

Organic & Biomolecular Chemistry

This article is part of the

OBC 10th anniversary
themed issue

All articles in this issue will be gathered together
online at

www.rsc.org/OBC10



Cite this: *Org. Biomol. Chem.*, 2012, **10**, 5753

www.rsc.org/obc

COMMUNICATION

The direct catalytic asymmetric aldol reaction of α -substituted nitroacetates with aqueous formaldehyde under base-free neutral phase-transfer conditions†‡

Seiji Shirakawa, Kensuke Ota, Shogo J. Terao and Keiji Maruoka*

Received 29th December 2011, Accepted 30th January 2012

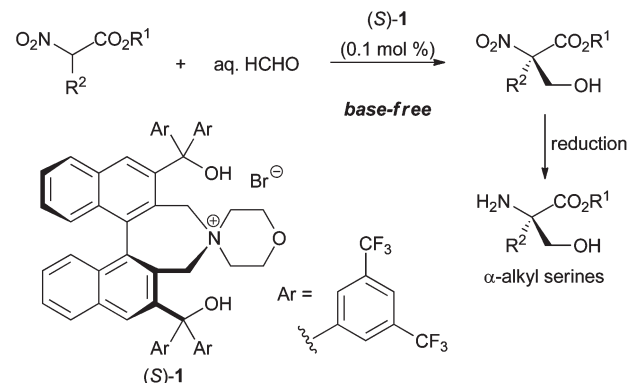
DOI: 10.1039/c2ob07193b

Enantioselective direct aldol reaction of α -substituted nitroacetates with aqueous formaldehyde for the synthesis of α -alkyl serines has been achieved under base-free neutral phase-transfer conditions with a bifunctional chiral phase-transfer catalyst.

For over two decades, asymmetric phase-transfer catalysis based on the use of structurally well-defined chiral quaternary ammonium salts as phase-transfer catalysts has been a topic of great scientific interest, and recent enormous efforts have resulted in notable achievements, making it feasible to perform various stereoselective bond formations under phase-transfer conditions with aqueous or solid bases.¹ Among them, development of highly enantioselective direct aldol reactions,² which are one of the most important reactions in organic synthesis, is a formidable challenge in phase-transfer chemistry. Although a few examples of direct catalytic asymmetric aldol reactions under phase-transfer conditions have been reported,^{3,4} the stereoselectivity of such aldol products is low to moderate in most cases, except one example.⁴ The main reason for modest selectivity of the reactions originates from the retro-aldol reaction, which is difficult to suppress under *basic* phase-transfer conditions.⁵ In the course of our study on the development of asymmetric reactions under phase-transfer conditions, we have recently discovered the hitherto unknown base-free *neutral* phase-transfer reaction system in enantioselective conjugate additions.⁶ In this context, we are interested in the application of this attractive base-free neutral reaction system to the direct aldol reaction. Here we wish to report direct catalytic asymmetric aldol reaction of α -substituted nitroacetates with aqueous formaldehyde, which is one of the most convenient C1 sources in organic synthesis,⁷ under base-free neutral phase-transfer conditions with low catalyst

loading (0.1 mol%). This reaction offers a practical synthetic method for optically active α -alkyl serines as biologically important compounds (Scheme 1).⁸

We first investigated the effect of ester moiety of 2-nitropropanoate in asymmetric aldol reaction with aqueous formaldehyde under base-free neutral conditions (Table 1, entries 1–4). Attempted reaction of methyl 2-nitropropanoate and aqueous formaldehyde in toluene/H₂O (1 : 1) under the influence of bifunctional chiral phase-transfer catalyst (*S*)-**1** with low catalyst loading (0.1 mol%) at room temperature (25 °C) for 24 hours afforded an aldol product **2a** in high yield with almost no enantioselectivity (entry 1). Exchange of the alkyl group of ester moiety to bulky *tert*-butyl group gave the aldol product **2b** with low enantioselectivity (entry 2). Pleasingly, the use of benzyl 2-nitropropanoate improved the enantioselectivity (35% ee, entry 3), and further improvement of enantioselectivity was attained using diphenylmethyl 2-nitropropanoate as a substrate in toluene/H₂O (68% ee, entry 4). With the diphenylmethyl 2-nitropropanoate as a key substrate for the reaction, solvent effect was investigated (Table 1, entries 4–7). Although the use of dichloromethane and cyclopentyl methyl ether (CPME) as organic solvents instead of toluene caused the decrease of enantioselectivities (entries 5 and 6), the reaction in mesitylene/H₂O enhanced enantioselectivity (80% ee, entry 7). The highest enantioselectivity was attained when lower temperature (0 °C) was



Scheme 1 Direct asymmetric aldol reaction under base-free neutral phase-transfer conditions.

Laboratory of Synthetic Organic Chemistry and Special Laboratory of Organocatalytic Chemistry, Department of Chemistry, Graduate School of Science, Kyoto University, Sakyo, Kyoto 606-8502, Japan.
E-mail: maruoka@kuchem.kyoto-u.ac.jp; Fax: +81-75-753-4041;
Tel: +81-75-753-4041

† This article is part of the *Organic & Biomolecular Chemistry* 10th Anniversary issue.

‡ Electronic supplementary information (ESI) available: Experimental details and characterization data for new compounds. See DOI: 10.1039/c2ob07193b

Table 1 Optimization of reaction conditions^a

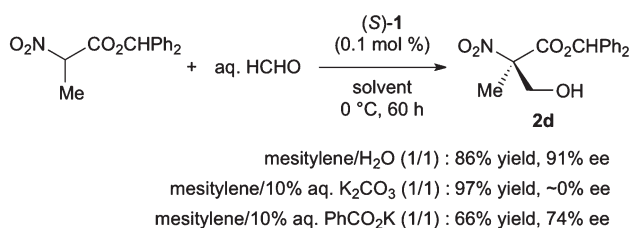
$\text{O}_2\text{N}-\text{CH}(\text{Me})-\text{CO}_2\text{R}^1 + \text{aq. HCHO} \xrightarrow[\text{rt, 24 h}]{\text{(S)-1 (0.1 mol \%), solvent/H}_2\text{O (1/1)}} \text{O}_2\text{N}-\text{CH}(\text{Me})-\text{CH}(\text{OH})-\text{CO}_2\text{R}^1 \quad \mathbf{2}$				
Entry	R ¹	Solvent	Yield ^b (%)	ee ^c (%)
1	Me	Toluene	91 (2a)	~0
2	<i>t</i> -Bu	Toluene	98 (2b)	7
3	Bn	Toluene	99 (2c)	35
4	CHPh ₂	Toluene	98 (2d)	68
5	CHPh ₂	CH ₂ Cl ₂	55 (2d)	51
6	CHPh ₂	CPME ^d	89 (2d)	29
7	CHPh ₂	Mesitylene	79 (2d)	80
8 ^e	CHPh ₂	Mesitylene	86 (2d)	91
9 ^e	Bn	Mesitylene	98 (2c)	87

^a Reaction conditions: 2-nitropropanoate (0.050 mmol) and 37% aqueous formaldehyde (0.25 mmol) in the presence of 0.1 mol% of (S)-**1** in organic solvent (1.0 mL)/H₂O (1.0 mL) at room temperature (25 °C) for 24 h. ^b Yield of isolated products. ^c Determined by chiral HPLC analysis. ^d CPME = cyclopentyl methyl ether. ^e Reaction was performed at 0 °C for 60 h.

Table 2 Direct asymmetric aldol reaction of α-substituted nitroacetates with aqueous formaldehyde^a

$\text{O}_2\text{N}-\text{CH}(\text{R}^2)-\text{CO}_2\text{CHPh}_2 + \text{aq. HCHO} \xrightarrow[\text{0 °C, 60 h}]{\text{(S)-1 (0.1 mol \%), mesitylene/H}_2\text{O (1/1)}} \text{O}_2\text{N}-\text{CH}(\text{R}^2)-\text{CH}(\text{OH})-\text{CO}_2\text{CHPh}_2 \quad \mathbf{3}$			
Entry	R ²	Yield ^b (%)	ee ^c (%)
1	Me	86 (2d)	91
2 ^d	Me	76 (2d)	91
3	Et	70 (3a)	83
4	<i>n</i> -Pr	71 (3b)	81
5	<i>n</i> -Bu	86 (3c)	81
6 ^e	(CH ₃) ₂ CHCH ₂ CH ₂	77 (3d)	82
7	CH ₂ =CHCH ₂ CH ₂	70 (3e)	76
8 ^f	BocNH(CH ₂) ₃ CH ₂	62 (3f)	74

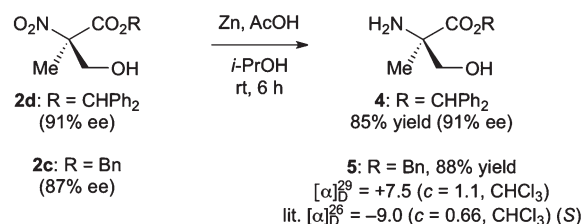
^a Reaction conditions: α-substituted nitroacetate (0.050 mmol) and 37% aqueous formaldehyde (0.25 mmol) in the presence of 0.1 mol% of (S)-**1** in mesitylene (1.0 mL)/H₂O (1.0 mL) at 0 °C for 60 h. ^b Yield of isolated products. ^c Determined by chiral HPLC analysis. ^d Reaction was performed in mesitylene/H₂O = 1 : 10. ^e Reaction was performed with 0.5 mol% of (S)-**1** for 48 h. ^f Reaction was performed with 0.5 mol% of (S)-**1**.

**Scheme 2** Effect of aqueous base solution.

employed in mesitylene/H₂O with prolonged reaction time (91% ee, entry 8).^{9,10} The reaction using benzyl 2-nitropropanoate under this optimized reaction conditions also gave the aldol product **2c** with high enantioselectivity (87% ee, entry 9).

It should be noted that the reaction under ordinary phase-transfer conditions using aqueous base solutions, such as aqueous K₂CO₃, caused a serious decrease in enantioselectivity (Scheme 2).¹¹ Even with PhCO₂K as a relatively mild base, decrease of enantioselectivity was observed in the reaction. These results clearly indicate that the neutral phase-transfer conditions are crucially important to obtain high enantioselectivity in the present reaction.

With optimal reaction conditions in hand, we studied the substrate generality of the direct asymmetric aldol reaction of α-substituted nitroacetates with aqueous formaldehyde under the neutral phase-transfer conditions (Table 2). Various types of nitroacetates were found to be employable for the reaction. The reaction of nitroacetates with a simple alkyl chain gave the corresponding aldol products in good to high enantioselectivities (81–91% ee, entries 1–6). The nitroacetates possessing functional groups were also employable for the reaction to give corresponding products **3e** and **3f** in good enantioselectivities (74–76% ee, entries 7 and 8). It should be noted that even in the water-rich biphasic reaction system (mesitylene/H₂O = 1 : 10),

**Scheme 3** Reduction of the nitro group on products.

the reaction gave the product with high enantioselectivity (entry 2).¹²

The nitro group of resulting aldol products **2** and **3** can be readily reduced to obtain α-alkyl serines. For example, treatment of aldol products **2d** and **2c** with acetic acid in iso-propanol in the presence of zinc¹³ gave the corresponding α-methylserines **4** and **5**, which are core structure of biologically active natural products such as conagenin¹⁴ and piperazimycins,¹⁵ in 85 and 88% yields, respectively, without loss of enantioselectivity (Scheme 3). The absolute configuration of product **5** was assigned to be *R* by comparison of the optical rotation with the literature value.^{14d}

In summary, we have developed the enantioselective direct aldol reaction of α-substituted nitroacetates with aqueous formaldehyde for the synthesis of α-alkyl serines as biologically important compounds. The base-free neutral phase-transfer conditions with a bifunctional chiral phase-transfer catalyst are indispensable to obtain high enantioselectivity. The present report demonstrates a valuable example of hitherto difficult highly enantioselective direct aldol reactions catalyzed by tetraalkylammonium bromide. Further investigations on the neutral phase-transfer reaction system using a chiral bifunctional ammonium salt to produce important compounds are currently underway.

Acknowledgements

This work was partially supported by a Grant-in-Aid for Scientific Research from JSPS, MEXT (Japan) and The Association for the Progress of New Chemistry.

Notes and references

- For representative reviews on asymmetric phase-transfer catalysis see: (a) M. J. O'Donnell, in *Catalytic Asymmetric Synthesis*, ed. I. Ojima, Verlag Chemie, New York, 1993, ch. 8; (b) T. Shioiri, in *Handbook of Phase-Transfer Catalysis*, ed. Y. Sasson and R. Neumann, Blackie Academic & Professional, London, 1994, ch. 14; (c) A. Nelson, *Angew. Chem., Int. Ed.*, 1999, **38**, 1583; (d) T. Shioiri and S. Arai, in *Stimulating Concepts in Chemistry*, ed. F. Vogtle, J. F. Stoddart and M. Shibasaki, Wiley-VCH, Weinheim, 2000, p. 123; (e) M. J. O'Donnell, in *Catalytic Asymmetric Synthesis*, ed. I. Ojima, Wiley-VCH, New York, 2nd edn, 2000, ch. 10; (f) M. J. O'Donnell, *Aldrichimica Acta*, 2001, **34**, 3; (g) K. Maruoka and T. Ooi, *Chem. Rev.*, 2003, **103**, 3013; (h) M. J. O'Donnell, *Acc. Chem. Res.*, 2004, **37**, 506; (i) B. Lygo and B. I. Andrews, *Acc. Chem. Res.*, 2004, **37**, 518; (j) J. Vachon and J. Lacour, *Chimia*, 2006, **60**, 266; (k) T. Ooi and K. Maruoka, *Angew. Chem., Int. Ed.*, 2007, **46**, 4222; (l) T. Hashimoto and K. Maruoka, *Chem. Rev.*, 2007, **107**, 5656; (m) T. Ooi and K. Maruoka, *Aldrichimica Acta*, 2007, **40**, 77; (n) K. Maruoka, *Org. Process Res. Dev.*, 2008, **12**, 679; (o) K. Maruoka, *Asymmetric Phase Transfer Catalysis*, Wiley-VCH, Weinheim, 2008; (p) S.-S. Jew and H.-G. Park, *Chem. Commun.*, 2009, 7090; (q) S. Shirakawa and K. Maruoka, in *Catalytic Asymmetric Synthesis*, ed. I. Ojima, John Wiley & Sons, Hoboken, New Jersey, 3rd edn, 2010, ch. 2C; (r) K. Maruoka, *Chem. Rec.*, 2010, **10**, 254.
- For representative reviews on direct asymmetric aldol reaction see: (a) B. Alcaide and P. Almendros, *Eur. J. Org. Chem.*, 2002, 1595; (b) M. Shibasaki, S. Matsunaga and N. Kumagai, in *Modern Aldol Reactions*, ed. R. Mahrwald, Wiley-VCH, Weinheim, 2004, ch. 6, vol. 2; (c) W. Notz, F. Tanaka and C. F. Barbas III, *Acc. Chem. Res.*, 2004, **37**, 580; (d) S. Mukherjee, J. W. Yang, S. Hoffmann and B. List, *Chem. Rev.*, 2007, **107**, 5471; (e) B. M. Trost and C. S. Brindle, *Chem. Soc. Rev.*, 2010, **39**, 1600.
- (a) C. M. Gasparski and M. J. Miller, *Tetrahedron*, 1991, **47**, 5367; (b) S. Arai, K. Hasegawa and A. Nishida, *Tetrahedron Lett.*, 2004, **45**, 1023; (c) S. Mettath, G. S. C. Srikanth, B. S. Dangerfield and S. L. Castle, *J. Org. Chem.*, 2004, **69**, 6489; (d) M. B. Andrus, J. Liu, Z. Ye and J. F. Cannon, *Org. Lett.*, 2005, **7**, 3861; (e) K. Hasegawa, S. Arai and A. Nishida, *Tetrahedron*, 2006, **62**, 1390; (f) B. Ma, J. L. Parkinson and S. L. Castle, *Tetrahedron Lett.*, 2007, **48**, 2083.
- (a) T. Ooi, M. Taniguchi, M. Kameda and K. Maruoka, *Angew. Chem., Int. Ed.*, 2002, **41**, 4542; (b) T. Ooi, M. Kameda, M. Taniguchi and K. Maruoka, *J. Am. Chem. Soc.*, 2004, **126**, 9685; see also: (c) T. Kano, Q. Lan, X. Wang and K. Maruoka, *Adv. Synth. Catal.*, 2007, **349**, 556; (d) M. Kitamura, S. Shirakawa, Y. Arimura, X. Wang and K. Maruoka, *Chem.-Asian J.*, 2008, **3**, 1702.
- For discussion on the retro-aldol reaction under phase-transfer conditions see ref. 3e and 4b.
- (a) R. He, S. Shirakawa and K. Maruoka, *J. Am. Chem. Soc.*, 2009, **131**, 16620; (b) L. Wang, S. Shirakawa and K. Maruoka, *Angew. Chem., Int. Ed.*, 2011, **50**, 5327; (c) S. Shirakawa, S. J. Terao, R. He and K. Maruoka, *Chem. Commun.*, 2011, **47**, 10557.
- Direct asymmetric aldol reactions with aqueous formaldehyde, see: (a) R. Kuwano, H. Miyazaki and Y. Ito, *Chem. Commun.*, 1998, 71; (b) H. Torii, M. Nakadai, K. Ishihara, S. Saito and H. Yamamoto, *Angew. Chem., Int. Ed.*, 2004, **43**, 1983; (c) J. Casas, H. Sundén and A. Córdova, *Tetrahedron Lett.*, 2004, **45**, 6117; (d) N. Mase, A. Inoue, M. Nishio and K. Takabe, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 3955; (e) S. Mouri, Z. Chen, S. Matsunaga and M. Shibasaki, *Chem. Commun.*, 2009, 5138; (f) S. Kobayashi, M. Kokubo, K. Kawasumi and T. Nagano, *Chem.-Asian J.*, 2010, **5**, 490; see also: (g) S. Ishikawa, T. Hamada, K. Manabe and S. Kobayashi, *J. Am. Chem. Soc.*, 2004, **126**, 12236; (h) M. Kokubo, C. Ogawa and S. Kobayashi, *Angew. Chem., Int. Ed.*, 2008, **47**, 6909.
- Catalytic asymmetric synthesis of α -alkyl serine derivatives, see: (a) Y. Ito, M. Sawamura, E. Shirakawa, K. Hayashizaki and T. Hayashi, *Tetrahedron Lett.*, 1988, **29**, 235; (b) S.-S. Jew, Y.-J. Lee, J. Lee, M. J. Kang, B.-S. Jeong, J.-H. Lee, M.-S. Yoo, M.-J. Kim, S.-H. Choi, J.-M. Ku and H.-G. Park, *Angew. Chem., Int. Ed.*, 2004, **43**, 2382; (c) K. Nakayama and K. Maruoka, *Tetrahedron Lett.*, 2008, **49**, 5461; (d) C.-B. Ji, Y.-L. Liu, Z.-Y. Cao, Y.-Y. Zhang and J. Zhou, *Tetrahedron Lett.*, 2011, **52**, 6118.
- The reactions using ammonium hydroxide and phenoxide of (S)-**1**, which are prepared by exchange of the bromide anion of (S)-**1** to hydroxide and phenoxide anions, gave the product **2d** in similar enantioselectivities to the ammonium bromide with slightly low yields [(S)-**1**-PhO⁻: 67% yield, 90% ee; (S)-**1**-OH⁻: 60% yield, 91% ee]. The effect of other catalysts was shown in Scheme S1, ESI.†
- The reaction in mesitylene without addition of water except the water in formaldehyde solution proceeded sluggishly. The same effect of water was observed in conjugate additions under base-free neutral phase-transfer conditions; see ref. 6.
- Even in the absence of catalyst (S)-**1**, the reaction proceeded in mesitylene/aqueous K₂CO₃ by the effect of base.
- The reaction in pure water without mesitylene proceeded sluggishly owing to the low solubility of nitroacetate and catalyst in water.
- N. V. Yashin, E. B. Averina, Y. K. Grishin, T. S. Kuznetsova and N. S. Zefirov, *Synlett*, 2006, 279.
- (a) T. Yamashita, M. Iijima, H. Nakamura, K. Isshiki, H. Naganawa, S. Hattori, M. Hamada, M. Ishizuka, T. Takeuchi and Y. Iitaka, *J. Antibiot.*, 1991, **44**, 557; (b) S. Hatakeyama, H. Fukuyama, Y. Mukugi and H. Irie, *Tetrahedron Lett.*, 1996, **37**, 4047; (c) D. Enders, M. Bartsch and J. Runsink, *Synthesis*, 1999, 243; (d) S. Sano, T. Miwa, K. Hayashi, K. Nozaki, Y. Ozeki and Y. Nagao, *Tetrahedron Lett.*, 2001, **42**, 4029; (e) Y. Matsukawa, M. Isobe, H. Kotsuki and Y. Ichikawa, *J. Org. Chem.*, 2005, **70**, 5339.
- (a) E. D. Miller, C. A. Kauffman, P. R. Jensen and W. Fenical, *J. Org. Chem.*, 2007, **72**, 323; (b) W. Li, J. Gan and D. Ma, *Angew. Chem., Int. Ed.*, 2009, **48**, 8891.