_8 as the deuterium source, the nickel catalysis enabled the α-selective deuteration of *N*-sulfonyl ketimines (Scheme 1d).

Our investigation began with the transfer hydrogenation of *N*-sulfonylimine **1a** with 5% of $Ni(OTf)_2$ in isopropanol at 80 °C over 24 h (Figure 2). Molecular sieves were introduced to prevent the hydrolysis of **1a**. A number of chiral ligands were examined to determine a suitable ligand for the model reaction. To our delight, many electron-rich diphosphine ligands can promote the transfer hydrogenation of **1a**. In particular, three ligands, (*S*)-binapine,[18] (*R*)-Ph-BPE[19] and (*R*)-CyPF-*t*Bu,[20] produced **2a** in >90% yield with >89% ee. Among these three ligands, (*S*)-binapine gave the highest yield of **2a** (99%), whereas (*R*)-Ph-BPE displayed the best enantioselectivity (97% ee). Other aromatic diphosphine ligands, Pybox ligand, and *N*-heterocyclic carbene ligand had either low catalytic activity or no activity at all.

With the three best ligands in hand, we carefully tuned the reaction parameters to determine the optimal reaction conditions (Table 1). The reaction system is sensitive to the anions of nickel salts. $Ni(OTf)_2$ presented the best catalytic

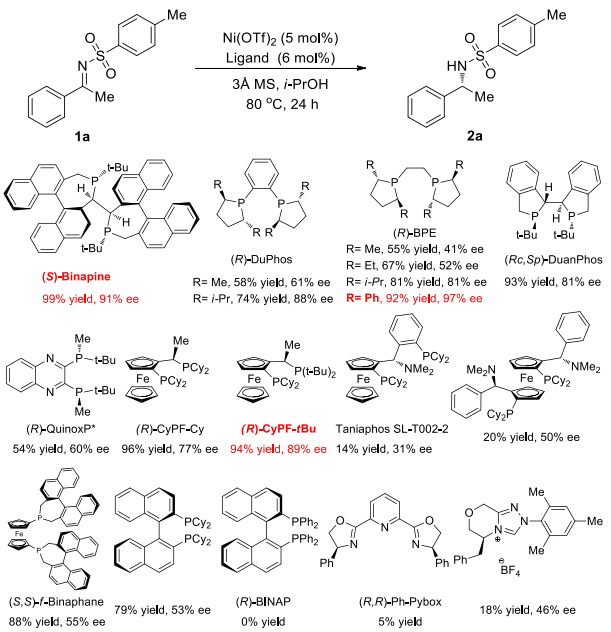


Figure 2. Ligand screening.

activity, affording **2a** in nearly quantitative yield with 91% ee (Table 1, entry 1). $Ni(NO_3)_2{\cdot}6H_2O$ also promoted the formation of **2a** in 85% yield with 92% ee (entry 2). Other nickel salts, such as $NiBr_2(DME)$, $NiCl_2(DME)$, $Ni(acac)_2$, $Ni(OAc)_2{\cdot}4H_2O$, and $NiSO_4$, were inactive in the hydrogenation (entries 3−7). We next screened the alcoholic solvent (entries 9 and 10). Ethanol and butanol were also good solvents for the reaction, enabling the formation of **2a** in 91−93% yield with 92% ee, respectively. When 10 equiv of isopropanol in toluene was used as the solvent, the hydrogenation reaction proceeded smoothly, providing **2a** in 90% yield with 87% ee (entry 11). Later, we were gratified to find that when 2 mol % nickel catalyst was used and the temperature was lowered to 60 °C, the yield was also almost quantitative, and the ee increased to 95% (entry 12). The use of 1 mol % nickel catalyst led to 98% yield and 92% ee (entry 13). The catalytic activity of (*R*)-Ph-BPE was relatively lower than that of (*S*)-binapine. For example, with ethanol as the solvent, a nickel catalyst of 6% (*R*)-Ph-BPE afforded **2a** in 86% yield with 94% ee (entry 14). The yield of **2a** decreased to 58%, but the ee value increased to 98% when heated at 60 °C for 24 h with 2.5 mol % (*R*)-Ph-BPE (entry 15).

Under the optimal conditions of using 2 mol % $Ni(OTf)_2$/(*S*)-binapine, we examined the substrate scope of *N*-sulfonylimine (Scheme 2). *N*-Tosyl imines derived from aryl alkyl ketones and heteroaryl methyl ketones with different electronic properties gave the desired products (**2b−q**) in high yields with up to 98% ee. Notably, the catalyst promoted the hydrogenation of phenyl thienyl imine to afford *N*-tosylamine **2r** in 96% yield with 91% ee. The challenging phenyl tolyl imine gave hydrogenation product **2s** in 82% yield with 76% ee. *N*-Tosyl alkyl imines were also tested. The hydrogenation of *N*-tosyl *tert*-butyl methyl imines resulted in **2t** in 81% yield with 99.8% ee. *N*-Tosyl isopropyl methyl imine was hydrogenated with (*R*)-Ph-BPE, leading to **2u** in 99% yield with 95% ee. The $Ni(OTf)_2$/(*S*)-binapine is also efficient for *N*-benzenesulfonimide and *N*-methanesulfonimide imines (**2v−w**). A *N*-tosyl imine derived from chalcone was treated with 5 mol % $Ni(OTf)_2$/(*R*)-Ph-BPE at 60 °C for 24 h. It produced

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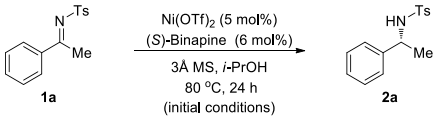
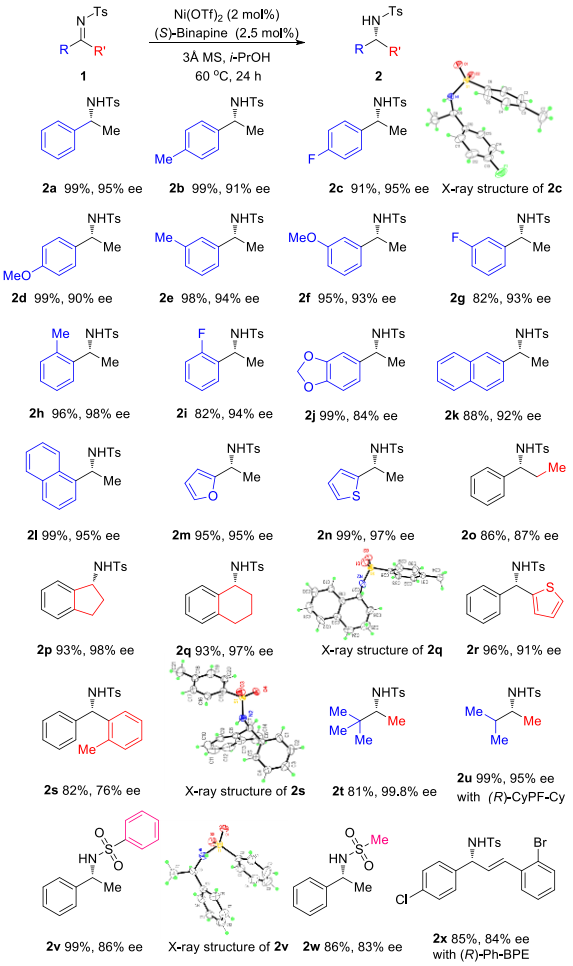
Table 1. Optimization of Reaction Conditions[a]



entry	changes from initial conditions	yield (%)[b]	ee (%)[c]
1	none	99	91
2	$Ni(NO_3)_2{\cdot}6H_2O$ instead of $Ni(OTf)_2$	85	92
3	$NiBr_2(DME)$	<10	
4	$NiCl_2(DME)$	<10	
5	$Ni(acac)_2$	<10	
6	$NiSO_4$	<10	
7	$Ni(OAc)_2{\cdot}4H_2O$	<10	
8	MeOH instead of *i*-PrOH	37	92
9	EtOH	93	92
10	*n*-BuOH	91	92
11	10 equiv of *i*-PrOH in toluene	90	87
12	2% $Ni(OTf)_2$, 2.5% (*S*)-binapine, 60 °C (optimized conditions)	99	95
13	1% $Ni(OTf)_2$, 1.2% (*S*)-binapine, 60 °C	98	92
14	6% (*R*)-Ph-BPE as ligand, in EtOH	86	94
15	2% $Ni(OTf)_2$, 2.5% (*R*)-Ph-BPE, 60 °C	58	98

[a]Initial reaction conditions: **1a** (0.2 mmol), $Ni(OTf)_2$ (5 mol %), (*S*)-binapine (6 mol %) in isopropanol (0.6 mL) at 80 °C for 24 h. [b]Yield of the isolated product. [c]Determined by chiral-phase HPLC.

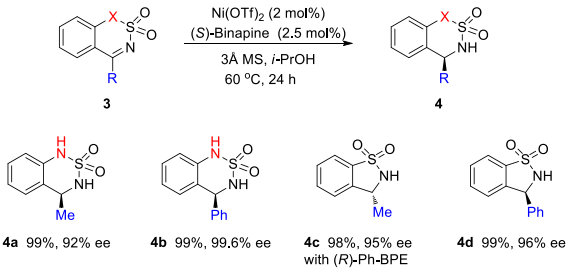
Scheme 2. Asymmetric Transfer Hydrogenation of *N*-Sulfonyl Imines



2x in 85% yield with 84% ee. The C=C bond was retained, and chloro and bromo substituents were well tolerated in the catalytic system. The 1*R* absolute configuration of hydrogenation products was confirmed by X-ray diffraction analysis (**2c**, **2q**, **2s**, and **2v**).[21]

To further extend the substrate scope, we also attempted the asymmetric hydrogenation of cyclic *N*-sulfonyl imines (Scheme 3). Under the standard conditions, six-membered

Scheme 3. Asymmetric Transfer Hydrogenation of Cyclic *N*-Sulfonyl Imines



cyclic *N*-sulfonyl imines bearing a methyl or phenyl group were hydrogenated to benzosultams **4a** and **4b** in quantitative yields with up to 99.6% ee. Five-membered benzosultam products **4c** and **4d** were formed in the asymmetric hydrogenation with 94 and 90% ee, respectively.

Taking note of the high efficiency and wide scope of the nickel catalysis, we applied the catalyst to the asymmetric transfer deuteration of *N*-tosyl imine **1a** with deuterated alcohols. The reaction of **1a** in the cheapest methanol-d_4 with 5 mol % nickel catalyst at 100 °C for 48 h only gave the deuterated product **5a** in 25% yield with 90% ee. Fortunately, the deuteration of **1a** in 2-propanol-d_8[22] proceeded smoothly. Deuteride selectively added to the α-position of **1a**, affording **5a** in 99% yield with 94% ee and 98% deuterium content (Scheme 4). No deuteration occurred at the methyl and phenyl groups. The deuteration of **1a** on a 1 mmol scale using

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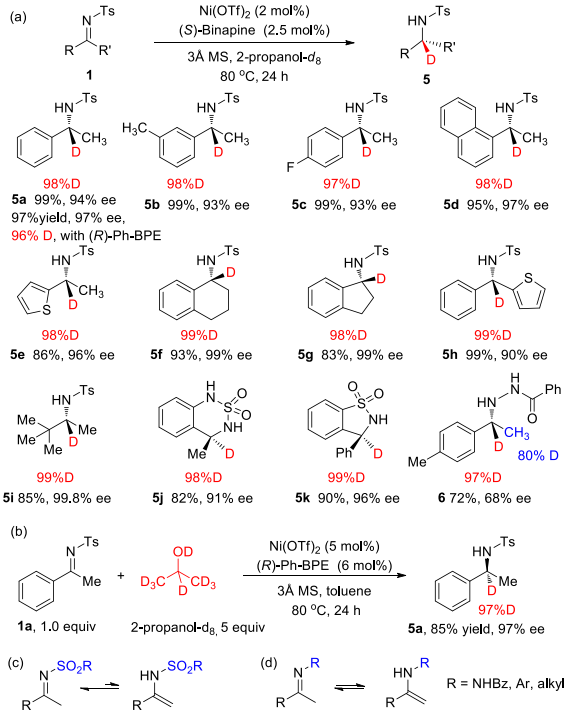
Scheme 4. Asymmetric Transfer Deuteration of Imines

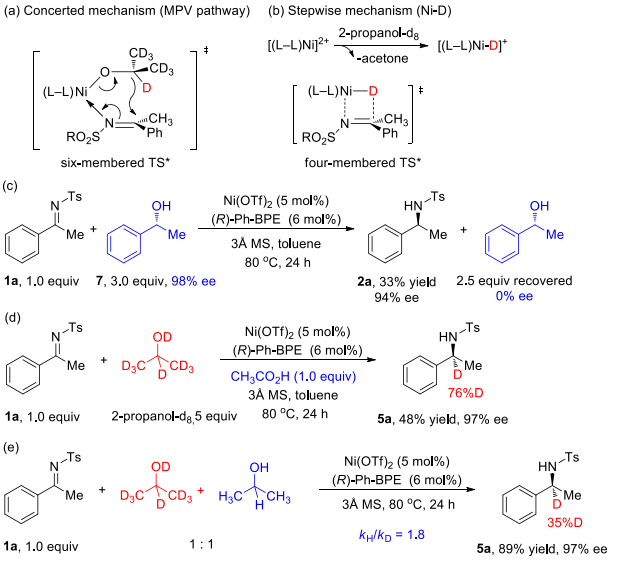


(*R*)-Ph-BPE produced 97% of **5a** with 97% ee and 96% deuterium content. Afterward, we selected some representative imines from Schemes 2 and 3 to test their deuteration reaction. As can be seen in Scheme 4 a, all of the *N*-tosyl imine and cyclic sulfonyl imine substrates underwent asymmetric transfer deuteration smoothly, producing **5a**−**k** with excellent α-selectivity and enantioselectivity and >97% deuterium contents. Note that it is not necessary to use 2-propanol-d_8 as the solvent. Stoichiometric deuterated alcohol is enough for this transformation. For example, using 5 mol % of Ni(OTf)$_2$/(*R*)-Ph-BPE and 5 equiv of 2-propanol-d_8 in toluene solvent (or *t*-BuOH solvent), **5a** was obtained in 85% yield with 97% ee and 97% deuterium content (Scheme 4b).

It is worth noting that both α- and β-CH deuterated products are usually obtained due to the imine−enamine tautomerization in the previously reported deuteration reactions (Scheme 1).[15,16] To our delight, no deuteration was observed at the adjacent methyl group of **5a**−**k** in our nickel catalysis of *N*-tosyl imines. In contrast, the deuteration of benzoyl hydrazone should be performed at 120 °C for 24 h to afford hydrazine **6** in 72% yield with 68% ee and 97% D at the α-position and 80% D at β-CH$_3$. Other imines, such as *N*-aryl imines, do not react under nickel catalysis, even with longer time and higher temperature. The high α-selectivity and mild deuteration conditions of sulfonyl imines versus other imines proved that a strong electron-withdrawing sulfonyl group can inhibit the imine−enamine tautomerization process (Scheme 4c,d) and make C$_1$ more electron-deficient to favor the attack of the hydride.

There are two possible mechanisms for the deuteration of sulfonyl imine: (1) The first one is a concerted mechanism in which deuterium was directly transferred from 2-propanol-d_8 to imine through a chairlike six-membered transition state (Scheme 5a) like Meerwein−Ponndorf−Verley (MPV) reduction. (2) The second is a stepwise mechanism via a nickel(II) deuteride [Ni−D] intermediate (Scheme 5b). We

Scheme 5. Mechanism Studies



then conducted a series of experiments to differentiate the two possibilities.

The MPV pathway has been suggested by the iridium-catalyzed transfer hydrogenation of ketones.[23] In the iridium-catalyzed transfer hydrogenation of imines using alcohols as a hydrogen donor, Zhao and coworkers revealed that the structure of alcohols influenced the enantioselectivity of hydrogenation and proposed a concerted mechanism with iridium alkoxide transition states.[24] In our method, methanol, ethanol, and *n*-butanol gave the same ee value (92%) using Ni(OTf)$_2$/(*S*)-binapine (Table 1, entries 8−10). Using the 98% ee (*R*)-1-phenylethanol **7** as a hydrogen donor and Ni(OTf)$_2$/(*R*)-Ph-BPE as the catalyst, **2a** was obtained in 30% yield with 94% ee (Scheme 5c). This enantioselectivity is similar to the results of using ethanol (94% ee, Table 1, entry 14). Notably, the ee of the recovered **7** was 0%, which may form through a reversible dehydrogenation−hydrogenation process. The above observations proved that the enantioselectivity is independent of alcohol, and the MPV concerted mechanism can be ruled out.

We then conducted other experiments to capture the possible [Ni−D] intermediate. When 1 equiv of acetic acid was added to the reaction, it produced **5a** in 48% yield with 97% ee and 76% D (Scheme 5d). A similar experiment using wet toluene as the solvent afforded **5a** in 80% yield with 93% ee and 91% D. Compared with 97%D in dry toluene (Scheme 4b), the decrease in deuterium content indicates the existence of the [Ni−D] intermediate. The partial loss of deuterium can be attributed to the equilibrium between [Ni−D] and the proton of acetic acid or water. A competition of 2-propanol and 2-propanol-d_8 was conducted and resulted in **5a** with 35% D (Scheme 5f). We estimate the kinetic isotope effect (KIE) of the whole catalytic reaction to be k_H/k_D = 1.8, which support a stepwise C−D bond cleavage and a new C−D bond-forming pathway.

The α-deuterated chiral *N*-tosylamines can be easily converted to other chiral building blocks. For instance, a sample of **5a** with 97% ee and 98% D reacted with *o*-bromobenzyl bromide **8** to provide dibenzoazepine **9** in 75% yield without decreasing the enantiomeric excess and deuterium content (Scheme 6a).[25] **5a** underwent intra-

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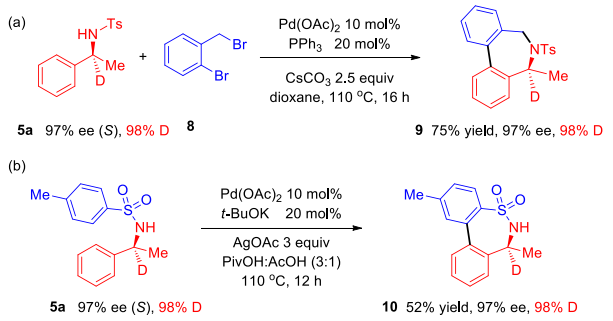
Scheme 6. Deuterated Product Derivatizations



molecular oxidative coupling, resulting in optically pure biaryl sultams **10** in 52% yield with 97% ee and 98% deuterium content (Scheme 6b).[26] The sulfonyl group could be removed to afford α-deuterated chiral amine, which could be further transformed to several chiral pharmaceuticals and bioactive compounds.[3]

In summary, we have developed a nickel-catalyzed enantioselective transfer hydrogenation of imines for the synthesis of a wide variety of chiral sulfonamides. By using cheap and harmless 2-propanol-d_8 as the deuterium source, we realized the α-selective deuteration of *N*-tosyl imines, producing α-deuterated chiral amines with excellent deuterium contents and enantioselectivity. Mechanism studies revealed that the reaction may go through a stepwise pathway with [Ni−D] as the key intermediate.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02921.

Experimental details and spectral characteristics of products (PDF)

Accession Codes

CCDC 1976290−1976293 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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