

N-Spiro Chiral Quaternary Ammonium Bromide Catalyzed Diastereo- and Enantioselective Conjugate Addition of Nitroalkanes to Cyclic α,β -Unsaturated Ketones under Phase-Transfer Conditions

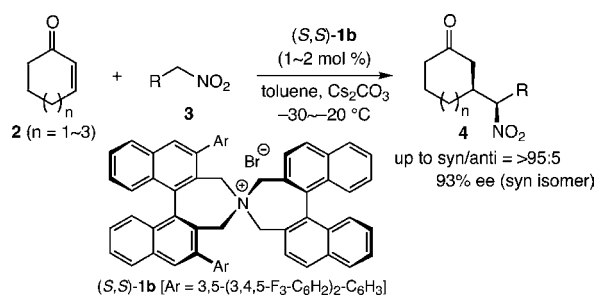
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ABSTRACT



Conjugate addition of various prochiral nitroalkanes to cyclic α,β -unsaturated ketones was found to be efficiently catalyzed by *N*-spiro C₂-symmetric chiral quaternary ammonium bromide **1b** possessing a 3,5-bis(3,4,5-trifluorophenyl)phenyl substituent under solid–liquid phase-transfer conditions to afford the corresponding γ -nitro ketones in excellent chemical yields with unprecedented levels of diastereo- and enantiocontrol.

The conjugate addition of appropriate stabilized carbanions to α,β -unsaturated carbonyl compounds represents one of the fundamental synthetic operations for the construction of carbon–carbon bonds in organic chemistry.¹ Among conceivable combinations of stabilized carbanions and unsaturated carbonyl substrates, the systems involving nitroalkanes are attractive due to the diversity of the further functional group transformations of the conjugate adducts such as selective reduction to amino carbonyl compounds.² Therefore, notable efforts toward establishing the catalytic enantioselective versions have been made on the basis of the

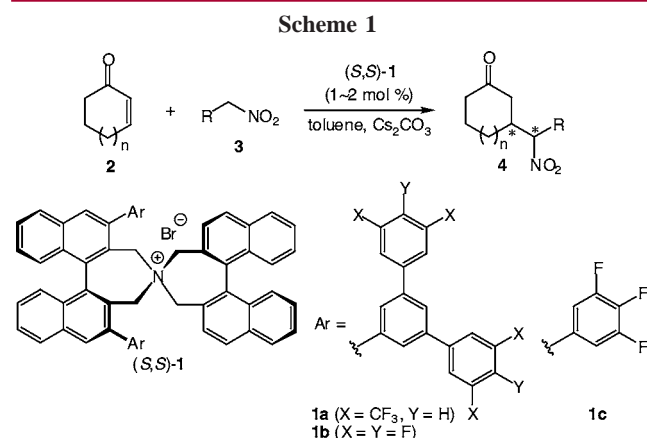
different types of strategies.^{2–5,7} Nevertheless, catalytic asymmetric addition of nitroalkanes to cyclic α,β -unsaturated ketones has only been reported for very few systems.⁵ In 1994, Yamaguchi and co-workers discovered the effectiveness of rubidium prolinate as a catalyst for the addition of nitropropane to cyclohexenone,^{5a,b} and quite recently, Han-

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(3) For review on catalytic asymmetric conjugate addition of stabilized carbanions, see: (a) Yamaguchi, M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 3, Chapter 31.2. (b) Yamaguchi, M. In *Comprehensive Asymmetric Catalysis Supplement 1*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 2004; p 151.

(1) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon Press: Oxford, 1992.

essian disclosed that the utilization of L-proline as catalyst in the presence of *trans*-2,5-dimethylpiperazine significantly improved the enantioselectivity of the addition of various nitroalkanes to cyclic enones.^{5c} Despite these important contributions, however, control of both the relative and absolute configuration of two adjacent stereogenic carbon centers newly created during this bond-forming event still remains as a challenging problem to be solved. Herein, we wish to communicate that the conjugate addition of a series of prochiral nitroalkanes to cyclic α,β -unsaturated ketones can be efficiently catalyzed by *N*-spiro chiral quaternary ammonium bromide of type **1**^{6,7} under solid–liquid phase-transfer conditions to afford the corresponding γ -nitro ketones with high diastereo- and enantioselectivities (Scheme 1).



On the basis of promising activity of chiral quaternary ammonium bromide **1a** in the conjugate addition of nitroalkanes to alkylidenemalonates under phase-transfer conditions,⁷ we initially explored the possible utility of this catalyst in the addition of nitropropane (**3a**) to cyclohexenone (**2a**). Thus, a mixture of **2a**, Cs₂CO₃ (1 equiv), and **1a** (1 mol %) in toluene was treated with **3a** at 0 °C and then stirred at the same temperature for 40 min, affording the corresponding conjugate adduct **4a** almost quantitatively. Here, preferential formation of the syn isomer was observed (syn/anti = 87:13), and fortunately, its enantiomeric excess was determined to be 76% ee (entry 1 in Table 1). This promising result prompted us to further survey catalysts of this type, and we found that **1b** having the 3,5-bis(3,4,5-trifluorophenyl)phenyl group as the 3,3'-aromatic substituent (Ar) provided the highest levels of both diastereo- and enantiocontrols (entry 2). The importance of the *m*-terphenyl-derived structure of the Ar moiety for attaining sufficient reactivity and selectivity was evident from the diminished efficiency and stereoselectivities of the reaction under the influence of **1c**^{6a,c} (entry 3). Efforts were then made toward the optimization of the reaction conditions, which revealed that decreasing the substrate concentration at lower reaction temperature delivered a beneficial effect on the diastereo- and enantioselectivities as included in Table 1. Consequently, syn-**4a** was obtained predominantly (syn/anti = 98:2) with 92% ee by performing the conjugate addition at 0.05 M substrate

Table 1. Optimization of the Conjugate Addition of Nitropropane (**3a**) to Cyclohexenone (**2a**) under Phase-Transfer Conditions^a

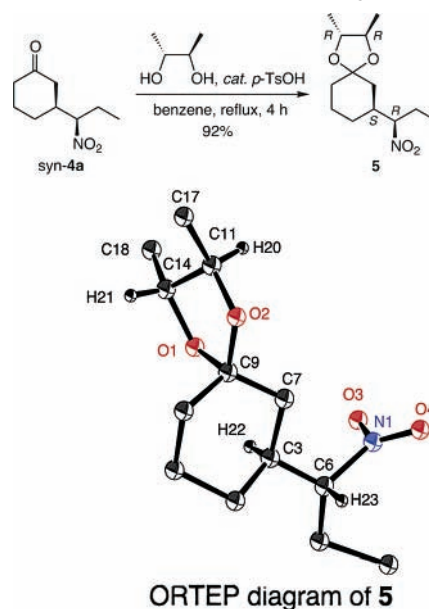
entry	catal 1	conc (M)	<i>T</i> (°C)	reaction time (h)	% yield ^b	syn/anti ^c	% ee ^d	
							syn	anti
1	1a	0.3	0	0.6	99	87:13	76	30
2	1b	0.3	0	0.5	97	93:7	80	39
3	1c	0.3	0	15	95	78:22	21	4
4	1b	0.3	0	1	98	94:6	84	45
5	1b	0.1	0	1	99	94:6	86	47
6	1b	0.05	−20	6	99	96:4	91	57
7	1b	0.05	−40	36	91	98:2	92	37
8 ^e	1b	0.05	−40	22	97	98:2	91	40

^a Unless otherwise specified, the reaction was conducted with 5 equiv of nitropropane (**3a**) in the presence of 1 equiv of Cs₂CO₃ and 1 mol % of (*S,S*)-**1** in toluene under the given reaction conditions. The relative and absolute configurations of the conjugate addition product **4a** were determined by a single-crystal X-ray diffraction analysis after derivatization to its acetal with (2*R*,3*R*)-butanediol. See Scheme 2. ^b Isolated yield. ^c Determined by GLC analysis. ^d Enantiopurity of **4a** was determined by GLC analysis using a chiral column [Astec Chiralcel I-TA (30 m × 0.25 mm)]. ^e With 3 equiv of Cs₂CO₃.

concentration and at −40 °C (entry 7). It should be noted that the use of excess Cs₂CO₃ led to substantial rate acceleration without sacrificing the stereoselectivities (entry 8).

The relative and absolute stereochemistries of syn-**4a** were unequivocally determined by X-ray crystallographic analysis after conversion to the corresponding acetal **5** with (2*R*,3*R*)-

Scheme 2. Stereochemical Assignment



butanediol as shown in Scheme 2. Assuming the predominant generation of the *E*-nitronate,⁸ the observed high syn selectivity could not be fully rationalized by the nonchelate, acyclic extended transition-state model.⁹ This stereochemical preference may be accounted for by the severe steric congestion caused by the chiral quaternary ammonium cation, overwhelming the repulsion between the cyclohexenone framework and the nitroalkane side chain (Et) (Figure 1, A

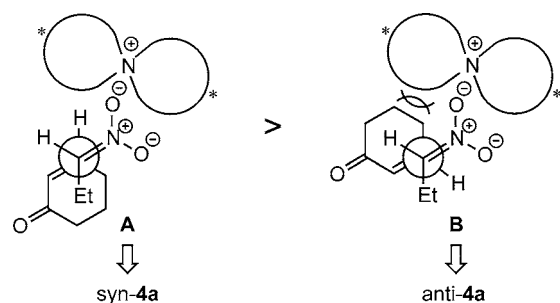


Figure 1. Plausible transition-state model.

vs B). Judging from the product configuration, the chiral ammonium cation should effectively shield the *re*-face of the nitronate, and the selective approach of the cyclic enone from the *si*-face should result.

Based on the above findings, we selected the catalysis of **1b** at $-20\text{ }^{\circ}\text{C}$ (0.05 M substrate concentration) as optimal conditions in terms of both asymmetric induction and reaction efficiency and applied it in further experiments to probe the substrate scope. The representative results summarized in Table 2 clearly demonstrate the potential of this phase-transfer-catalyzed conjugate addition protocol. Various prochiral

Table 2. Catalytic Asymmetric Conjugate Addition of Nitroalkanes (**3**) to Cyclic α,β -Unsaturated Ketones (**2**) under Phase-Transfer Conditions^a

entry	2	3 (R)	react time (h)	% yield ^b (syn/anti) ^c	%ee ^d	prod.
1	2a (n = 1)	PhCH ₂	4	99 (>95:5)	93	4b
2 ^e	2a	CH ₂ =CH(CH ₂) ₂	15	99 (>95:5)	90	4c
3 ^f	2a	<i>i</i> -Pr	24	97 (>95:5)	83	4d
4 ^{e,f}	2a	<i>c</i> -HexCH ₂	80	98 (95:5)	91	4e
5	2a	EtO ₂ CCH ₂	14	99 (89:11)	90	4f
6	2b (n = 2)	Et	18	99 (88:12)	85	4g
7	2c (n = 3)	Et	16	96 (64:36)	82	4h
8	2d	Et	4	94 (>95:5)	81	4i

^a Unless otherwise noted, the reaction was conducted with 5 equiv of **3** in the presence of 3 equiv of Cs₂CO₃ and 1 mol % of (*S,S*)-**1b** in toluene at $-20\text{ }^{\circ}\text{C}$ for the given reaction time. Assignment of the relative and absolute configurations was deduced from that of **4a**. ^b Isolated yield. ^c Determined by ¹H and ¹³C NMR analyses. ^d Enantiopurity of the major syn-**4** was determined by HPLC analysis using a chiral column. For details, see the Supporting Information. ^e Performed at $-30\text{ }^{\circ}\text{C}$. ^f With 2 mol % of **1b**.

nitroalkanes were employed for the addition to cyclohexenone, and the corresponding γ -nitro ketones were obtained in excellent chemical yields with high diastereo- and enantioselectivities (entries 1–5). It should be noted that steric constraints arising from the β - and γ -substituent of nitroalkane can be overcome by using 2 mol % of **1b** (entries 3 and 4). As an acceptor, cycloheptenone and even cyclooctenone were found to be a good candidate, though insufficient diastereocontrol was observed in the case of cyclooctenone probably due to its conformational flexibility (entries 6 and 7). Moreover, the reaction with cyclohexenone derivative possessing additional functionalities such as 2-cyclohexen-1,4-dione monoketal appeared feasible with high efficiency and stereoselectivities (entry 8).

In conclusion, we have demonstrated the effectiveness of the chiral phase-transfer catalysis of *N*-spiro chiral quaternary ammonium bromide **1b** for the highly diastereo- and enantioselective conjugate addition of nitroalkanes to cyclic α,β -unsaturated ketones. This study certainly expands the scope of our approach, and also implies the possibility of elaborat-

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ing even more versatile catalyst systems for the synthetically attractive yet relatively underdeveloped conjugate addition chemistry of nitroalkanes.

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Supporting Information Available: Representative experimental procedure, spectroscopic characterization, and ^1H and ^{13}C NMR spectra of new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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