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Selective Activation of Enantiotopic C(sp^3)−Hydrogen by Means of Chiral Phosphoric Acid: Asymmetric Synthesis of Tetrahydroquinoline Derivatives

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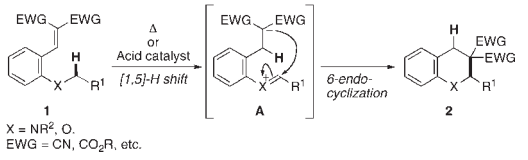
Supporting Information

ABSTRACT: Chiral phosphoric acid-catalyzed asymmetric C−H functionalization has been achieved. In this process, enantiotopic C(sp^3)−hydrogen is selectively activated by chiral phosphoric acid to afford tetrahydroquinoline derivatives with excellent enantioselectivities (up to 97% ee).

The direct and selective replacement of carbon−hydrogen bonds for further functionalization represents an important and longstanding goal in synthetic organic chemistry.[1] Because such replacement has enabled the transformation of C−H bonds into C−C and/or C−X bonds (X = O, N, halogens, etc.) without prefunctionalization (such as halogenation, triflation, etc.), much effort has been exerted to develop novel C−H functionalization methodologies.

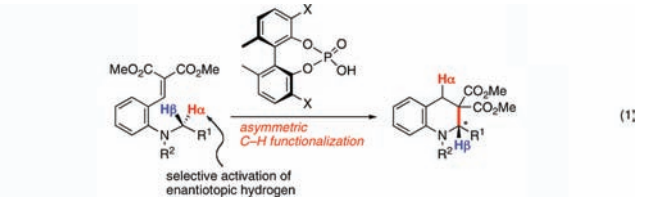
Recently, C(sp^3)−H bond functionalization mediated by an internal redox process has attracted considerable attention because of its unique features (Scheme 1):[2] (1) the C−H bond α to the heteroatom of **1** is cleaved via the [1,5]-hydride shift to give zwitterionic intermediate **A**, and (2) subsequent 6-endo cyclization affords cyclized product **2**.[3−5] It has been noted that Brønsted acids can be employed to trigger the key [1,5]-hydride shift. Our group and other groups have reported that strong Brønsted acids (such as TsOH or TfOH) work as effective activators of the internal redox process.[6,7] Inspired by these features, we turned our attention to the development of an asymmetric version of these types of reactions, focusing on chiral phosphoric acids[8,9] as the chiral source.

Scheme 1. C(sp^3)−H Functionalization via an Internal Redox Process



There are only four precedents for the enantioselective internal redox reaction. Three of them are chiral metal-catalyzed reactions involving magnesium, cobalt, and gold.[10a,c,d] Quite recently, Kim and co-workers disclosed that an organocatalyst (diarylprolinol silyl ether) is also effective for this type of transformation.[10b] Although they achieved the construction of a tetrahydroquinoline skeleton in a highly enantioselective manner, in-depth investigations of the transition state model were not conducted, and thus, a better understanding of the origin of the stereoselectivity is desired.

We report herein a novel chiral phosphoric acid-catalyzed asymmetric C−H bond functionalization via a hydride shift/cyclization sequence. This strategy enabled us to construct a pharmacologically important, optically active tetrahydroquinoline skeleton with good to excellent enantioselectivity. Detailed investigation of the origin of the stereoselectivity indicated that the selective activation of enantiotopic C(sp^3)−hydrogen occurred in our system (eq 1).



Biphenyl phosphoric acid (*S*)-**5** bearing either (**a**) 2,4-bis(trifluoromethyl)phenyl groups or (**b**) 4-nitro-2-trifluoromethylphenyl groups at the 3 and 3′ positions turned out to be a highly effective catalyst for the enantioselective internal redox reaction of benzylidene malonate **3** (Table 1).[11] The desired tetrahydroquinoline **4a** was obtained in good yield with excellent enantioselectivity (83%, 95% ee; entry 1). Substrates with an electron-donating group (methyl or methoxy) or an electron-withdrawing group (bromo) meta or para to the nitrogen atom yielded **4** with excellent selectivities (92% ee or higher, except for the *p*-bromo compound **4f**) upon tuning of the reaction conditions (solvent and temperature; entries 2−6). As in our previous report,[2l] a substituent ortho to the nitrogen atom enhanced the reactivity, affording the desired tetrahydroquinoline derivative **4g** in good yield within a short reaction time with excellent enantioselectivity (81%, 5.5 h, 95% ee; entry 7). Naphthyl-type products (**4h** and **4i**) were obtained with excellent enantioselectivities (91 and 97% ee, respectively; entries 8 and 9). Although no chemoselective hydride shift between the benzyl and ethyl groups was observed (**4j**/**4k** = 1.2/1; entry 10), the enantioselectivities were also extremely high when binaphthyl phosphoric acid **6b** was employed (94% ee for **4j** and 86% ee for **4k**). The non-benzylic product **4l** was obtained in excellent yield with good enantioselectivity (quant., 70% ee; entry 11). The absolute configurations of these products [except **4j** and **4k** obtained

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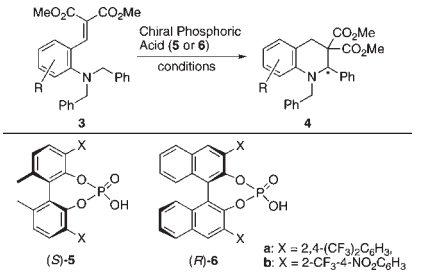
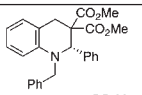
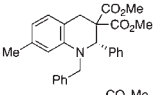
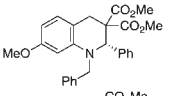
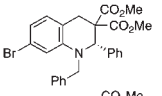
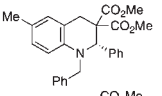
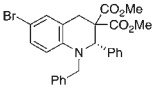
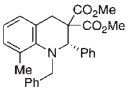
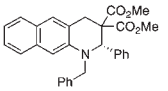
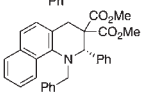
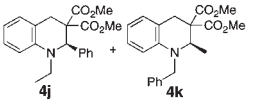
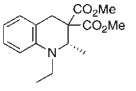
Table 1. Substrate Scope of Asymmetric Internal Redox Reaction[a]



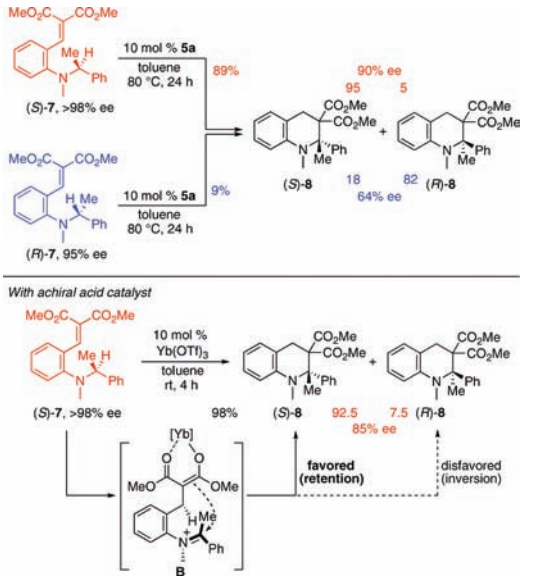
entry	product		time (h)	yield (%)[b]	ee (%)[c]
1		**4a**	40	83	95
2[d]		**4b**	44	90	97
3[e]		**4c**	48	45	95
4[f]		**4d**	48	69	92
5[g]		**4e**	36	82	93
6[h]		**4f**	48	82	70
7		**4g**	5.5	81	95
8		**4h**	48	62	91
9		**4i**	5	95	97
10[i]		**4j** + **4k**	48	81 (**4j**/**4k**= 1.2/1)	94[j] 86[k]
11[l]		**4l**	64	Quant.	70

[a] Unless otherwise noted, all of the reactions were conducted with 0.1 mmol of benzylidene malonate **3** and 10 mol % **5a** in 2.0 mL of toluene at 80 °C. [b] Isolated yield. [c] Determined by chiral HPLC. [d] In 1:1 toluene/CH_2Cl_2. [e] At 120 °C in *p*-xylene. [f] At 110 °C in 1:1 toluene/$(CH_2Cl)_2$. [g] **5b** was employed instead of **5a**. [h] At 110 °C. [i] With **6b** at 70 °C. [j] ee of **4j**. [k] ee of **4k**. [l] With **5b** at 70 °C.

using (*R*)-binaphthol-derived catalyst **6b**] were surmised to be *S* by analogy to **4d**, whose absolute stereochemistry was unambiguously established by single-crystal X-ray analysis.[12,13]

The internal redox reactions of chiral benzylidene malonates (*S*)-**7** and (*R*)-**7** (using 10 mol % **5a** in toluene at 80 °C; Scheme 2) gave intriguing information that helped us clarify

Scheme 2. Highly Stereoselective Nature of the Acid-Catalyzed Internal Redox Reaction



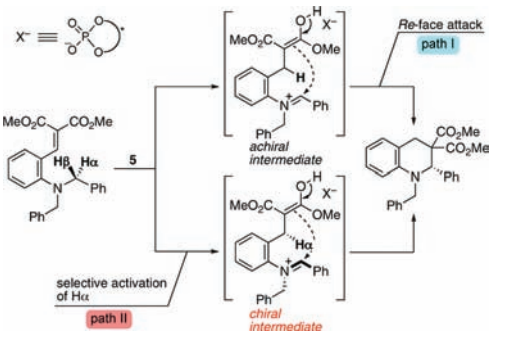


Figure 1. Two plausible reaction pathways.

the reaction mechanism: the enantiomers exhibited totally different reactivities. Whereas (*S*)-**7** underwent the redox reaction in 24 h to give cyclized product **8** in good yield with excellent selectivity (90% ee) in favor of the *S* enantiomer (retention product), the reaction of (*R*)-**7** was sluggish and furnished **8** in less than 10% yield after 24 h with 64% ee in favor of the *R* enantiomer.[14] Notably, even treatment of (*S*)-**7** with an achiral acid catalyst [$Yb(OTf)_3$] afforded **8** in the optically active form (85% ee) with the *S* enantiomer being predominant.[14] According to Reinhoudt's pioneering result,[15] we rationalized this stereochemical outcome as follows: the chiral information in **7** did not completely disappear through the hydride shift process and was memorized[16] as a helical chirality in cationic intermediate **B**. Subsequent nucleophilic attack occurred predominantly from the same face of the transferred hydrogen to give (*S*)-**8**.[17,18]

We had assumed that the stereoselectivity in **4** was determined by the enantiofacial selection of the nucleophilic attack on the iminium cation (path I in Figure 1).[19] However, the above results suggested that this was not the case in our reaction and that the stereoselectivity was mostly controlled at the time of the hydride shift process (path II); in other words, the unprecedented selective activation of

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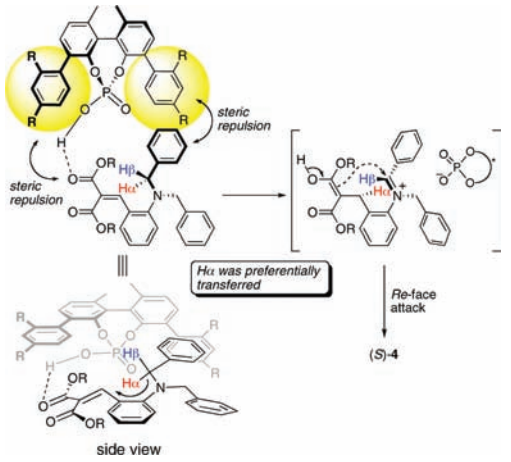

Figure 2. Plausible transition state.

enantiotopic hydrogen by a chiral phosphoric acid did occur in our system.[20,21]

We propose for this asymmetric reaction the transition state shown in Figure 2. Because of the steric repulsion between the aromatic ring of the *N*-benzyl group and the aromatic group at the 3 or 3′ position of the catalyst, the benzyl group is located on the opposite side (β-side) relative to the aromatic ring at the 3 or 3′ position.[21] In this case, Hβ is too far away to be transferred to the olefinic carbon, and as a result, Hα migrates preferentially. Subsequent highly stereoselective cyclization affords (*S*)-**4** as the major enantiomer.

In summary, we have developed a chiral phosphoric acid-catalyzed asymmetric C(sp^3)−H functionalization. A range of substrates are viable in our reaction: various *N*,*N*-dibenzyl substrates and some *N*-alkyl substrates afforded tetrahydroquinoline derivatives with good to excellent enantioselectivities. It is worth noting that this process involves the selective activation of enantiotopic hydrogen by means of a chiral phosphoric acid. Further investigations into the development of another chiral transformation by exploiting this type of reaction are underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures, analytical and spectroscopic data for new compounds, copies of NMR and HPLC spectra, and crystallographic data for **4d** and **s30** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) For the detailed screening of catalysts and substrates, see the Supporting Information.

(12) Substrates possessing an N-cyclic moiety such as an isoquinoline, isoindoline, pyrrolidine, or piperidine ring yielded low enantioselectivities (less than 10% ee).

(13) Phosphoric acid derivatives **5** and **6** were used after washing with 6 N HCl.

(14) The absolute configuration of (*S*)-**8** was determined by X-ray analysis of the corresponding monobrominated product **s30**. For more details, see the Supporting Information.

(15) In the 1980s, the Reinhoudt group found the thermal version of the highly stereoselective internal redox reaction. In their case, the chiral information of the starting material was completely converted into the cyclized product. For more details, see refs 3e, 4c, and 4g.

(16) This kind of asymmetric transformation is recognized as "*memory of chirality*". For leading references, see: (a) Kawabata, T.; Yahiro, K.; Fuji, K. *J. Am. Chem. Soc.* **1991**, *113*, 9694. (b) Fuji, K.; Kawabata, T. *Chem.—Eur. J.* **1998**, *4*, 373. (c) Zhao, H.; Hsu, D. C.; Carlier, P. R. *Synthesis* **2005**, 1.

(17) The significant decrease in the enantioselectivity when (*R*)-**7** was used implies the existence of "matched" and "mismatched" modes in the cyclization step. The reason for this stereomutation is unclear and under investigation.

(18) Treatment of (*S*)-**7** with *rac*-binaphthyl phosphoric acid **6a** afforded (*S*)-**8** with 85% ee, although the chemical yield was low (15%). We also tried the achiral acid catalyst (biphenyl phosphoric acid). Although high temperature and a longer reaction time were required (in toluene at refluxing temperature for 68 h), the stereochemical information was retained at an acceptable level. The cyclized adduct (*S*)-**8** was obtained with 54% ee in 40% chemical yield. For more details, see the Supporting Information.

(19) Seidel[10a] and Feng[10c] proposed that enantiofacial selection of the iminium cation is the key factor leading to the high enantioselectivity.

(20) The selective activation of enantiotopic C(sp^3)−hydrogen takes place in metal-catalyzed enantioselective nitrene or carbenoid insertion reactions. For selected recent references, see: (a) Davies, H. M. L.; Manning, J. R. *Nature* **2008**, *451*, 417. (b) Milczek, E.; Boudet, N.; Blakey, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 6825. (c) Zalatan, D. N.; Du Bois, J. *J. Am. Chem. Soc.* **2008**, *130*, 9220.

(21) The key [1,5]-hydride shift took place suprafacially. For more details, see refs 4c and 4g and references cited therein.