Catalytic asymmetric synthesis of 1,1-disubstituted tetrahydro-β-carbolines by phase-transfer catalyzed alkylations†

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Efficient catalytic asymmetric synthesis of 1,1-disubstituted tetrahydro-β-carbolines has been achieved *via* asymmetric alkylation of 1-cyanotetrahydro-β-carbolines using a binaphthyl-modified *N*-spiro-type chiral phase-transfer catalyst. This is a valuable example of hitherto difficult highly enantioselective alkylations at α-carbon of the cyano group under phase-transfer conditions.

The structure of 1-substituted tetrahydro-β-carboline appears in many important natural products and biologically active compounds, hence numerous synthetic efforts especially in a stereoselective manner have been made to build up this structure.[1–5] Several efficient catalytic methods were developed for the synthesis of these compounds *via* asymmetric hydrogenations,[3] Mannich-type reactions,[4] and Pictet–Spengler reactions.[5] On the other hand, only two examples of the catalytic asymmetric synthesis of 1,1-disubstituted tetrahydro-β-carbolines of type **1** possessing a chiral quaternary carbon center[6] have been reported recently,[7] despite the importance of these compounds in natural product chemistry[8] and medicinal chemistry[9] (Fig. 1). Notably, these two examples included similar Pictet–Spengler-type intramolecular cyclizations, and the structural motif of the obtained products was limited to a tetracyclic lactam structure. For these reasons, the development of novel catalytic asymmetric methods for the synthesis of different types of 1,1-disubstituted tetrahydro-β-carbolines **1** is highly desirable.[10]

Our strategy for the synthesis of 1,1-disubstituted tetrahydro-β-carbolines of type **1** involves asymmetric phase-transfer alkylation[11,12] of racemic 1-cyanotetrahydro-β-carboline **2**, which can be prepared easily from 3,4-dihydro-β-carboline *via* cyanation (Scheme 1).[13] The electron-withdrawing nature of the cyano group in compound **2** offers appropriate reactivity for phase-transfer alkylations, and the cyano group of alkylation product **3** can be transformed into various useful functional groups. Although many examples of phase-transfer catalyzed asymmetric alkylations at α-carbon of the carbonyl group to create quaternary stereocenter *via* ammonium enolate **A** (Scheme 2) are known,[11,12] only limited examples of the alkylations at α-carbon of the cyano group *via* intermediate **B** (Scheme 2) have been reported[14,15] despite the high synthetic utility of this group. Here we wish to report highly enantioselective alkylations of 1-cyanotetrahydro-β-carbolines **2** under mild phase-transfer conditions. The present reaction is a valuable example of hitherto difficult highly enantioselective α-alkylations of cyano compounds under these conditions.

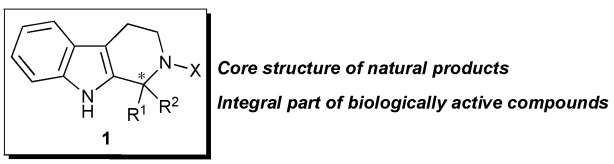
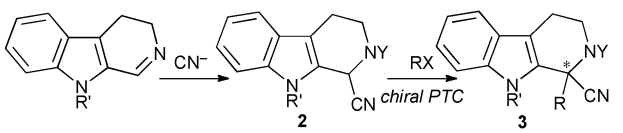


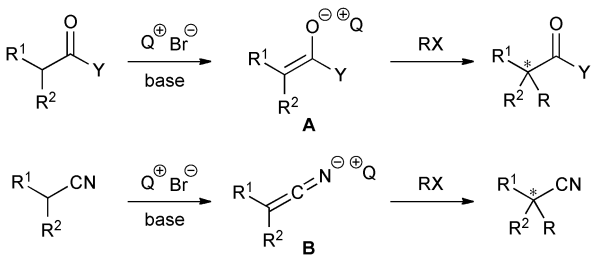
Fig. 1 1,1-Disubstituted tetrahydro-β-carboline.

As a key substrate for the asymmetric synthesis of 1,1-disubstituted tetrahydro-β-carboline of type **1** under phase-transfer conditions, 1-cyanotetrahydro-β-carboline **2a** was selected as a model substrate. An attempted reaction of 1-cyanotetrahydro-β-carboline **2a** with benzyl bromide (1.2 equiv.) in aqueous KOH/toluene under the influence of *N*-spiro-type phase-transfer catalyst (*S*,*S*)-**4a** (2 mol%) at 0 °C for 24 h afforded benzylation product **3a** with 71% ee (Table 1, entry 1). Switching the 3,3′-aromatic substituent (Ar) of the catalyst to a 3,5-bis(trifluoromethyl)phenyl group (**4b**) resulted in improved enantioselectivity, and the product **3a** was obtained with high enantioselectivity (94% ee, entry 2). Further screening of 3,3′-aromatic substituent (Ar) of (*S*,*S*)-**4**[16] did not improve the enantioselectivity (entries 3 and 4). The use of phase-transfer catalyst (*S*)-**5**,[17] which has one binaphthyl unit, gave a product with moderate enantioselectivity (entry 5).

With optimal reaction conditions in hand, we further studied the generality of the asymmetric alkylation of 1-cyanotetrahydro-β-carboline **2a** under the influence of chiral phase-transfer catalyst (*S*,*S*)-**4b**, as shown in Table 2. A series of benzylic bromides with different steric and electronic properties



Scheme 1 Synthetic scheme of 1,1-disubstituted tetrahydro-β-carboline.



Scheme 2 Phase-transfer catalyzed alkylations.

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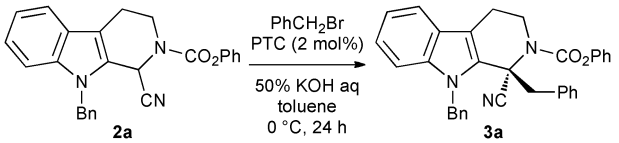
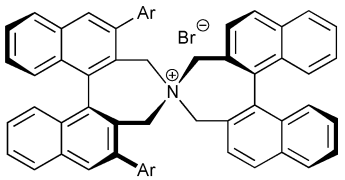
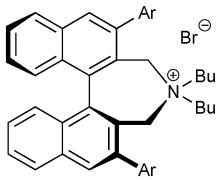
Table 1 Screening of chiral phase-transfer catalysts[a]





(*S*,*S*)-**4**



(*S*)-**5**: Ar = 3,5-$(CF_3)_2$-C_6H_3

4a: Ar = 3,4,5-F_3-C_6H_2
4b: Ar = 3,5-$(CF_3)_2$-C_6H_3
4c: Ar = 3,5-(*t*-Bu)$_2$-C_6H_3
4d: Ar = 3,5-[3,5-$(CF_3)_2$-C_6H_3]$_2$-C_6H_3

Entry	PTC	Yield[b] (%)	ee[c] (%)
1	**4a**	45	71
2	**4b**	72	94
3	**4c**	51	92
4	**4d**	61	70
5	**5**	69	79

[a] Reaction conditions: **2a** (0.050 mmol) and benzyl bromide (0.060 mmol) in the presence of 2 mol% of chiral phase-transfer catalyst (PTC) in 50% aqueous KOH (0.25 mL)/toluene (0.50 mL) at 0 °C for 24 h. [b] Yield of isolated products. [c] Determined by chiral HPLC analysis.

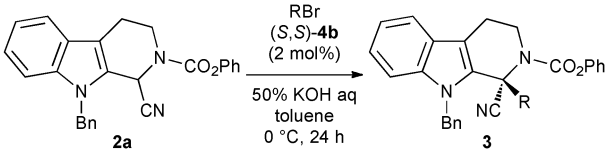
were tolerated, thus allowing the preparation of structurally diverse, enantioenriched 1,1-disubstituted tetrahydro-β-carbolines (90–96% ee, entries 1–7). The alkyl halide containing a heteroaromatic ring could also be applied to the reaction with high enantioselectivity (95% ee, entry 8). The reaction with cinnamyl bromide gave the product **3i** in good yield with moderate enantioselectivity (entry 9).[18] The absolute configuration of **3d** was determined by X-ray diffraction analysis.[19]

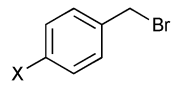
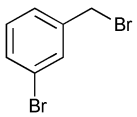
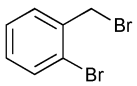
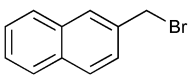
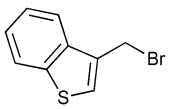
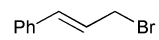
Other types of 1-cyanotetrahydro-β-carbolines **2** were found to be employable for the reaction (Table 3). The introduction of electron-donating and electron-withdrawing substituents on the aromatic ring of tetrahydro-β-carboline core gave high enantioselectivities (92–96% ee, entries 1 and 2). The use of *N*-methyl and *N*-allyl substituted tetrahydro-β-carbolines also gave high enantioselectivities (92–94% ee, entries 3 and 4).

The cyano group of the alkylation products **3** and **6** can be readily transformed to other functional groups. For example, the optically active alkylation product **3a** was subjected to alkaline hydrolysis to furnish amide derivative **7** possessing a tetracyclic hydantoin structure (Scheme 3), which was observed in biologically active compounds.[20]

In summary, we have successfully developed the highly enantioselective alkylation of 1-cyanotetrahydro-β-carbolines for the synthesis of 1,1-disubstituted tetrahydro-β-carbolines under mild phase-transfer conditions. The cyano group of the products was easily transformed to other functional groups. The present report illustrates a valuable example of hitherto difficult highly enantioselective alkylations at α-carbon of the cyano group under phase-transfer conditions. Further investigations on the phase-transfer catalyzed asymmetric alkylations of cyano compounds to produce important compounds are currently underway.

Table 2 Asymmetric alkylation of a 1-cyanotetrahydro-β-carboline **2a**[a]



Entry	RBr	Yield[b] (%)	ee[c] (%)
1	 X = H	72 (**3a**)	94
2	X = Me	60 (**3b**)	92
3	X = F	88 (**3c**)	95
4	X = Br	76 (**3d**)	96
5		78 (**3e**)	94
6		66 (**3f**)	90
7		75 (**3g**)	93
8		61 (**3h**)	95
9[d]		86 (**3i**)	60

[a] Reaction conditions: **2a** (0.050 mmol) and alkyl halide (0.060 mmol) in the presence of 2 mol% of (*S*,*S*)-**4b** in 50% aqueous KOH (0.25 mL)/toluene (0.50 mL) at 0 °C for 24 h. [b] Yield of isolated products. [c] Determined by chiral HPLC analysis. [d] The reaction was performed at −20 °C.

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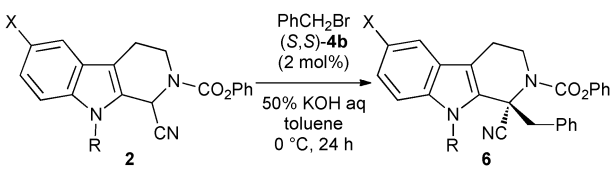
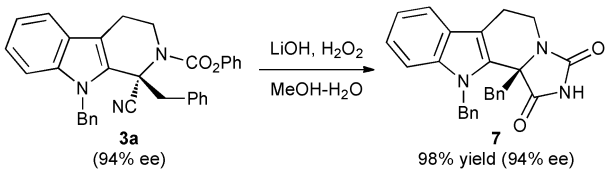
Table 3 Asymmetric benzylation of 1-cyanotetrahydro-β-carbolines **2**[a]



Entry	X	R	Yield[b] (%)	ee[c] (%)
1[d]	MeO	$PhCH_2$	77 (**6a**)	92
2	Cl	$PhCH_2$	87 (**6b**)	96
3	H	Me	89 (**6c**)	92
4	H	CH_2=$CHCH_2$	84 (**6d**)	94

[a] Reaction conditions: **2** (0.050 mmol) and benzyl bromide (0.060 mmol) in the presence of 2 mol% of (*S*,*S*)-**4b** in 50% aqueous KOH (0.25 mL)/toluene (0.50 mL) at 0 °C for 24 h. [b] Yield of isolated products. [c] Determined by chiral HPLC analysis. [d] The reaction was performed at −20 °C.



Scheme 3 Transformation of the alkylation product **3a**.

Notes and references

1 For reviews, see: (*a*) Z. Czarnocki, A. Siwicka and J. Szawkało, *Curr. Org. Synth.*, 2005, **2**, 301; (*b*) E. L. Larghi, M. Amongero, A. B. J. Bracca and T. S. Kaufman, *ARKIVOC*, 2005, (xii), 98.

2 Examples of enantioselective synthesis, see: (*a*) M. Nakamura, A. Hirai and E. Nakamura, *J. Am. Chem. Soc.*, 1996, **118**, 8489; (*b*) H. Yamada, T. Kawata, M. Matsumizu, A. Nishida, K. Yamaguchi and M. Nakagawa, *J. Org. Chem.*, 1998, **63**, 6348; (*c*) A. R. Hajipour and M. Hantehzadeh, *J. Org. Chem.*, 1999, **64**, 8475.

3 (*a*) N. Uematsu, A. Fujii, S. Hashiguchi, T. Ikariya and R. Noyori, *J. Am. Chem. Soc.*, 1996, **118**, 4916; (*b*) L. F. Tietze, Y. Zhou and E. Töpken, *Eur. J. Org. Chem.*, 2000, 2247; (*c*) C. Li and J. Xiao, *J. Am. Chem. Soc.*, 2008, **130**, 13208; (*d*) L. Evanno, J. Ormala and P. M. Pihko, *Chem.–Eur. J.*, 2009, **15**, 12963; (*e*) N. Haraguchi, K. Tsuru, Y. Arakawa and S. Itsuno, *Org. Biomol. Chem.*, 2009, **7**, 69.

4 (*a*) T. Itoh, M. Yokoya, K. Miyauchi, K. Nagata and A. Ohsawa, *Org. Lett.*, 2003, **5**, 4301; (*b*) T. Itoh, M. Yokoya, K. Miyauchi, K. Nagata and A. Ohsawa, *Org. Lett.*, 2006, **8**, 1533.

5 (*a*) M. S. Taylor and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2004, **126**, 10558; (*b*) J. Seayad, A. M. Seayad and B. List, *J. Am. Chem. Soc.*, 2006, **128**, 1086; (*c*) M. J. Wanner, R. N. S. van der Haas, K. R. de Cuba, J. H. van Maarseveen and H. Hiemstra, *Angew. Chem., Int. Ed.*, 2007, **46**, 7485; (*d*) N. V. Sewgobind, M. J. Wanner, S. Ingemann, R. de Gelder, J. H. van Maarseveen and H. Hiemstra, *J. Org. Chem.*, 2008, **73**, 6405.

6 K. Christoffers and A. Baro, *Quaternary Stereocenters: Challenges and Solutions for Organic Synthesis*, Wiley-VCH, Weinheim, 2005.

7 (*a*) I. T. Raheem, P. S. Thiara, E. A. Peterson and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2007, **129**, 13404; (*b*) M. E. Muratore, C. A. Holloway, A. W. Pilling, R. I. Storer, G. Trevitt and D. J. Dixon, *J. Am. Chem. Soc.*, 2009, **131**, 10796.

8 (*a*) R. Sakai, K. L. Rinehart, Y. Guan and A. H.-J. Wang, *Proc. Natl. Acad. Sci. U. S. A.*, 1992, **89**, 11456; (*b*) F. C. Seaman and L. H. Hurley, *J. Am. Chem. Soc.*, 1998, **120**, 13028; (*c*) R. Menchaca, V. Martínez, A. Rodríguez, N. Rodríguez, M. Flores, P. Gallego, I. Manzanares and C. Cuevas, *J. Org. Chem.*, 2003, **68**, 8859.

9 (*a*) T. Nagyl, L. Jeannin, J. Sapil, J. Y. Laronze, P. Renard, B. Pfeifferz and J. G. Bizot-Espiard, *Eur. J. Med. Chem.*, 1995, **30**, 575; (*b*) K. Pari, C. S. Sundari, S. Chandani and D. Balasubramanian, *J. Biol. Chem.*, 2000, **275**, 2455; (*c*) D. Fokas, L. Yu and C. M. Baldino, *Mol. Diversity*, 2005, **9**, 81; (*d*) B. K. S. Yeung, B. Zou, M. Rottmann, S. B. Lakshminarayana, S. H. Ang, S. Y. Leong, J. Tan, J. Wong, S. Keller-Maerki, C. Fischli, A. Goh, E. K. Schmitt, P. Krastel, E. Francotte, K. Kuhen, D. Plouffe, K. Henson, T. Wagner, E. A. Winzeler, F. Petersen, R. Brun, V. Dartois, T. T. Diagana and T. H. Keller, *J. Med. Chem.*, 2010, **53**, 5155.

10 Stoichiometric amounts of chiral silicon Lewis acid promoted asymmetric synthesis of 1,1-disubstituted tetrahydro-β-carbolines of type **1***via* Pictet–Spengler reaction, see: F. R. Bou-Hamdan and J. L. Leighton, *Angew. Chem., Int. Ed.*, 2009, **48**, 2403.

11 For representative reviews on asymmetric phase-transfer catalysis, see: (*a*) T. Shioiri, in *Handbook of Phase-Transfer Catalysis*, ed. Y. Sasson and R. Neumann, Blackie Academic & Professional, London, 1997, ch. 14; (*b*) M. J. O'Donnell, in *Catalytic Asymmetric Syntheses*, ed. I. Ojima, Wiley-VCH, New York, 2nd edn, ch. 10, 2000; (*c*) K. Maruoka and T. Ooi, *Chem. Rev.*, 2003, **103**, 3013; (*d*) M. J. O'Donnell, *Acc. Chem. Res.*, 2004, **37**, 506; (*e*) B. Lygo and B. I. Andrews, *Acc. Chem. Res.*, 2004, **37**, 518; (*f*) T. Ooi and K. Maruoka, *Angew. Chem., Int. Ed.*, 2007, **46**, 4222; (*g*) T. Hashimoto and K. Maruoka, *Chem. Rev.*, 2007, **107**, 5656; (*h*) K. Maruoka, *Asymmetric Phase Transfer Catalysis*, Wiley-VCH, Weinheim, 2008; (*i*) S. Shirakawa and K. Maruoka, in *Catalytic Asymmetric Synthesis*, ed. I. Ojima, John Wiley & Sons, Hoboken, New Jersey, 3rd edn, ch. 2C, 2010.

12 For representative examples from our group on phase-transfer catalyzed asymmetric alkylations to create quaternary carbon center, see: (*a*) T. Ooi, M. Takeuchi, M. Kameda and K. Maruoka, *J. Am. Chem. Soc.*, 2000, **122**, 5228; (*b*) T. Ooi, T. Miki, M. Taniguchi, M. Shiraishi, M. Takeuchi and K. Maruoka, *Angew. Chem., Int. Ed.*, 2003, **42**, 3796; (*c*) T. Ooi, K. Fukumoto and K. Maruoka, *Angew. Chem., Int. Ed.*, 2006, **45**, 3839; (*d*) T. Hashimoto, K. Sakata and K. Maruoka, *Angew. Chem., Int. Ed.*, 2009, **48**, 5014.

13 S. Veeraraghavan and F. D. Popp, *J. Heterocycl. Chem.*, 1981, **18**, 909.

14 D. Brózda, K. Hoffman and M. D. Rozwadowska, *Heterocycles*, 2006, **67**, 119.

15 Asymmetric alkylations of α-cyanocarboxylates, see: (*a*) K. Nagata, D. Sano and T. Itoh, *Synlett*, 2007, 547; (*b*) K. Nagata, D. Sano, Y. Shimizu, M. Miyazaki, T. Kanemitsu and T. Itoh, *Tetrahedron: Asymmetry*, 2009, **20**, 2530.

16 (*a*) T. Ooi, M. Kameda and K. Maruoka, *J. Am. Chem. Soc.*, 2003, **125**, 5139; (*b*) K. Maruoka, E. Tayama and T. Ooi, *Proc. Natl. Acad. Sci. U. S. A.*, 2004, **101**, 5824; (*c*) T. Ooi, M. Kameda, M. Taniguchi and K. Maruoka, *J. Am. Chem. Soc.*, 2004, **126**, 9685.

17 (*a*) M. Kitamura, S. Shirakawa and K. Maruoka, *Angew. Chem., Int. Ed.*, 2005, **44**, 1549; (*b*) M. Kitamura, S. Shirakawa, Y. Arimura, X. Wang and K. Maruoka, *Chem.–Asian J.*, 2008, **3**, 1702.

18 The reaction with simple alkyl halide such as methyl iodide did not give the target product, probably due to the low reactivity of methyl iodide.

19 CCDC 787177.

20 (*a*) M. L. Lopez-Rodriguez, M. J. Morcillo, B. Benhamu, E. Fernandez, J. Serrano and L. Orensanz, *Chem. Pharm. Bull.*, 1995, **43**, 941; (*b*) S. Hotha, J. C. Yarrow, J. G. Yang, S. Garrett, K. V. Renduchintala, T. U. Mayer and T. M. Kapoor, *Angew. Chem., Int. Ed.*, 2003, **42**, 2379; See also, ref. 9*c*.