Journal Pre-proofs

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PII:	S0040-4039(19)31185-2
DOI:	https://doi.org/10.1016/j.tetlet.2019.151394
Reference:	TETL 151394
To appear in:	Tetrahedron Letters
Received Date:	18 October 2019
Revised Date:	9 November 2019
Accepted Date:	12 November 2019



Please cite this article as: Zhou, Q., Meng, W., Feng, X., Du, H., Yang, J., Chiral Phosphoric Acid Catalyzed Asymmetric Transfer Hydrogenation of Bulky Aryl Ketones with Ammonia Borane, *Tetrahedron Letters* (2019), doi: https://doi.org/10.1016/j.tetlet.2019.151394

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Graphical Abstract

A chiral phosphoric acid catalyzed transfer hydrogenation of bulky aryl ketones was realized with ammonia borane with up to 77% ee.





Tetrahedron Letters

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Chiral Phosphoric Acid Catalyzed Asymmetric Transfer Hydrogenation of Bulky Aryl Ketones with Ammonia Borane

Qiwen Zhou^{a,b}, Wei Meng^{b,c}, Xiangqing Feng^{b,c,*}, Haifeng Du^{b,c,*} and Jing Yang^{a,*}

^aState Key Laboratory of Chemical Resource, Beijing Key Laboratory of Bioprocess, College of Life Science and Technology, Beijing University of Chemical Technology, Beijing 100029, China.

^bBeijing National Laboratory of Molecular Sciences, CAS Key Laboratory of Molecular Recognition and Function, Institute of Chemistry, Chinese Academy of Sciences, Beijing 100190, China.

^cUniversity of Chinese Academy of Sciences, Beijing 100049, P. R. China.

ARTICLE INFO

Article history: Received Received in revised form Accepted Available online

Keywords: Chiral phosphoric acid Asymmetric transfer hydrogenation Bulky aryl ketones Ammonia borane

Chiral secondary alcohols are universal building blocks and usually have biological activity, and exist widely in the natural products and synthetic chemistry.¹ The catalytic asymmetric reduction of ketones such as hydrogenation,² transfer hydrogenation,³ and Corey-Bakshi-Shibata (CBS) reduction,⁴ provides the most straightforward way for preparing optically pure secondary alcohols. Great success has been achieved in this field. However, only a few reports on the asymmetric reduction of bulky ketones have been reported.⁵ For example, in 2005, Novori and co-workers reported a BINAP/PICA-Ru complex catalyzed asymmetric hydrogenation of *tert*-alkyl ketones with excellent yields and enantioselectivities.^{5a} Clarke group developed a variety of chiral ruthenium catalysts for the hydrogenation and transfer hydrogenation of bulky ketones.^{5b-e} Very recently, Clarke and co-workers also developed a manganese catalyst based chiral P,N,N ligand for bulky ketones to give up to 97% ee.^{5f} Despite these advances, to the best of our knowledge, the metal-free asymmetric reduction of bulky ketones has seldom been reported.

Ammonia borane (AB) is an ideal hydrogen storage material as well as a good hydrogen source for transfer hydrogenations.^{6,7} However, only a very few examples on the asymmetric transfer hydrogenation with ammonia borane as hydrogen source have

ABSTRACT

An asymmetric transfer hydrogenation of bulky aryl ketones with ammonia borane was successfully realized with chiral phosphoric acid (CPA) as catalyst and water as additive. A variety of optically active secondary alcohols were obtained in good to high yields with up to 77% ee. The reaction likely proceeded through a Brønsted acid-promoted double-hydrogen transfer between ketones and ammonia borane via a six-membered concerted transition state.

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been reported (Figure 1).⁸ In 1984, Williams and co-workers described an asymmetric reduction of aromatic ketones with ammonia-borane complexes of chiral tetraphenyl-18-crown-6 derivatives to give 67% ee.^{8a} Recently, our group developed a frustrated Lewis pair (FLP) of (*R*)-*tert*-butylsulfamide and Piers' borane for the asymmetric transfer hydrogenation with ammonia borane.^{8d-g} Very recently, we designed a renewable chiral ammonia borane derived from chiral phosphoric acid (CPA) and ammonia borane, which was a reactive species for asymmetric transfer hydrogenation of imines, β -enamino esters, and enamine cyanides.^{8h,i} Herein, we wish to report our efforts on the chiral phosphoric acid⁹ catalyzed asymmetric transfer hydrogenation of bulky ketones with ammonia borane.



Figure 1. Representative examples on asymmetric reductions with ammonia borane.

The asymmetric transfer hydrogenation of ketones **1a-e** was initially carried out in dichloromethane at 30 $^{\circ}$ C for 4 h by using

^{*} Corresponding author at: Beijing University of Chemical Technology, Beijing 100029, China (J. Yang), and Institute of Chemistry, Chinese Academy of Sciences, Beijing 100190, China (X. Feng, and H. Du).

E-mail addresses: yangj@mail.buct.edu.cn (J. Yang), fxq@iccas.ac.cn (X. Feng), haifengdu@iccas.ac.cn (H. Du).

hydrogen source. As shown in Scheme 1, all these reactions went smoothly to afford the corresponding secondary alcohol 4a-e in quantitative conversions. It was found that increasing steric hindrance of ketones could lead an improvement of ee's. Less bulky acetophenone (1a) and propiophenone (1b) gave racemic products. While ketones 1d and 1e containing a tert-butyl group could give 17% and 19% ee, respectively.



Scheme 1. CPA catalyzed asymmetric transfer hydrogenation of ketones.

To further improve the enantioselectivity, the CPA catalysts, additives and the reaction conditions were next investigated. Solvents had an obvious influence on the enantioselectivity, and benzene could give 47% ee (Table 1, entries 1-3). When H₂O was used as an additive, the ee could be improved up to 55% (Table 1, entries 4-6). CPAs 2b-e were then evaluated for this reaction, and CPA 2a proved to be a better catalyst (Table 1, entries 5 vs 7-10). We were pleased to find that 67% ee was obtained when CS₂ was used as a solvent (Table 1, entry 11). When MeOH was used as an additive, a similar result was afforded (Table 1, entry 12).

Table 1. Evaluation of CPA catalysts and optimization of reaction conditions^a



^aAll reactions were carried out with ketone 1e (0.1 mmol), CPA 2 (10 mol %), and NH₃·BH₃ 3a (1.1 equiv) in solvent (0.5 mL) for 4 h at room temperature.

With the optimal catalyst, solvent, and additive in hand (Table 1, entry 11), the reaction conditions were further optimized. The temperature had a slight impact on reaction the enantioselectivities (Table 2, entries 1-3). Decreasing the loading of CPA 2a from 10 mol % to 0.5 mol % resulted in a little higher ee's without loss of reactivities (Table 2, entries 4-7). When 0.1 mol % of CPA 2a was used, the ee was dropped sharply from 73% to 59% (Table 2, entry 8). Various ammonia boranes 3b-d were subsequently studied for the asymmetric transfer hydrogenation of ketone 1e. Unfortunately, these ammonia boranes bearing methyl groups on the nitrogen atom were not suitable hydrogen sources (Table 2, entries 9-11).

Table 2. Optimization of reaction conditions^a

able 2. Optimization of reaction conditions								
	OMe of the other of the other of the other	-	CPA 2a (x mol % AB 3 (1.1 equiv) H ₂ O (1.1 equiv) rt, CS ₂	a (x mol %) 1.1 equiv) t, CS ₂ 4e				
Entry	2a (mol %)	AB		Time (h)	$\begin{array}{c} \text{Conv} \\ (\%)^b \end{array}$	Ee (%) ^c		
1	10	3a		4	99	67		
2^d	10	3a		7	99	61		
3 ^e	10	3 a		4	99	66		
4	5	3 a		7	99	70		
5	2	3a		7	99	70		
6	1	3a		9	99	73		
7	0.5	3a		12	99	73		
8	0.1	3a		12	91	59		

¹ A11	reactions	were car	ried out	with	ketone	1e	(0.1	mmol).	2a.	H ₂ O	(1.1)
11	0.5	Ν	Ie ₃ N·BH ₃	3 (3d)		12		nr^{f}			
10	0.5	N	$1e_2NH \cdot B$	H ₃ (3 0	c)	12		43		rac	

12

75

rac

MeNH₂·BH₃ (3b)

equiv) and AB (3) (1.1 equiv) in CS₂ (0.5 mL) at room temperature.

^bThe conversion was determined by crude ¹H NMR.

°The ee was determined by chiral HPLC.

dAt 0 °C.

9

0.5

°At 40 °C

^fNo reaction.



Scheme 2. CPA-catalyzed asymmetric transfer hydrogenation of ketones.

A variety of bulky ketones **1e-v** were subjected the asymmetric transfer hydrogenation under the optimal conditions. As shown in Scheme 2, all these reactions proceeded smoothly to give the corresponding secondary alcohols **4e-v** in 71-97% yields with 43-77% ee's. It was found that the *ortho*-substituted groups, especially the alkoxy groups gave a little better ee's. While the *meta-* and *para*-substituents generally gave relatively lower ee's. The reduction of ketones **1t-v** containing other bulky groups instead of *tert*-butyl groups afforded the desired products **4t-v** in high yields with 44-73% ee's.







Scheme 4. Control experiment with chiral ammonia borane.



Figure 3. DFT calculation for the hydrogen transfer process.

In order to have a better insight into the asymmetric transfer hydrogenation of bulky ketones, ³¹P NMR studies were carried out. As shown in Figure 2b, treating CPA **2a** with ammonia borane (**3a**) (1.0 equiv) in CS₂ for 0.5 h, besides the generation of chiral ammonia borane **5**, some CPA **2a** were still unchanged. In contrast, all the CPA could be converted into chiral ammonia borane **5** within 10 min in toluene (Figure 2d). Distinct our previous work,^{8h,i} chiral ammonia borane **5** might not be a reactive species in the current reaction due to the slow reaction of CPA **2a** and ammonia borane (**3a**).

Chiral ammonia borane **5** was prepared in toluene conveniently (Scheme 4). When treating ketone **1e** with chiral ammonia borane **5** (1.0 equiv) in CS₂ at room temperature for 10 h, no reduction occurred. Chiral ammonia borane **5** as the reactive species could therefore be precluded. According to the reported work,⁷ as well the free CPA existing in the current catalytic system, an asymmetric induction model was proposed, in which the CPA promoted the double hydrogen transfer between ketones and ammonia borane via six-membered transition state (Scheme 4). Theoretical investigations on M06-2X/6-31G(d) level provides a further support for this assumption. As shown in Figure 3, two concert transition states were located with a 1.2 kcal/mol energy difference in gas phase, indicating a preference for (*S*)-stereoselectivity, which is in consistent with the experiment results.

In summary, a chiral phosphoric acid catalyzed asymmetric transfer hydrogenation of bulky aryl ketones was realized using ammonia borane as hydrogen source and water as an additive. With as low as 0.5 mol % of catalyst, a variety of bulky ketones were effective substrates to furnish the corresponding optically active secondary alcohols in 71-97% yields with 43-77% ee's. Notably, distinct from our previous work, the current reaction was likely though a chiral Brønsted acid catalysis with a double hydrogen transfer between ketones and ammonia borane via a six-membered concerted transition state. Further efforts on searching for more effective catalysts and exploring more detailed mechanism are underway in our laboratory.

Acknowledgements

We are grateful for generous financial support from the National Natural Science Foundation of China (91856103, 21871269 and 21521002).

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Supplementary Material

Supplementary data (the procedures for the transfer hydrogenation, characterization and data for the determination of ee's along with NMR spectra) associated with this article can be found in the online version.

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4 Re ammonia borane were realized.

- Optically active secondary alcohols were obtained in good to high yields with up to 77% ee.
- 3. A chiral phosphoric acid was used as an effective chiral catalyst.