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Asymmetric conjugate additions of α-substituted-α-cyanoacetates to acetylenic ketones by chiral phase transfer catalysis

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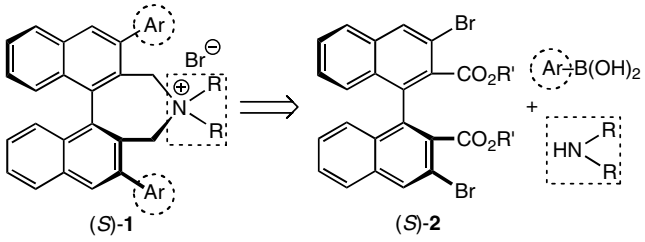
Abstract—Asymmetric conjugate addition of α-substituted-α-cyanoacetates to acetylenic ketones has been achieved with high enantioselectivity and moderate *E*/*Z* selectivity under the influence of our recently designed, binaphthyl-modified 3,5-bis[3,5-bis(trifluoromethyl)phenyl]phenyl substituted phase transfer catalyst.

Design of new, chiral catalysts for effecting very efficient and/or hitherto unknown asymmetric transformations has become increasingly important in current asymmetric catalysis.[1] Accordingly, we recently reported our case study on this subject by suitably designing certain chiral phase transfer catalysts as promising organocatalysts.[2] Our strategy is based on our recent finding of a very active, chiral phase transfer catalyst of type (*S*)-**1** (Ar = 3,4,5-F_3–C_6H_2; R = Bu) for the asymmetric alkylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester.[3] Since catalyst (*S*)-**1** can be readily prepared from three components, that is, a chiral binaphthyl part (*S*)-**2**, an arylboronic acid ($ArB(OH)_2$), and a secondary amine (R_2NH) (Scheme 1) as described previously,[3a] the appropriate modification of $ArB(OH)_2$ and R_2NH parts should give a newly designed catalyst for the development of a novel asymmetric transformation. Indeed, by using the combination of 3,5-bis[3,5-bis(trifluoromethyl)phenyl]phenylboronic acid and morpholine, a new spiro-type phase transfer catalyst **4** has been designed for effecting a hitherto unknown asymmetric conjugate addition of α-substituted-α-cyanoacetates **5** to acetylenic esters **6** ($R^2 = OBu^t$) with high enantioselectivity and moderate *E*/*Z* selectivity (Scheme 2).[2,4,5] This observation led us to examine the possibility of using another acetylenic carbonyl derivative as conjugate acceptor. For instance, so far there is only one successful example for asymmetric conjugate additions to an acetylenic ketone,[6] and hence use of this substrate as conjugate acceptor is quite appealing. Here, we wish to report asymmetric conjugate addition of α-substituted-α-cyanoacetates to acetylenic ketones under phase transfer conditions.



Scheme 1.

Attempted reaction of *t*-butyl α-benzyl-α-cyanoacetate **5** ($R^1 = CH_2Ph$) and 3-butyn-2-one **6** (R^2 = Me) with K_2CO_3 (2 equiv) in the presence of a catalytic amount (1 mol %) of (*S*)-**3a** in toluene at 0 °C for 1.5 h gave rise to conjugate adducts **7** ($R^1 = CH_2Ph$; R^2 = Me) in 97% yield with the *E*/*Z* ratio of 2.3:1. The enantiomeric excesses of (*E*)- and (*Z*)-**7** ($R^1 = CH_2Ph$; R^2 = Me) were found to be 16% and 7%, respectively, as shown in Table 1 (entry 1). In contrast, however, conjugate addition with catalyst (*S*)-**4b** under similar conditions produced conjugate adducts **7** ($R^1 = CH_2Ph$; R^2 = Me) in 99% yield (*E*/*Z* ratio of 1.5:1) with moderate enantioselectivity (60/62% ee) (entry 2). In addition, use of catalyst (*S*)-**4a** under similar conditions afforded adducts **7** ($R^1 = CH_2Ph$; R^2 = Me) in 99% yield (*E*/*Z* ratio of

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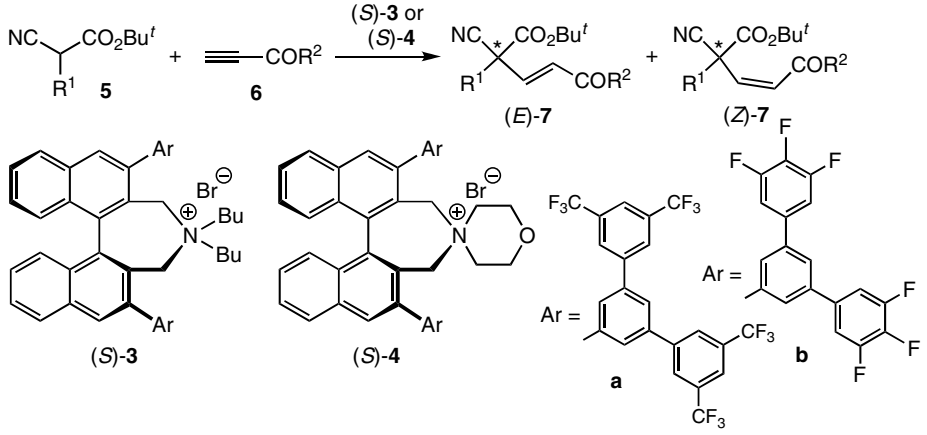
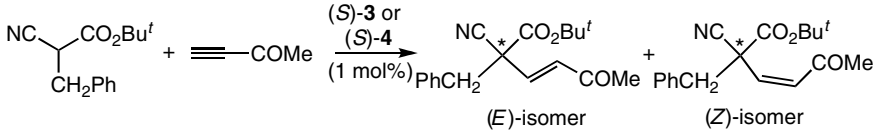


Scheme 2.

Table 1. Catalytic enantioselective conjugate addition of α-benzylcyanoacetate to acetylenic methyl ketone with (*S*)-**3** or (*S*)-**4** under phase transfer condition[a]



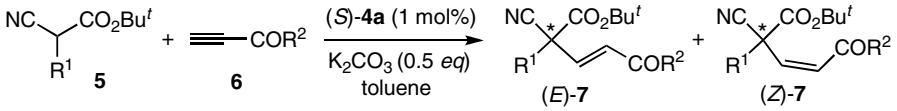
Entry	Catalyst	Base (equiv)	Solvent	Condition (°C, h)	Yield[b] (%) (*E*/*Z*)[c]	ee[d] (%)
1	(*S*)-**3a**	K_2CO_3 (2)	Toluene	0, 1.5	97 (2.3/1)	16/7
2	(*S*)-**4b**	K_2CO_3 (2)	Toluene	0, 2	99 (1.5/1)	60/62
3	(*S*)-**4a**	K_2CO_3 (2)	Toluene	0, 2	99 (3.0/1)	80/77
4	(*S*)-**4a**	K_2CO_3 (0.5)	Toluene	0, 2	99 (3.4/1)	81/78
5	(*S*)-**4a**	K_2CO_3 (0.1)	Toluene	0, 2	99 (3.3/1)	80/77
6	(*S*)-**4a**	K_2CO_3 (0.5)	Toluene	−40, 2	99 (2.7/1)	88/86
7	(*S*)-**4a**	Cs_2CO_3 (0.5)	Toluene	0, 2	99 (2.6/1)	81/78
8	(*S*)-**4a**	K_2CO_3 (0.5)	CPME	0, 2	99 (2.0/1)	75/74
9	(*S*)-**4a**	K_2CO_3 (0.5)	Ether	0, 2	99 (2.4/1)	76/79
10	(*S*)-**4a**	K_2CO_3 (0.5)	THF	0, 2	95 (1.8/1)	62/64
11	(*S*)-**4a**	K_2CO_3 (0.5)	Mesitylene	0, 2	99 (2.7/1)	81/76
12	(*S*)-**4a**	K_2CO_3 (0.5)	Cumene	0, 2	92 (1.4/1)	31/18
13	(*S*)-**4a**	K_2CO_3 (0.5)	*o*-Xylene	0, 2	84 (2.8/1)	80/77
14	(*S*)-**4a**	K_2CO_3 (0.5)	*m*-Xylene	0, 2	97 (2.4/1)	82/76
15	(*S*)-**4a**	K_2CO_3 (0.5)	TBME	0, 2	99 (2.4/1)	76/80
16	(*S*)-**4a**	Cs_2CO_3 (0.5)	*m*-Xylene	0, 2	99 (2.3/1)	82/73
17	(*S*)-**4a**	K_2CO_3 (0.5)	*m*-Xylene	−40, 3	99 (2.2/1)	88/82

[a] Unless otherwise specified, the reaction was carried out with 1.5 equiv of acetylenic methyl ketone in the presence of 1 mol % of (*S*)-**3** or (*S*)-**4** under the given reaction conditions.
[b] Isolated yield.
[c] Determined by ^1H NMR analysis.
[d] Enantiomeric excess of the conjugate adducts was determined by HPLC analysis using a chiral column with hexane/isopropanol as solvent.

3.0:1) with higher enantioselectivity (80/77% ee) (entry 3). The amount of K_2CO_3 as base could be reduced to 0.5 and even 0.1 equiv (entries 4 and 5). By using the lower temperature (−40 °C), the enantioselectivity was increased to 88/86% ee (entry 6). Use of Cs_2CO_3 (0.5 equiv) in place of K_2CO_3 as base gave a similar result in terms of *E*/Z selectivity and the enantioselectivity (entry 7). The solvent effect was studied in detail as indicated in entries 8–15, and among several solvents, toluene and *m*-xylene gave the best results in terms of the enantioselectivity (entries 6 and 17).

With the optimum reaction conditions, we carried out asymmetric conjugate addition with other substrates, and some selected examples are listed in Table 2. Several characteristic features of the present reactions are as follows: (1) Both *primary*- and *secondary*-alkyl-substituted α-cyanoesters can be utilized to achieve the high enantioselectivity. (2) Acetylenic ketones **6** possessing *primary*-, *secondary*- and *tertiary*-alkyl groups are also employable. (3) In particular, combination of cyanoacetate **5** ($R^1 = CH_2CH_2Ph$) and acetylenic ketone **6** ($R^2 = t$-Bu) exhibited the highest enantioselectivity (entry 13). (4)

Table 2. Catalytic enantioselective conjugate addition of cyanoacetates to acetylenic ketones with (*S*)-**4a** under phase transfer condition[a]

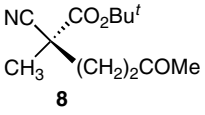


Entry	Ester **5** (R^1)	Ketone **6** (R^2)	Condition (°C, h)	Yield[b] (%) (*E*/*Z*)[c]	ee[d] (%)
1	CH_2Ph	Me	−40, 2	99 (2.7/1)	88/86
2	CH_2Ph	Ph	−40, 3	98 (2.1/1)	69/71
3	CH_2Ph	$CH_2CH(CH_3)_2$	−40, 4	95 (4.4/1)	83/79
4	CH_2Ph	$CH_2C(CH_3)_3$	−40, 6	99 (5.0/1)	85/80
5	CH_2Ph	Cyclohexyl	−40, 8	94 (4.3/1)	82/64
6	CH_2Ph	*t*-Bu	−40, 24	98 (4.3/1)	86/83
7	*i*-Pr	Me	−40, 48	70 (1.6/1)	86/89
8	*o*-Me-benzyl	Me	−40, 4	97 (2.2/1)	90/85
9	$CH_2C(CH_3)_3$	Me	−40, 2	96 (2.9/1)	85/86
10	CH_2CH_3	Me	−40, 2	80 (3.6/1)	72/75
11	CH_2CH_2Ph	Me	−40, 3	99 (2.3/1)	85/69
12	CH_2CH_2Ph	Cyclohexyl	−40, 24	99 (3.0/1)	78/81
13	CH_2CH_2Ph	*t*-Bu	−40, 24	99 (3.3/1)	93/87
14	Me	Me	−40, 2	99 (2.2/1)	71/64

[a] Unless otherwise specified, the reaction was carried out with 1.5 equiv of acetylenic ketone in the presence of 1 mol % of (*S*)-**4a** and 0.5 equiv of K_2CO_3 in toluene under the given reaction conditions.
[b] Isolated yield.
[c] Determined by ^1H NMR analysis.
[d] Enantiomeric excess of the conjugate adducts was determined by HPLC analysis using a chiral column with hexane/isopropanol as solvent.

An all-carbon quaternary stereocenter can be constructed in this asymmetric transformation.[7]

The absolute configuration of the conjugate adducts, (*E*)-**7** ($R^1 = R^2 = Me$) and (*Z*)-**7** ($R^1 = R^2 = Me$) (entry 14 in Table 2) was firmly determined to be *S* by conversion to the known cyanoketo ester **8** with the catalytic hydrogenation (*cat.* Pd/C, H_2, MeOH).[8]



8

A typical experimental procedure of catalytic enantioselective conjugate addition of α-substituted-α-cyanoacetates to acetylenic ketones under phase transfer conditions is as follows (entry 6 in Table 1): To a reaction vessel containing cyanoacetate **5** ($R^1 = CH_2Ph$) (69.4 mg, 0.3 mmol) and chiral ammonium salt (*S*)-**4a** (4.4 mg, 0.003 mmol, 1 mol %) were added toluene (3.0 mL) and 3-butyn-2-one **6** ($R^2 = Me$) (35 μL, 0.45 mmol, 1.5 equiv) under Ar. After the reaction system was cooled to −40 °C, K_2CO_3 (21 mg, 0.15 mmol, 0.5 equiv) was added in a single portion. The reaction mixture was stirred vigorously at the same temperature for 2 h, quenched with saturated NH_4Cl solution (10 mL), extracted with diethyl ether (10 mL), dried over Na_2SO_4 and concentrated. The *E*/*Z* ratio was determined to be 2.7:1 by ^1H NMR analysis of the crude sample. Separation of these *E*/*Z* isomers by column chromatography on silica gel with hexane/ethyl acetate (10:1–4:1) as eluant afforded (*E*)-**7** and (*Z*)-**7** ($R^1 = CH_2Ph$; $R^2 = Me$) in 99% combined yield. The enantiomeric excess of these (*E*)-**7** and (*Z*)-**7** ($R^1 = CH_2Ph$; $R^2 = Me$) was determined by chiral HPLC analysis [(*E*)-**7** ($R^1 = CH_2Ph$; $R^2 = Me$): DAICEL CHIRALCEL OD-H, isopropanol/hexane = 1:30, flow rate = 0.5 mL/min, $\lambda = 220$ nm, retention time: 18.8 min (major) and 22.2 min (minor); (*Z*)-**7** ($R^1 = CH_2Ph$; $R^2 = Me$): DAICEL CHIRALCEL AS-H, isopropanol/hexane = 1:30, flow rate = 0.5 mL/min, $\lambda = 220$ nm, retention time: 25.5 min (minor) and 27.4 min (major)].

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References and notes

1. Reviews: (a) *Comprehensive Asymmetric Catalysis I–III*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; (b) *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000; (c) *Comprehensive Asymmetric Catalysis Supplement 1*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 2004.
2. Wang, X.; Kitamura, M.; Maruoka, K. *J. Am. Chem. Soc.* **2007**, *129*, 1038.
3. (a) Kitamura, M.; Shirakawa, S.; Maruoka, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 1549; (b) Han, Z.; Yamaguchi, Y.; Kitamura, M.; Maruoka, K. *Tetrahedron Lett.* **2005**, *46*, 8555.
4. Grossman, R. B.; Comesse, S.; Rasne, R. M.; Hattori, K.; Delong, M. N. *J. Org. Chem.* **2003**, *68*, 871, and related references cited therein.
5. (a) Taylor, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2003**, *125*, 11204; (b) Taylor, M. S.; Zalatan, D. N.; Lerchner, A.

M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2005**, *127*, 1313; (c) Li, H.; Song, J.; Liu, X.; Deng, L. *J. Am. Chem. Soc.* **2005**, *127*, 8948; (d) Wang, Y.; Liu, X.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 3928; (e) Wu, F.; Hong, R.; Khan, J.; Liu, X.; Deng, L. *Angew. Chem., Int. Ed.* **2006**, *45*, 4301.

6. Bella, M.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 5672.
7. (a) *Quaternary Stereocenters: Challenges and Solutions for Organic Synthesis*; Christoffers, J., Baro, A., Eds.; Wiley-VCH: Weinheim, 2005; (b) Douglas, C. J.; Overman, L. E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5363; (c) Denissova, I.; Barriault, L. *Tetrahedron* **2003**, *59*, 10105.
8. Sawamura, M.; Hamashima, H.; Ito, Y. *Tetrahedron* **1994**, *50*, 4439.