Asymmetric Synthesis

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Palladium-Catalyzed Asymmetric Hydrogenolysis of *N*-Sulfonyl Aminoalcohols via Achiral Enesulfonamide Intermediates**

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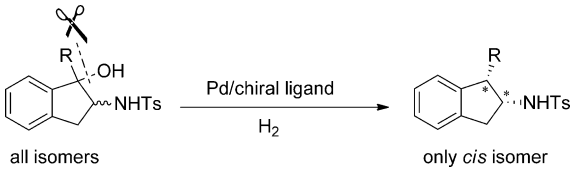
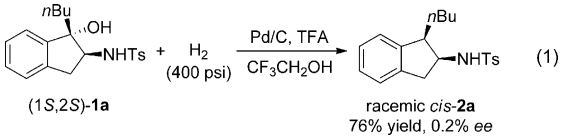
Hydrogenolysis is an important synthetic method in organic chemistry,[1] and has been widely applied in industrial processes,[2] natural product synthesis,[3] and the removal of waste materials.[4] In practice, most hydrogenolysis reactions have been used for the synthesis of racemic or achiral compounds. Very few studies on asymmetric homogeneous hydrogenolysis have been reported. The first example, reported by Chan and Coleman, was a homogeneous asymmetric hydrogenolysis of sodium epoxysuccinate through desymmetrization with chiral rhodium catalysts with moderate enantioselectivity.[5] Subsequently, a water-soluble sulfonated-phosphine–rhodium catalyst system for the asymmetric hydrogenolysis of epoxides was described by Bakos et al., but the products were obtained with only 39% *ee*.[6] Kündig and co-workers documented a desymmetrization of *meso* dihalide complexes by asymmetric hydrogenolysis, which led to planar chiral organometallic complexes.[7] Very recently, asymmetric hydrogenolysis of racemic tertiary alcohols was also successfully developed.[8] Despite considerable efforts, these reactions are far from ideal because of low optical enrichment of the hydrogenolysis product and a relatively limited range of substrates. Therefore, the search for an efficient strategy for homogeneous asymmetric hydrogenolysis and extension of the scope of such processes to a wider range of substrates is still of great significance.

Palladium has been extensively investigated as a heterogeneous hydrogenolysis catalyst.[9] In contrast, palladium-catalyzed homogeneous asymmetric hydrogenolysis is still rare.[7] Recently, homogeneous palladium catalysts were successfully utilized for the asymmetric hydrogenation of ketones,[10] imines,[11] heteroaromatic compounds,[12] and enesulfonamides[13] by us and other research groups. Considering the straightforward synthesis of *N*-sulfonyl aminoalcohols from commercially available starting materials and the usefulness of the hydrogenolysis products, chiral amines with two contiguous stereogenic centers,[14] we speculated that a chiral palladium catalyst system could be applied for the homogeneous asymmetric hydrogenolysis of *N*-sulfonyl aminoalcohols (Scheme 1). Herein, we report the palladium-catalyzed formal asymmetric hydrogenolysis of *N*-sulfonyl aminoalcohols to give chiral amines with two contiguous stereocenters with up to 94% *ee*. Furthermore, both "dynamic kinetic asymmetric transformation" and "dynamic kinetic resolution" phenomena were observed.



Scheme 1. Stereoconvergent palladium-catalyzed formal asymmetric hydrogenolysis of *N*-sulfonyl aminoalcohols.

Prior to our study, we wanted to synthesize the chiral *N*-((1*R*,2*S*)-1-butyl-2,3-dihydro-1*H*-inden-2-yl)-4-methylbenzenesulfonamide **2a** by hydrogenolysis of the benzylic hydroxy group of the *N*-sulfonyl aminoalcohol (1*S*,2*S*)-**1a**[15] with Pd/C as the catalyst in the presence of trifluoroacetic acid (TFA). Surprisingly, although the reaction proceeded smoothly [Eq. (1)], the stereogenic center of the C–N bond was also racemized: only racemic *cis*-**2a** was obtained in 76% yield. This observation suggested that an achiral intermediate might be involved in this process, and that the asymmetric hydrogenolysis of racemic *N*-sulfonyl aminoalcohols might be possible. In this context, we began to study the homogeneous palladium-catalyzed asymmetric hydrogenolysis of racemic *N*-sulfonyl aminoalcohols.



(1)

First, racemic **1a** was chosen as a model substrate. Asymmetric hydrogenolysis proceeded in the presence of trifluoroacetic acid (TFA) in trifluoroethanol (TFE) with chiral $Pd(OCOCF_3)_2$/(*R*)-synphos (**L1**) as the catalyst to afford the desired product in 84% yield with 69% *ee* and higher than 20:1 diastereoselectivity (Table 1, entry 1). As expected, use of the antipode of the (*R*)-synphos ligand resulted in the opposite configuration (Table 1, entry 2), thus suggesting that the stereoselectivity is completely controlled by the chiral catalyst. These observations excited our interest and encouraged us to further explore this formal hydrogenolysis reaction. Subsequently, the effect of the Brønsted acid on the enantioselectivity and reactivity was investigated.

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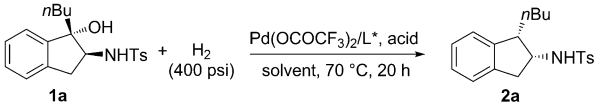
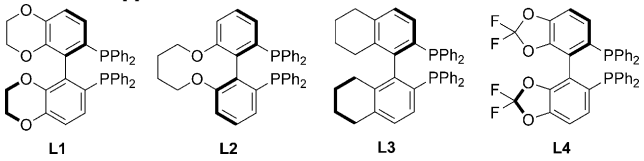
Table 1: Optimization of the reaction conditions for the formal asymmetric hydrogenolysis of *N*-sulfonyl aminoalcohol **1a**.[a]

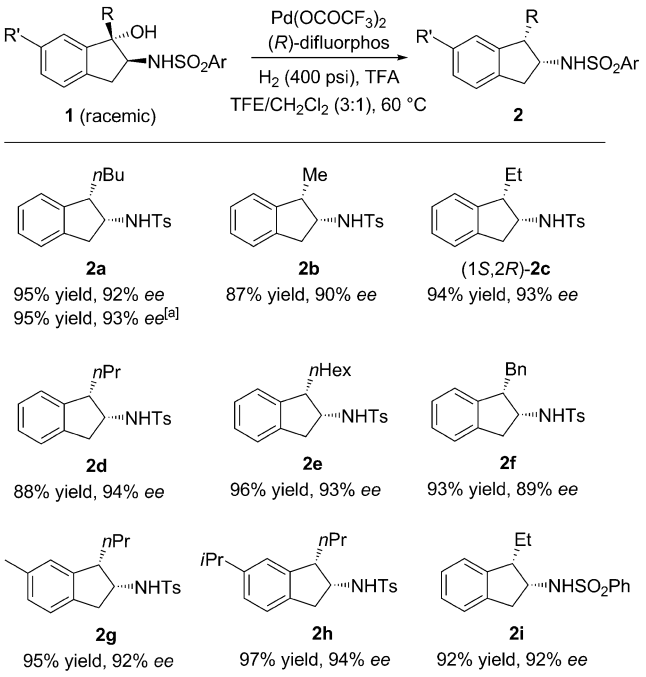


1a **2a**

Entry	Solvent	Ligand	Acid	Yield [%][b]	*ee* [%][c]
1	TFE	(*R*)-**L1**	TFA	84	69
2	TFE	(*S*)-**L1**	TFA	87	68 (+)
3	TFE	(*R*)-**L1**	TsOH	N/A	–
4	TFE	(*R*)-**L1**	$PhCO_2H$	N/A	–
5[d]	TFE	(*R*)-**L1**	TFA	90	70
6[d]	TFE	(*R*)-**L2**	TFA	92	59
7[d]	TFE	(*R*)-**L3**	TFA	95	62
8[d]	TFE	(*R*)-**L4**	TFA	75	86
9[d,e]	TFE/CH_2Cl_2 (3:1)	(*R*)-**L4**	TFA	73	92
10[d,e,f]	TFE/CH_2Cl_2 (3:1)	(*R*)-**L4**	TFA	95	92

[a] Reaction conditions: **1a** (45 mg, 0.125 mmol), $Pd(OCOCF_3)_2$ (0.9 mg, 2.0 mol%), ligand (2.4 mol%), acid (1 equiv), H_2 (400 psi), solvent (3 mL), 70°C, 20 h. [b] The yield and diastereomeric ratio (d.r. > 20:1 in all cases) were determined by ^{1}H NMR spectroscopy. N/A = not applicable. [c] The *ee* value was determined by HPLC. [d] The reaction was carried out with 2 equivalents of TFA. [e] The reaction was carried out at 60°C. [f] The reaction was carried out for 60 h.





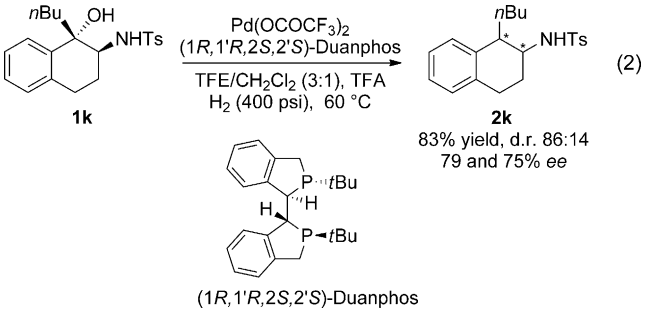
Scheme 2. Palladium-catalyzed formal asymmetric hydrogenolysis of *N*-sulfonyl aminoalcohols **1**. Reaction conditions: **1** (0.125 mmol), $Pd(OCOCF_3)_2$ (0.9 mg, 2.0 mol%), (*R*)-difluorphos (2.1 mg, 2.4 mol%), TFA (2.0 equiv), H_2 (400 psi), TFE/CH_2Cl_2 (3:1; 3 mL), 60°C, 60 h. All products were obtained with d.r. > 20:1, as determined by ^{1}H NMR spectroscopy. [a] The opposite absolute configuration was observed with the chiral ligand (*S*)-difluorphos.

Strong Brønsted acids, such as *p*-toluenesulfonic acid (Table 1, entry 3), afforded complex mixtures. None of the desired product but instead the dehydration product enesulfonamide **3** was observed in the presence of weak benzoic acid (Table 1, entry 4). Fortunately, trifluoroacetic acid provided the desired product, albeit with moderate enantioselectivity. When the amount of acid was increased to 2.0 equivalents, the yield and *ee* value were slightly improved (Table 1, entry 1 versus 5).

We further evaluated the influence of the chiral ligand. Of various commercially available chiral diphosphine ligands, electron-withdrawing (*R*)-difluorphos (**L4**), which was reported by Genêt and co-workers in 2004,[16] proved to be the most favorable in view of enantioselectivity (Table 1, entry 8). A survey of solvents indicated that the combination of TFE and dichloromethane in a ratio of 3:1 was the best choice with respect to enantioselectivity and reactivity (92% *ee*; Table 1, entries 8 and 9). Full conversion was observed without loss of enantioselectivity when the reaction was prolonged to 60 h (Table 1, entry 10).

Under the optimized conditions, the palladium-catalyzed asymmetric hydrogenolysis of *N*-sulfonyl aminoalcohols **1a–i** was explored (Scheme 2). Generally, alkyl-substituted substrates performed very well, and the length of the alkyl chain had little influence on enantioselectivity. Interestingly, the benzyl-substituted product **2f** was formed smoothly with excellent enantioselectivity (89% *ee*) by hydrogenolysis of the corresponding aminoalcohol. Moreover, when a methyl or isopropyl group was introduced at the 6-position of substrates, the transformation still displayed high reactivity and enantioselectivity (products **2g** and **2h**). As expected, the replacement of (*R*)-difluorphos with (*S*)-difluorphos resulted in the formation of product **2a** with the opposite configuration and essentially the same *ee* value (93%).

The asymmetric formal hydrogenolysis of cyclic *N*-sulfonyl aminoalcohol **1k** with a six-membered ring was also successful [Eq. (2)]. The desired hydrogenolysis product **2k** was obtained with moderate enantioselectivity and diastereoselectivity with $Pd(OCOCF_3)_2$/Duanphos as the catalyst.

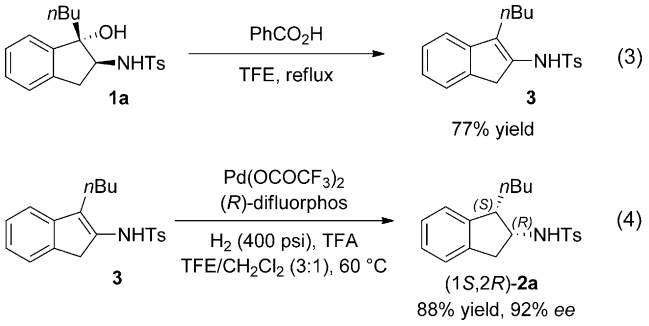


(2)

We were able to determine the absolute configuration of the products of asymmetric hydrogenolysis on the basis of product **2c**. Slow diffusion of hexane into a solution of optically pure *cis*-(−)-**2c** with 99% *ee* in dichloromethane

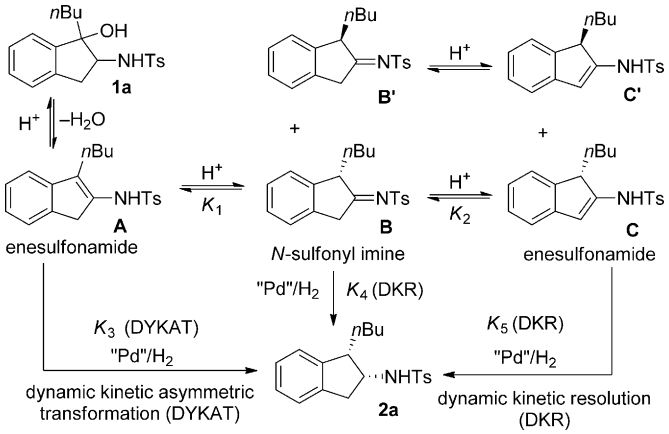
gave a single crystal suitable for X-ray diffraction, which established the absolute configuration of this isomer as 1*S*,2*R*.[17]

To gain insight into the reaction process, we conducted several further experiments. During our evaluation of the influence of acids, the dehydration product was obtained with benzoic acid [Scheme 3, Eq. (3)]. This result suggested that



Scheme 3. Mechanistic investigation.

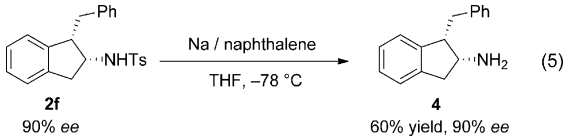
the achiral enesulfonamide **3** might be involved in the transformation. To our delight, when the enesulfonamide intermediate **3** was subjected to asymmetric hydrogenation under the standard reaction conditions, the desired product *cis*-(1*S*,2*R*)-**2a** was obtained with identical enantioselectivity [Scheme 3, Eq. (4)]. On the basis of these experimental results, deuterium-labeling experiments,[18] and previous studies on the asymmetric hydrogenation of enesulfonamides,[13] we propose a stepwise hydrogenation process (Scheme 4):



Scheme 4. Plausible reaction pathway for the stereoconvergent hydrogenolysis of *N*-sulfonyl aminoalcohols.

First, substrate **1a** is dehydrated in the presence of trifluoroacetic acid to give the achiral enesulfonamide intermediate **A**, the acid-catalyzed isomerization of which gives *N*-sulfonylimine **B** and enesulfonamide **C**. Asymmetric hydrogenation of enesulfonamide **A**, *N*-sulfonylimine **B**, or enesulfonamide **C** then delivers the desired product.[18] Indeed, both a typical dynamic kinetic asymmetric transformation[19] and a dynamic kinetic resolution process are involved in this formal asymmetric hydrogenolysis reaction.

To demonstrate the practical utility of our methodology, we focused on the development of a facile and expeditious route to a chiral calcium-channel antagonist. Removal of the *p*-toluenesulfonyl group in **2f** with sodium/naphthalene furnished the chiral amine **4** [Eq. (5)], which has been shown to be a calcium-channel antagonist for the treatment of ischemic stroke.[20]



In conclusion, a stereoconvergent palladium-catalyzed formal asymmetric hydrogenolysis of *N*-sulfonyl aminoalcohols was successfully developed with a chiral palladium complex as the catalyst in the presence of trifluoroacetic acid to provide direct and facile access to chiral 2,3-dihydro-1*H*-inden-2-amine derivatives with two contiguous stereogenic centers with up to 94% *ee*. The reaction pathway involves Brønsted acid catalyzed dehydration to afford the enesulfonamide, acid-catalyzed enamine/imine isomerization, and palladium-catalyzed asymmetric hydrogenation of the enesulfonamide and *N*-sulfonylimine: a process based on a dynamic kinetic asymmetric transformation. Notably, the present enantioselective reactions represent the first success in the homogeneous palladium-catalyzed formal asymmetric hydrogenolysis of *N*-sulfonyl aminoalcohols.

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[17] CCDC 874017 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
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