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Highly Enantioselective Reformatsky Reaction of Ketones: Chelation-Assisted Enantioface Discrimination

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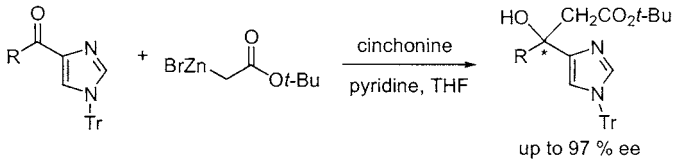
ABSTRACT



Highly enantioselective Reformatsky reaction of ketones was accomplished using cinchona alkaloids as chiral ligands. Chelation with the sp²-nitrogen adjacent to the reactive carbonyl center contributed the enantioface discrimination for the high enantioselectivities.

The asymmetric Reformatsky reaction is a versatile and straightforward approach to obtaining chiral alcohols (β-hydroxy esters), a motif found in biologically active compounds and synthetic intermediates.[1] Although a variety of asymmetric Reformatsky reactions have been developed,[2,3] there have been no reports so far of efficient methods for achieving high enantioselectivity in useful chemical yield. Furthermore, in most cases, aromatic aldehydes have been employed as substrates, and there are few examples of asymmetric Reformatsky reactions with ketones. Representative work was reported by Soai et al.,[3] in which chiral tertiary alcohols were obtained from aryl ketones in moderate enantioselectivity using *N*,*N*-dialkylnorephedrines as chiral ligands. This moderate selectivity might be attributed to poor enantioface discrimination of the ketone due to the bulkiness of both carbonyl substituents. It was thought that this difficulty could be overcome by the introduction of a substituent that participates in the formation of a geometrically defined complex between zinc and the ketone as a reactive intermediate. Herein, we describe highly enantioselective Reformatsky reactions of ketones appended to a nitrogen-containing aromatic ring using cinchona alkaloids as chiral ligands.

In the course of our research into the synthesis of an optically active pharmaceutical compound, we were faced with the problem of developing an efficient and practical construction of a chiral tertiary alcohol. After setting our attention on the Reformatsky reaction, we screened several chiral ligands. We focused on chiral 1,2-amino alcohol derivatives, since a variety of these have been reported to be effective in the enantioselective organozinc addition to carbonyl compounds, including the Reformatsky reaction.[2,4] Cinchona alkaloids are among the most prominent and

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(1) For reviews, see: (a) *Organozinc Reagent*; Knohel, P., Philip, J., Eds.; Oxford University Press: New York, 1999. (b) Fürstner, A. *Synthesis* **1989**, 571.

(2) (a) Andrés, J. M.; Pedrosa, R.; Pérez-Encabo, A. *Tetrahedron* **2000**, *56*, 1217. (b) Ukaji, Y.; Yoshida, Y.; Inomata, K. *Tetrahedron: Asymmetry* **2000**, *11*, 733. (c) Andrés, J. M.; Martín, Y.; Pedrosa, R.; Pérez-Encabo, A. *Tetrahedron* **1997**, *53*, 3787. (d) Mi, A.; Wang, Z.; Zhang, J.; Jiang, Y. *Synth. Commun.* **1997**, *27*, 1469. (e) Mi, A.; Wang, Z.; Chen, Z.; Jiang, Y.; Chan, A. S. C.; Yang T. K. *Tetrahedron: Asymmetry* **1995**, *6*, 2641. (f) Mastantuono, A.; Pini, D.; Rolfini, C.; Salvadori, P. *Chirality* **1995**, *7*, 499. (g) Braun, M.; Vonderhagen, A.; Waldmüller, D. *Liebigs Ann.* **1995**, 1447. (h) Guetté, M.; Guetté, C. J.-P. *Tetrahedron* **1973**, *29*, 3659. (i) Zhang, Y.; Wu, W. *Tetrahedron: Asymmetry* **1997**, *8*, 3575.

(3) Soai, K.; Oshio, A.; Saito, T. *J. Chem. Soc., Chem. Commun.* **1993**, 811.

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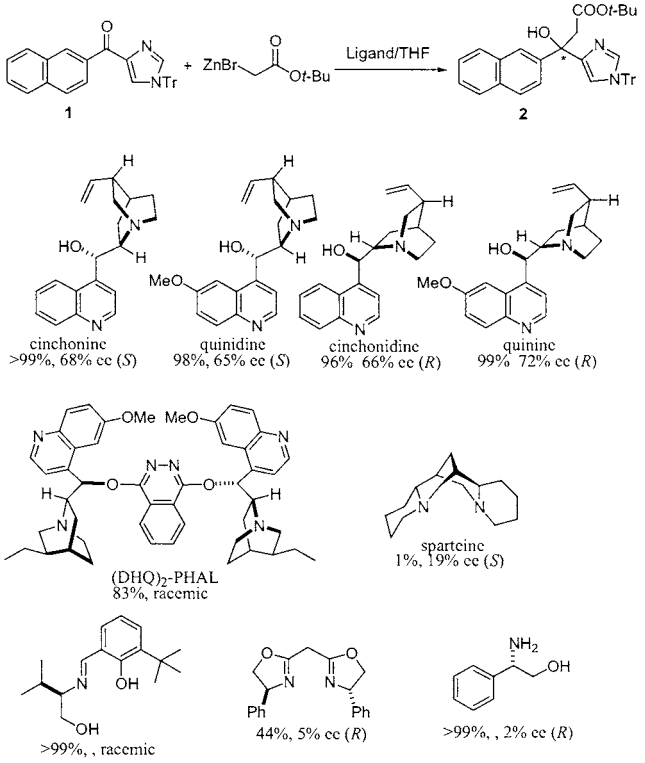
readily available 1,2-amino alcohols; however, to our knowledge, little is known about their usefulness in organozinc chemistry.[5,6]

We have found that, in the presence of 1 equiv of cinchonine, the Reformatsky reaction of aromatic ketone **1** proceeded quantitatively with moderate enantioselectivity (68% ee). Other cinchona alkaloids afforded high yields and similar enantioselectivities under these reaction conditions; however, ligands[7] such as $(DHQ)_2$−PHAL and sparteine gave disappointing enantioselectivities (Scheme 1).

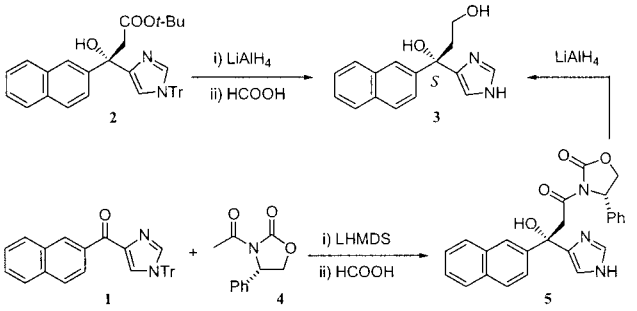
Scheme 1. Asymmetric Reformatsky Reaction of Ketone (**1**) with Chiral Ligands



The configuration of the tertiary alcohol center of **2** was determined to be *S* by conversion to diol **3** (Scheme 2) and comparison with enantiomerically pure diol **3** independently prepared from oxazolizinone derivatives **5**, the absolute configuration of which was determined by a single-crystal X-ray crystallographic analysis.

With the expectation that an additive that could interact with the zinc would change the chiral environment, we

Scheme 2. Determination of Absolute Configuration



introduced basic additives to the reaction mixture. We found that pyridine gave effective enhancement of reactivity and enantioselectivity (Table 1).[8]

Table 1. Effect of Additives in Asymmetric Reformatsky Reaction with Ketone (**1**)

entry[a]	additives (equiv)	yield (%)[b]	ee (%)[b]
1	none	>99	68
2	pyridine (1.0)	>99	76
3	pyridine (1.5)	>99	81
4	pyridine (2.0)	>99	85
5	pyridine (4.0)	>99	85
6	quinoline (4.0)	>99	65
7	*i*-Pr_2EtN (4.0)	>99	70
8	DBU (4.0)	93	6

[a] General reaction conditions: $BrZnCH_2CO_2t$-Bu (3.5 equiv) and cinchonine (1.0 equiv) at 0 °C in THF. [b] Determined by HPLC analysis using a Daicel CHIRALPAK AD (9/1 hexane/2-propanol).

The enantioselectivity was improved by increasing the amount of pyridine added, and the adduct **2** was obtained in good enantiomeric excess (85% ee) in the presence of over 2 equiv of pyridine. However, the addition of *i*-Pr_2EtN had no effect on enantioselectivity and the use of DBU resulted in a marked reduction in enantiomeric excess.

Table 2 summarizes selected results obtained for the Reformatsky reaction of ketone **1** under different conditions. The use of a catalytic amount of cinchonine (0.5 equiv, entry 1) resulted in a decrease in the enantioselectivity (74% ee), whereas excellent enantioselection (94∼95% ee) was obtained in the presence of a slight excess of cinchonine (1.25 and 1.5 equiv, entries 3 and 4, respectively). Lowering the reaction temperature improved enantioselectivity slightly, and the optimal yield and enantiomeric excess were obtained when the reaction was conducted at −40 °C (entry 6). Importantly, after the reaction was completed, the cinchonine could be easily separated from the adduct by simple extraction with aqueous acids and subsequently recovered

(4) (a) Pu, L.; Yu, H.-B. *Chem. Rev.* **2001**, *101*, 757. (b) Dosa, P. I.; Fu, G. C. *J. Am. Chem. Soc.* **1998**, *120*, 445. (c) Ramón, D. J.; Yus, M. *Tetrahedron* **1998**, *54*, 5651.

(5) Stereoselective addition of dialkylzincs to aldehydes catalyzed by cinchona alkaloids has been reported: Smaardijk, A. A.; Wynberg, H. *J. Org. Chem.* **1987**, *52*, 135.

(6) Enantioselective indium-induced Reformatsky-type reaction using cinchona alkaloids has been reported: Johar, P. S.; Araki, S.; Butsugan, Y. *J. Chem. Soc., Perkin Trans. 1* **1992**, 711.

(7) (a) Lowenthal, R. E.; Abiko, A.; Masamune, S. *Tetrahedron Lett.* **1990**, *31*, 6005. (b) Hayashi, M.; Miyamoto, Y.; Inoue, T.; Oguni, N. *J. Org. Chem.* **1993**, *58*, 1515.

(8) Pyridine enhances the enatioselectivity and also accelerates the reaction at low temperatures. In the absence of the pyridine, the reaction with the ketone **1** was not completed even after 12 h at −40 °C (∼80%); however, the reaction was completed within 4 h in the presence of 4 equiv of pyridine (Table 2).

Table 2. Effect of Cinchonine Amount and Reaction Temperature in Asymmetric Reformatsky Reaction with Ketone (**1**)

entry[a]	cinchonine (equiv)	temp (°C)	yield (%)[b]	ee (%)[b]
1	0.50	0	>99	74
2	1.00	0	>99	85
3	1.25	0	>99	94
4	1.50	0	>99	93
5	1.50	rt	97	82
6	1.50	−40	97	97
7	1.50	−78	34	98

[a] General reaction conditions: $BrZnCH_2CO_2t$-Bu (3.5 equiv) and pyridine (4.0 equiv) in THF. [b] Determined by HPLC analysis using a Daicel CHIRALPAK AD (9/1 hexane/2-propanol).

by extraction from the alkalinized aqueous layer. Furthermore, when cinchonidine, a pseudoenantiomer of cinchonine, was used as a chiral ligand, the opposite enantiomer of **2** was isolated in comparable enantioselection (92% ee) and yield (>99%).

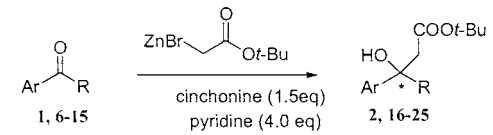
To investigate the scope of the reaction, the Reformatsky reaction with a variety of ketones was carried out under the optimal conditions (Table 3).[9] We found that the enantioselectivity depends critically on the structure of the substrate.

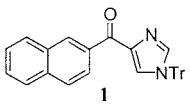
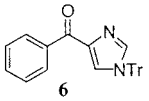
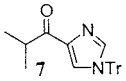
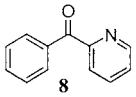
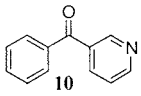
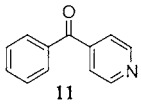
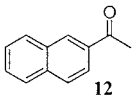
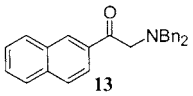
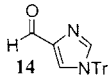
In the case of 4-imidazolyl ketones **1**, **6**, and **7**, the enantiomeric excesses of the products exceeded 94%. High enantioselectivity was also obtained in the reaction of 2-pyridyl ketones **8** and **9** in good yields. The absolute configuration of the product **18** from phenyl 2-pyridyl ketone **8** was proven to be *S* according to the same procedure described above (see Supporting Information). However, the reaction of 3- and 4-pyridyl ketones **10** and **11**, respectively, resulted in markedly decreased enantioselectivity, indicating that the position of the nitrogen of the ketone is crucial to achieving high enantioselectivity. The reaction of 2-acetylnaphthalene **12** or dibenzylamine derivative **13** also gave adducts with considerably diminished ee. These results suggest that, in the case of 4-imidazolyl and 2-pyridyl ketone, an sp^2-nitrogen adjacent to the carbonyl group serves as a coordination site with the zinc for the formation of a chelate, and such a fixed orientation should be requisite for the discrimination of the enantiotopic faces of the substrate.[10] In the reaction of 3- and 4-pyridyl ketones **10** and **11**, respectively, the sp^2-nitrogens on the pyridine ring are not able to form the chelate, which could contribute to the

(9) **Typical Experimental Procedure.** The Reformatsky reagent (0.47 M, 4.3 mL, 2.0 mmol) was added to a suspension of cinchonine (220 mg, 0.75 mmol) in dry THF (1.0 mL) at 0 °C under an argon atmosphere. After the mixture was stirred for 10 min, pyridine (0.15 mL, 2.0 mmol) was added, and the mixture was stirred for 20 min. The ketone (0.50 mmol) dissolved in dry THF (20 mL) was added to the mixture over a period of 10 min at −40 °C. After being stirred at the same temperature for 4 h, the resulting mixture was diluted with 1 N aqueous hydrochloric acid and extracted with ethyl acetate. The extracts were washed with saturated aqueous sodium hydrogen carbonate and brine followed by drying over sodium sulfate. After removal of the solvent in vacuo, the product was subjected to HPLC analysis.

(10) For recent reports on chelation-assisted enantioselective reaction using an sp^2-nitrogen as a directing group, see: (a) Porter, N. A.; Feng, H.; Kavrakova, I. K. *Tetrahedron Lett.* **1999**, *40*, 6713. (b) Sibi, M. P.; Shay, J. J.; Ji, J. *Tetrahedron Lett.* **1997**, *38*, 5955. (c) Kashima, C.; Takahashi, K.; Fukuchi, I.; Fukusawa, K. *Heterocycles* **1997**, *44*, 1.

Table 3. Asymmetric Reformatsky Reaction with Ketones and Related Compounds



entry[a]	substrate	product	yield (%)[b]	ee (%)[b]
1	 **1**	**2**	97	97 (*S*)[c]
2	 **6**	**16**	>99	97
3	 **7**	**17**	73	94
4	 **8**	**18**	98	90 (*S*)[c]
5	 **9**	**19**	94	86
6	 **10**	**20**	27	28
7	 **11**	**21**	41	13
8	 **12**	**22**	42	15
9	 **13**	**23**	>99	0
10	 **14**	**24**	84	66
11	 **15**	**25**	94	70

[a] General reaction conditions: $BrZnCH_2CO_2t$-Bu (3.5 equiv) and pyridine (4.0 equiv) at −40 °C in THF. [b] Determined by HPLC analysis. [c] Absolute configuration was determined after conversion of the corresponding diol (see Scheme 2 and Supporting Information).

enhanced reactivity and enantioselectivity, so the chemical yields and ees of the adducts are significantly decreased. In contrast to previously reported asymmetric Reformatsky reactions, aldehydes **14** and **15** gave only moderate enantioselectivities.

In summary, we have demonstrated a highly enantioselective Reformatsky reaction of ketones using cinchona alkaloids as chiral ligands, wherein the sp^2-nitrogen adjacent

to the reactive carbonyl center plays a pivotal role for the induction of the high enantioselectivity. The improvement of the enantioselectivity by the addition of pyridine is another noticeable point. The high enantioselection that was attained (up to 97% ee) exceeds all previous reports, even though the substrate is limited to carbonyl compounds possessing an adjacent sp^2-nitrogen. This strategy offers a feasible approach to the synthesis of various chiral tertiary alcohols or β-hydroxy esters, which are key intermediates for a number of pharmaceuticals. In addition, the procedure described herein is practical and applicable to the large-scale preparation of our key intermediate.

Acknowledgment. We thank Mr. A. Fujishima and Ms. K. Higashikawa for the determination of the single-crystal X-ray structure of **5**. We also thank Dr. S. Furuya, Dr. T. Taniguchi, Dr. S. Hashiguchi, Dr. M. Kawada, and Dr. T. Sohda for several helpful discussions and their encouragement throughout this work.

Supporting Information Available: Characterization of products, analytical procedures for the determination of enantiomeric excesses, and single-crystal X-ray structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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