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Catalytic asymmetric cleavage of sp^3 C–N bonds for access to highly enantioenriched *N*-benzylic sulfonamides†

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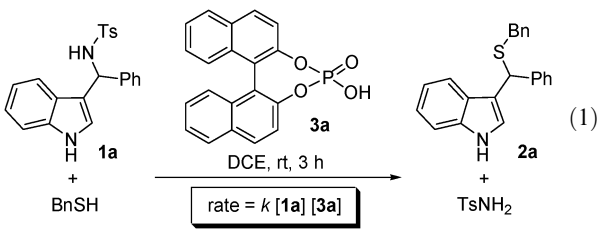
In the presence of 10 mol% of a chiral phosphoric acid, a variety of racemic *N*-benzylic sulfonamides having *N*-(3-indolyl)methyl groups smoothly undergo kinetic resolution with benzyl thiol at 0 °C or at room temperature and the remaining sulfonamides are recovered in moderate to excellent yields and with excellent ee.

Readily accessible *N*-benzylic sulfonamides are able to couple with a range of nucleophiles, such as aromatics, active methylene compounds, alkynes, thiols, sulfinic acids, and silanes, through sp^3 C–N bond cleavage under acidic conditions.[1–6] The choice of acidic catalyst highly depends on the nature of both *N*-benzylic sulfonamides and nucleophiles. Stereochemical studies have shown that the reaction proceeds in an S_N1 manner and hence requires sufficiently stable carbocations to be generated as intermediates (Scheme 1).[6] In addition, the acid-catalyzed sp^3 C–N bond cleavage has been demonstrated to be reversible by the fact that the optical purity of the remaining chiral sulfonamide decreases during the reaction.[6a]

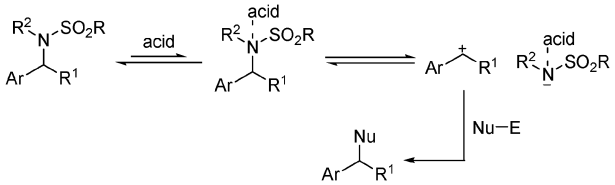
N-Benzylic sulfonamides having *N*-(3-indolyl)methyl groups are highly reactive and their sp^3 C–N bonds can be cleaved by relatively weak acids.[3,4] In 2008, Enders *et al.* reported a chiral *N*-triflyl phosphoramide-catalyzed kinetic resolution of racemic *N*-(3-indolyl)(aryl)methyl *p*-toluenesulfonamide with indole, wherein the optical purity of the remaining sulfonamide was found to be 66% ee when the conversion reached 55%.[7] Later, You *et al.* disclosed that a chiral phosphoric acid could catalyze the kinetic resolution of racemic *N*-(3-indolyl)(phenyl)methyl *p*-toluenesulfonamide with *N*-methyl indole and the sulfonamide was recovered in 49% yield and with 35% ee.[4b] Based on the mechanism depicted in Scheme 1, we envisioned that the enantioselectivity could be improved by employing an appropriate nucleophile, which was expected to reduce or even terminate the reversible sp^3 C–N bond cleavage by coupling quickly with the carbocation once it was generated from the sulfonamide in the presence of a chiral acid catalyst. Herein, we report a convenient access to optically active *N*-benzylic sulfonamides having *N*-(3-indolyl)methyl groups with excellent ee through a chiral phosphoric acid-catalyzed kinetic resolution of the corresponding racemic compounds with benzyl thiol.[8]

Previously we found that thiols could serve as highly reactive nucleophiles to couple with various *N*-benzylic sulfonamides in the presence of $TMSCl/ZnCl_2$ catalyst at room temperature.[6a] Our continued studies showed that the alkylation of thiols with *N*-benzylic sulfonamides having *N*-(3-indolyl)methyl groups could be efficiently catalyzed by weaker acids such as organic phosphoric acids. For example, the reaction of sulfonamide **1a** with benzyl thiol (1.1 equiv.) proceeded smoothly in the presence of 10 mol% of racemic phosphoric acid **3a** in 1,2-dichloroethane at room temperature to give thioether **2a** in 98% yield (eqn (1)). Consistent with an S_N1 mechanism proposed according to the stereochemical studies,[6] kinetics studies have shown that the reaction is first-order for both sulfonamide **1a** and phosphoric acid **3a**, and zero-order for benzyl thiol.[9]



(1)

Treatment of racemic sulfonamide **1a** with benzyl thiol (0.70 equiv.) and chiral phosphoric acid **3b** (10 mol%) at room temperature led to the formation of thioether **2a** in 60% yield as a racemic form (Table 1, entry 1).[10] Nevertheless, remaining sulfonamide **1a** was recovered in 36% yield and with 98% ee.[11] Encouraged by this result, a range of racemic *N*-(3-indolyl)(phenyl)methyl sulfonamides were examined under the same reaction conditions. Although the reaction rate was significantly affected by the *N*-sulfonyl group, the remaining



Scheme 1 S_N1 reaction of *N*-benzylic sulfonamides with nucleophiles.

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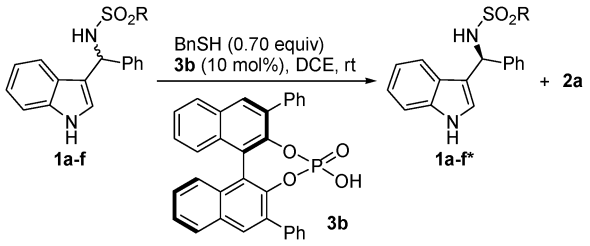
Table 1 Kinetic resolution of racemic *N*-(3-indolyl)(phenyl)methyl sulfonamides with benzyl thiol[a,b]



Entry	R	1a–f*	Time/h	Yield[c] (%)	ee[d] (%)
1[e]	4-MeC_6H_4	**1a***	7.5	36	98
2	4-$MeOC_6H_4$	**1b***	9	31	97
3	4-$O_2NC_6H_4$	**1c***	120	28	94
4	2-MeC_6H_4	**1d***	36	25	99
5	1-Naphthyl	**1e***	21	37	99
6[f]	Me	**1f***	36	28	99

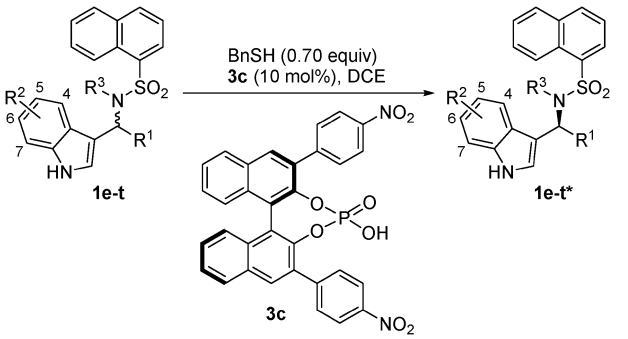
[a] Reaction conditions: racemic sulfonamide (0.10 mmol), benzyl thiol (0.70 equiv.), phosphoric acid **3b** (10 mol%), DCE (10 mL), rt. [b] Compounds **1a***, **1c***, and **1d*** are known, and the absolute configuration of the new products was assigned by analogy. [c] Isolated yield. [d] Determined by chiral stationary phase HPLC analysis. [e] Thioether **2a** was obtained in 60% yield as a racemic form. [f] The reaction was run in 4.0 mL of DCE at 0 °C.

sulfonamides were recovered in moderate to good yields and with excellent ee. Notably, the introduction of 1-naphthalenesulfonyl group to the substrate resulted in the best yield and enantioselectivity (Table 1, entry 5, 37% yield and 99% ee).

The employment of phosphoric acid **3c** instead of **3b** as the catalyst led to a faster kinetic resolution of racemic *N*-benzylic sulfonamides having *N*-(3-indolyl)methyl groups. A range of racemic *N*-(3-indolyl)methylic 1-naphthalenesulfonamides, bearing a variety of functional groups such as alkoxy, halo, cyano, and aromatic nitro, were subjected to the kinetic resolution with benzyl thiol in the presence of 10 mol% of phosphoric acid **3c** at 0 °C or at room temperature, and the remaining sulfonamides were recovered in good to excellent yields and with excellent ee (Table 2). Notably, in the substrate the R^1 group could be an aryl, a heteroaryl, or an alkyl group, the R^2 group could be a hydrogen, a halo, or an alkoxy group, and the R^3 group could be a hydrogen or an alkyl group. Although enantioenriched *N*-benzylic sulfonamides having *N*-(3-indolyl)methyl groups have been reported to be accessible through a chiral phosphoric acid-catalyzed Friedel–Crafts alkylation of indoles with *N*-sulfonyl imines, the kinetic resolution reaction affords higher ee when the R^1 group in the sulfonamide is an alkyl group.[12] Moreover, our protocol is unique in providing enantioenriched tertiary sulfonamides (Table 2, entries 14 and 15).

To gain insight into the origin of enantioselectivity, the reaction of racemic *N*-[3-(1-methylindolyl)](phenyl)methyl *p*-toluenesulfonamide (**1u**) with benzyl thiol was carried out in the presence of 10 mol% of phosphoric acid **3b** at room temperature (eqn (2)). In direct contrast to the reaction with racemic sulfonamide **1a** that bears an indole NH moiety (Table 1, entry 1), this reaction proceeded much slower and afforded very low enantioselectivity. This result clearly indicates that the indole NH moiety is essential for the sulfonamide

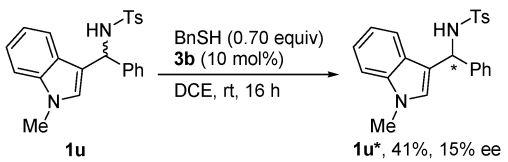
Table 2 Kinetic resolution of racemic *N*-benzylic sulfonamides with benzyl thiol[a]



Entry	R^1	R^2	R^3	1*	Temp/ °C	Time/ h	Yield[b] (%)	ee[c] (%)
1[d]	Ph	H	H	**1e***	0	8	47	97
2	4-$MeOC_6H_4$	H	H	**1g***	0	6	35	99
3	4-FC_6H_4	H	H	**1h***	0	26	42	98
4	4-ClC_6H_4	H	H	**1i***	0	55	42	97
5[e]	4-NCC_6H_4	H	H	**1j***	25	11	37	99
6[e]	4-$O_2NC_6H_4$	H	H	**1k***	25	16	41	99
7	2-MeC_6H_4	H	H	**1l***	0	19	36	99
8[e]	2-$O_2NC_6H_4$	H	H	**1m***	25	16	40	99
9	2-Thienyl	H	H	**1n***	0	14	44	92
10[e]	Cyclohexyl	H	H	**1o***	25	3	32	90
11	Ph	5-MeO	H	**1p***	25	3	31	99
12	Ph	5-Br	H	**1q***	25	9.5	38	99
13	Ph	6-Cl	H	**1r***	25	9	39	99
14[f]	Ph	H	Me	**1s***	0	5	31	98
15[f]	Ph	H	^{n}Pr	**1t***	0	8	40	99

[a] Reaction conditions: racemic sulfonamide (0.10 mmol), benzyl thiol (0.70 equiv.), phosphoric acid **3c** (10 mol%), DCE (6.7 mL), 0 °C or rt. [b] Isolated yield. [c] Determined by chiral stationary phase HPLC analysis. [d] 10 mL of DCE was used. [e] 2.0 mL of DCE was used. [f] 20 mL of DCE was used.

to be recovered in a high yield and ee from the kinetic resolution.[13]



(2)

Our experimental results allow us to propose the transition states shown in Fig. 1 to account for the stereochemical outcome, though no direct evidence is available at present. The indole NH moiety and the sulfonamide group of the substrate are tentatively organized with the chiral phosphoric acid through hydrogen bonding interactions,[13] and hence the chiral phosphoric acid is able to discriminate the two enantiomers of the substrate by interacting with their R^1 groups. In the case the R^1 group suffers steric repulsion from the chiral phosphoric acid (Fig. 1, **TS2**), the corresponding sulfonamide enantiomer is subjected to slow sp^3 C–N bond cleavage relative to the other enantiomer (Fig. 1, **TS1**) and consequently can be recovered after the other enantiomer is consumed by coupling with benzyl thiol.

In summary, we have provided a convenient access to highly enantioenriched *N*-benzylic sulfonamides through catalytic asymmetric cleavage of sp^3 C–N bonds. In the presence of

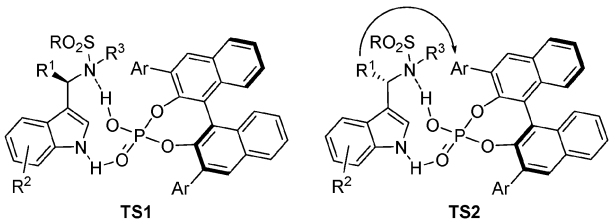


Fig. 1 Possible transition states for the chiral phosphoric acid-catalyzed sp^3 C–N bond cleavage.

10 mol% of a chiral phosphoric acid, a variety of racemic *N*-benzylic sulfonamides having *N*-(3-indolyl)methyl groups smoothly undergo kinetic resolution with benzyl thiol at 0 °C or at room temperature and the remaining sulfonamides are recovered in moderate to excellent yields and with excellent ee. The reaction has been demonstrated to proceed in an S_N1 manner on the basis of kinetics studies, which indicate that it is first-order for both the sulfonamide and the phosphoric acid, and zero-order for benzyl thiol.

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