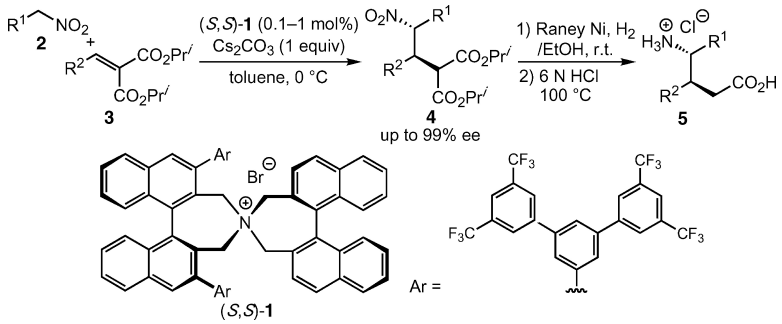
Communication

Highly Enantioselective Conjugate Addition of Nitroalkanes to Alkylidenemalonates Using Efficient Phase-Transfer Catalysis of *N*-Spiro Chiral Ammonium Bromides

Takashi Ooi, Shingo Fujioka, and Keiji Maruoka

J. Am. Chem. Soc., **2004**, 126 (38), 11790-11791• DOI: 10.1021/ja047047v • Publication Date (Web): 01 September 2004



More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Links to the 6 articles that cite this article, as of the time of this article download
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

J|A|C|S
COMMUNICATIONS

Published on Web 09/01/2004

Highly Enantioselective Conjugate Addition of Nitroalkanes to Alkylidenemalonates Using Efficient Phase-Transfer Catalysis of *N*-Spiro Chiral Ammonium Bromides

Takashi Ooi, Shingo Fujioka, and Keiji Maruoka*

Department of Chemistry, Graduate School of Science, Kyoto University, Sakyo, Kyoto 606-8502, Japan

Received May 20, 2004; E-mail: maruoka@kuchem.kyoto-u.ac.jp

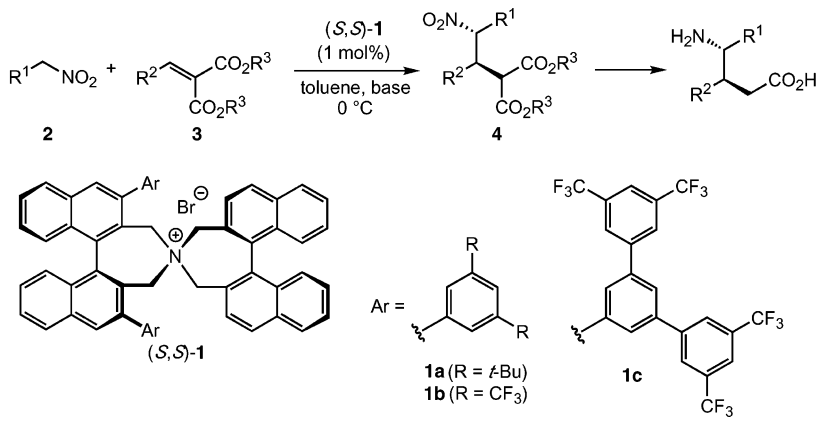
The nucleophilic addition of nitroalkanes to electron-deficient alkenes such as α,β-unsaturated carbonyl compounds offers a powerful synthetic tool for the preparation of useful precursors to various complex organic molecules having functionalities that can be derived from the nitro group.[1] Accordingly, the development of catalytic asymmetric variants constitutes an attractive yet challenging area in current organic chemistry,[1−3] and several important contributions have been reported to date.[3−5] However, all the previous successful examples have dealt with α,β-unsaturated ketones or aldehydes as an acceptor with unfortunate insufficiency in terms of catalytic activity, stereoselectivity, and general applicability. Herein we disclose the first highly enantioselective conjugate addition of nitroalkanes to alkylidenemalonates based on the utilization of efficient phase-transfer catalysis of appropriately designed chiral quaternary ammonium bromides of type **1**[6] (Scheme 1). This approach greatly expands the scope of the conjugate addition involving nitroalkanes as a donor substrate and provides a new and practical entry to optically active γ-amino acid derivatives.

First, we focused on the addition of nitropropane (**2a**) to diethyl benzylidenemalonate (**3a**) under phase-transfer conditions and examined the effect of base, catalyst structure, and ester substituent on the reactivity and selectivity. The reaction was initially conducted by simple mixing of **2a** (5 equiv) with **3a** in toluene at 0 °C in the presence of K_2CO_3 (1 equiv) as a base and chiral quaternary ammonium bromide **1a**[6b] (1 mol %) as catalyst, which proceeded slowly to give the desired conjugate addition product **4a** in only 49% yield (anti/syn = 64:36) with 45% ee (anti isomer) after 20 h (entry 1 in Table 1). The replacement of K_2CO_3 by Cs_2CO_3 provided a substantial rate enhancement to furnish **4a** in 91% yield after 10 h, albeit with a similar degree of stereoselectivity (entry 2). Thus, we moved on the evaluation of the catalyst structure by varying the 3,3′-aromatic substituents (Ar) and found that the introduction of an electron-withdrawing 3,5-bis(trifluoromethyl)phenyl group afforded a beneficial impact on the diastereo- and enantioselectivity, as evident from the results with catalyst **1b**[6c] (entry 3). Further, dramatic improvement of the catalytic activity and stereoselectivity was realized by employing catalyst **1c**,[6a] where the reaction was completed within 2 h to produce **4a** quantitatively with an anti/syn ratio of 81:19 and the enantiomeric excess of major anti isomer was revealed to be 94% ee (entry 4). Here, the use of diisopropyl benzylidenemalonate (**3b**) as an acceptor was found to be advantageous for even more rigorous enantiofacial differentiation and anti-**4b** was obtained with 97% ee, while an additional attempt with **3c** having a sterically more hindered *tert*-butyl ester moiety resulted in a diminished chemical yield and lower stereoselectivity (entries 5 and 6). It is particularly noteworthy that similar catalytic as well as chiral efficiency can be retained with only 0.1 mol % of **1c**, emphasizing the practical aspect of our approach (entry 7).

With this optimized condition in hand, we studied the scope of this new asymmetric conjugate addition protocol, and the representative results are summarized in Table 2. Generally, 1 mol % of **1c** with 1 equiv of Cs_2CO_3 was sufficient for the smooth reaction, giving **4** in nearly quantitative yield. With aryl alkylidenemalonates, the present system tolerated the incorporation of both electron-withdrawing and electron-donating substituents (entries 1−3). Alkyl alkylidenemalonates also appeared to be a good acceptor, and use of mesitylene as a solvent at a lower reaction temperature seemed to be essential for attaining an excellent enantioselectivity in the reaction with alkylidenemalonates having primary alkyl substituents (entries 4 and 5). In addition to nitropropane (**2a**), other nitroalkanes can be utilized as a donor substrate, and, notably, virtually complete stereochemical control was achieved with 2-methyl-1-nitropropane (entries 6−8). When nitromethane was used, performing the addition in mesitylene at −40 °C again led to a high level of enantioselectivity (entry 9).

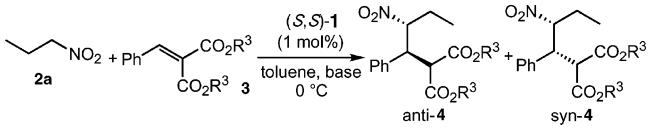
The optically active conjugate addition product **4** thus obtained can be readily derivatized into the corresponding γ-amino acid as exemplified in Scheme 2. The reduction of the nitro moiety of **4b**

Scheme 1



10.1021/ja047047v CCC: $27.50

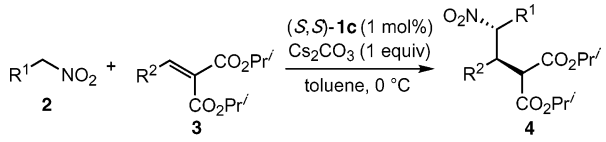
Table 1. Optimization of the Conjugate Addition of Nitropropane (**2a**) to Dialkyl Benzylidenemalonate (**3**)[a]



entry	1	R^3	base	reaction time (h)	yield[b] (%)	anti/syn[c,d]	% ee[d,e] anti	% ee[d,e] syn	product
1	**1a**	Et (**3a**)	K_2CO_3	20	49	64:36	45	16	**4a**
2	**1a**	Et	Cs_2CO_3	10	91	62:38	44	14	
3	**1b**	Et	Cs_2CO_3	10	98	76:24	74	24	
4	**1c**	Et	Cs_2CO_3	2	99	81:19	94	76	
5	**1c**	*i*-Pr (**3b**)	Cs_2CO_3	2.5	99	86:14	97	68	**4b**
6	**1c**	*t*-Bu (**3c**)	Cs_2CO_3	24	21	59:41	82	26	**4c**
7[f]	**1c**	*i*-Pr	Cs_2CO_3	12	99	86:14	97	63	**4b**

[a] Unless otherwise specified, the reaction was carried out with 5 equiv of nitropropane (**2a**) and 1 equiv of base in the presence of 1 mol % of (*S*,*S*)-**1** in toluene at 0 °C. [b] Isolated yield. [c] Determined by ^{1}H NMR analysis. [d] Assignment of the relative and absolute configurations of the major anti-**4** was deduced from that of **4j**.[6] [e] Enantiopurity was determined by HPLC analysis using a chiral column (DAICEL Chiralpak AD-H) with hexane-2-propanol as a solvent. [f] With 0.1 mol % of **1c** and 2 equiv of Cs_2CO_3.

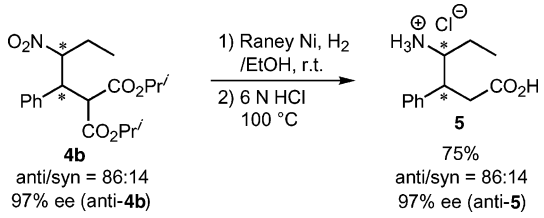
Table 2. Catalytic Asymmetric Conjugate Addition of Nitroalkanes **2** to Diisopropyl Alkylidenemalonates **3** under Phase-Transfer Conditions[a]



entry	**2** (R^1)	**3** (R^2)	react. time (h)	% yield[b] (anti/syn)[c,d]	% ee[d,e]	product
1	Et (**2a**)	*p*-F-C_6H_4	1	99 (89:11)	98	**4d**
2	Et	*p*-MeO-C_6H_4	3	97 (89:11)	96	**4e**
3	Et	2-Naph	3	99 (86:14)	96	**4f**
4	Et	*c*-Hex	10	99 (85:15)	95	**4g**
5[f,g]	Et	Me_2CHCH_2	24	97 (71:29)	98	**4h**
6	Me	Ph	2.5	99 (80:20)	97	**4i**
7	Me_2CH	Ph	5	99 (95:5)	99	**4j**
8[h]	$BnO(CH_2)_2$	Ph	2	99 (85:15)	96	**4k**
9[f]	H	Ph	20	99	88	**4l**

[a] Unless otherwise specified, the reaction was carried out with 5 equiv of **2** and 1 equiv of Cs_2CO_3 in the presence of 1 mol % of **1c** in toluene at 0 °C for the given reaction time. [b] Isolated yield. [c] Determined by ^{1}H NMR analysis. [d] Stereochemical assignment was deduced from that of **4j**, which was established by X-ray crystallographic analysis after the reduction of the nitro group and subsequent condensation with *N*-Z-L-proline.[7] [e] Enantiomeric excess of the major anti-**4** was determined by HPLC analysis using a chiral column (DAICEL Chiralpak AD-H) with hexane-2-propanol as a solvent. [f] Performed at −40 °C in mesitylene. [g] With 2 equiv of Cs_2CO_3. [h] With 2 equiv of 3-benzyloxy-1-nitropropane.

Scheme 2



with Raney Ni/H_2 in ethanol at room temperature followed by the treatment with 6 N HCl at 100 °C furnished the γ-amino acid hydrochloride **5** in 75% isolated yield without loss of diastereo- and enantiomeric excesses.

In conclusion, we have successfully demonstrated that the phase-transfer catalysis of *N*-spiro C_2-symmetric chiral quaternary ammonium bromide **1c** enabled the efficient, highly stereoselective conjugate addition of nitroalkanes to alkylidenemalonates under mild conditions. This practical method certainly provides a facile access to a variety of optically active γ-amino acid derivatives. Further applications of this new asymmetric conjugate addition procedure to the catalytic asymmetric synthesis of biologically active compounds are currently under investigation in our laboratory.

Acknowledgment. This work was partially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

Supporting Information Available: Representative experimental procedures and spectroscopic characterization of all new compounds, including stereochemical assignment (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Ono, N. *The Nitro Group in Organic Synthesis*; Wiley-VCH: New York, 2001, Chapter 4.

(2) For recent reviews on catalytic asymmetric Michael reaction, see: (a) Krause, N.; Hoffman-Röder, A. *Synthesis* **2001**, 171−196. (b) Sibi, M.; Manyem, S. *Tetrahedron* **2000**, *56*, 8033−8061. (c) Kanai, M.; Shibasaki, M. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley: New York, 2000; pp 569−592. (d) Tomioka, K.; Nagaoka, Y. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 3, Chapter 31.1.

(3) For review on catalytic asymmetric conjugate addition of stabilized carbanions, see: Yamaguchi, M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 3, Chapter 31.2.

(4) (a) Yamaguchi, M.; Shiraishi, T.; Igarashi, Y.; Hirama, M. *Tetrahedron Lett.* **1994**, *35*, 8233−8236. (b) Davis. A. P.; Dempsey, K. J. *Tetrahedron: Asymmetry* **1995**, *6*, 2829−2840. (c) Keller, E.; Veldman, N.; Spek, A. L.; Feringa, B. L. *Tetrahedron: Asymmetry* **1997**, *8*, 3403−3413. (d) Yamaguchi, M.; Igarashi, Y.; Reddy, R. S.; Shiraishi, T.; Hirama, M. *Tetrahedron* **1997**, *53*, 11223−11236. (e) Funabashi, K.; Saida, Y.; Kanai, M.; Arai, T.; Sasai, H.; Shibasaki, M. *Tetrahedron Lett.* **1998**, *39*, 7557−7558. (f) Hanessian, S.; Pham, V. *Org. Lett.* **2000**, *2*, 2975−2978. (g) Halland, N.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **2002**, *67*, 8331−8338. (h) Itoh, K.; Kanemasa, S. *J. Am. Chem. Soc.* **2002**, *124*, 13394−13395. (i) Allingham, M. T.; Howard-Jones, A.; Murphy, P. J.; Thomas, D. A.; Caulkett, P. W. R. *Tetrahedron Lett.* **2003**, *44*, 8677−8680.

(5) With phase-transfer catalysis: (a) Corey, E. J.; Zhang, F.-Y. *Org. Lett.* **2000**, *2*, 4257−4259. (b) Kim, D. Y.; Huh, S. C. *Tetrahedron* **2001**, *57*, 8933−8938.

(6) (a) Ooi, T.; Taniguchi, M.; Kameda, M.; Maruoka, K. *Angew. Chem., Int. Ed.* **2002**, *41*, 4542−4544. (b) Ooi, T.; Tayama, E.; Maruoka, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 579−582. (c) Ooi, T.; Miki, T.; Taniguchi, M.; Shiraishi, M.; Takeuchi, M.; Maruoka, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 3796−3798. (d) Ooi, T.; Sakai, D.; Takeuchi, M.; Tayama, E.; Maruoka, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 5868−5870. See also: (e) Ooi, T.; Doda, K.; Maruoka, K. *Org. Lett.* **2001**, *3*, 1273−1276. (f) Ooi, T.; Doda, K.; Maruoka, K. *J. Am. Chem. Soc.* **2003**, *125*, 2054−2055. (g) Ooi, T.; Doda, K.; Maruoka, K. *J. Am. Chem. Soc.* **2003**, *125*, 9022−9023.

(7) For details, see Supporting Information.

JA047047V