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New, Chiral Phase Transfer Catalysts for Effecting Asymmetric Conjugate Additions of α-Alkyl-α-cyanoacetates to Acetylenic Esters

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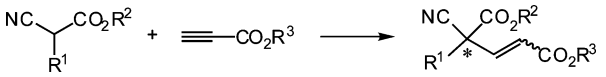
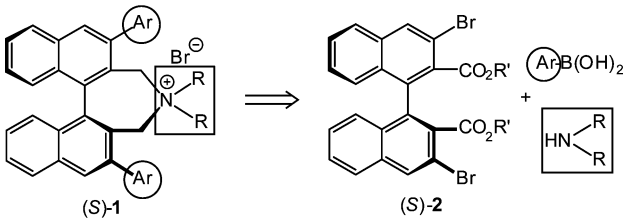
Asymmetric conjugate additions of carbon nucleophiles to α,β-unsaturated carbonyl systems constitute a highly valuable carbon−carbon bond formation in asymmetric synthesis, and hence considerable efforts have been devoted to the development of such asymmetric conjugate additions.[1] Accordingly, we have been intrigued for some time in the possibility of developing a hitherto unknown asymmetric conjugate addition of α-substituted-α-cyanoacetates to acetylenic esters under phase-transfer conditions. The combination of these substrates is quite appealing, because both α-substituted-α-cyanoacetates and acetylenic esters have been a difficult class of nucleophiles and electrophiles, respectively, in current asymmetric stereochemical control.[2] Indeed, even now there are only several very successful examples using α-substituted-α-cyanoacetates to effect certain asymmetric Michael reactions.[3] In addition, despite numerous examples of the conjugate additions to alkenoic esters, so far there are no successful asymmetric conjugate additions to acetylenic esters.[4] Furthermore, an all-carbon quaternary stereocenter can be constructed in this asymmetric transformation.[5]

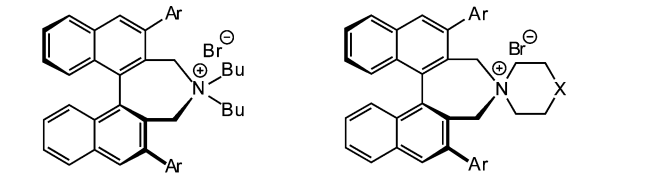


Our strategy is based on our recent finding of a very active chiral phase-transfer catalyst of type (*S*)-**1** (Ar = 3,4,5-F_3-C_6H_2; R = Bu) for the asymmetric alkylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester.[6] Since the catalyst (*S*)-**1** can be readily prepared from three components, 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,[6a] 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.

Scheme 1



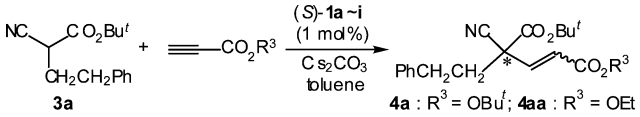
The attempted reaction of *t*-butyl α-(2-phenylethyl)-α-cyanoacetate (**3a**) and ethyl propiolate with Cs_2CO_3 in the presence of a catalytic amount (1 mol %) of spiro-type (*S*,*S*)-3,4,5-trifluorophenyl-NAS-bromide[7] in toluene at 0 °C for 2 h afforded conjugate adducts **4aa** in 96% yield (*E*/*Z* ratio = 2.1:1). The enantiomeric excesses of (*E*)- and (*Z*)-**4aa** were found to be 18 and 23%, respectively. The catalyst (*S*)-**1a**, which is found to be very active in the asymmetric alkylation of glycine derivative,[6a] showed higher enantioselectivity (55 and 72% ee's for (*E*)- and (*Z*)-**4aa**) (entry 1, Table 1). A somewhat lower enantioselectivity is observed with



(*S*)-**1a** (Ar = 3,4,5-F_3-C_6H_2)
(*S*)-**1b** (Ar = 3,5-$(CF_3)_2$-C_6H_3)
(*S*)-**1c** (Ar = 3,5-[3,5-$(CF_3)_2$-C_6H_3]$_2$-C_6H_3)

(*S*)-**1d** (Ar = 3,4,5-F_3-C_6H_2; X = CH$_2$)
(*S*)-**1e** (Ar = 3,4,5-F_3-C_6H_2; X = O)
(*S*)-**1f** (Ar = 3,4,5-F_3-C_6H_2; X = NPh)
(*S*)-**1g** (Ar = 3,5-$(CF_3)_2$-C_6H_3; X = O)
(*S*)-**1h** (Ar = 3,5-[3,4,5-F_3-C_6H_2]$_2$-C_6H_3; X = O)
(*S*)-**1i** (Ar = 3,5-[3,5-$(CF_3)_2$-C_6H_3]$_2$-C_6H_3; X = O)

Table 1. Effect of Ar and R Substituents in Chiral Phase Transfer Catalyst (*S*)-**1** in the Enantioselective Conjugate Addition of Cyanoacetates to Acetylenic Esters[a]



3a

4a : R^3 = OBu^t; **4aa** : R^3 = OEt

entry	ester (R^3)	catalyst	condition (°C, h)	% yield[b] (*E*/*Z*)[c]	% ee[d]
1	OEt	(*S*)-**1a**	0, 2	99 (1.7:1)	55/72
2	OEt	(*S*)-**1b**	0, 2	99 (3.2:1)	48/45
3	OEt	(*S*)-**1c**	0, 2	99 (3.7:1)	10/11
4	OEt	(*S*)-**1d**	0, 2	99 (4.4:1)	31/35
5	Oet	(*S*)-**1e**	0, 2	99 (2.2:1)	53/39
6	OEt	(*S*)-**1f**	0, 2	99 (2.8:1)	47/65
7	Oet	(*S*)-**1g**	0, 2	99 (2.7:1)	41/47
8	OEt	(*S*)-**1h**	0, 2	99 (2.7:1)	58/54
9	OEt	(*S*)-**1i**	0, 2	99 (2.8:1)	77/71
10	OBu^t	(*S*)-**1i**	0, 2	99 (2.9:1)	90/85
11	OBu^t	(*S*)-**1i**	−20, 3	99 (3.1:1)	91/82
12			−20, 4[e]	99 (3.4:1)	92/86
13			−20, 12[f]	99 (3.5:1)	92/88
14			−20, 12[g]	72 (4.5:1)	92/75
15	OBu^t	(*S*)-**1i**	−40, 6	99 (3.6:1)	94/84
16			−40, 16[e]	97 (4.0:1)	94/80
17			−40, 44[f]	90 (4.1:1)	93/87

[a] Unless otherwise specified, the reaction was carried out with 2 equiv of acetylenic ester in the presence of 1 mol % of (*S*)-**1** and 1.2 equiv of Cs_2CO_3 in toluene under the given reaction conditions. [b] Isolated yield. [c] Determined by ^1H NMR analysis. [d] Enantiopurity of the conjugate adducts was determined by HPLC analysis using a chiral column. [e] Use of 0.5 equiv of Cs_2CO_3. [f] Cs_2CO_3 (0.2 equiv). [g] Cs_2CO_3 (0.1 equiv).

3,5-bis(trifluoromethyl)phenyl-substituted catalyst (*S*)-**1b** (entry 2), and a sterically more hindered (*S*)-**1c** significantly lowered the enantioselectivity (entry 3). Among 3,4,5-trifluorophenyl-substituted spiro-type catalysts, (*S*)-**1d**−**f**, morphorine-derived (*S*)-**1e** gives better enantioselectivity (entry 5 vs entries 4 and 6). Again, 3,5-bis(trifluoromethyl)phenyl-substituted catalyst (*S*)-**1g** lowered the enantioselectivity to some extent (entry 7). With this catalyst, the solvent effect was investigated and the enantioselectivity found to decrease gradually from toluene to ether, *m*-xylene, and CPME. In contrast, 3,5-bis[3,5-bis(trifluoromethyl)phenyl]phenyl-substituted catalyst (*S*)-**1i** showed the better enantioselectivity than catalyst (*S*)-**1h** (entry 9 vs 8). A noticeable increase in enantiomeric excess to

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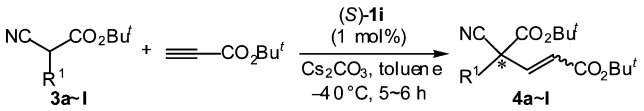
Table 2. Catalytic Enantioselective Conjugate Addition of Cyanoacetates to Acetylenic Esters with (*S*)-**1i** under Phase Transfer Condition[a]



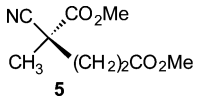
entry	cyanoacetate (R^1)	% yield[b]	*E*/*Z* ratio[c]	% ee[d] (confign)
1	$PhCH_2CH_2$ (**3a**)	99	3.6/1	94/84
2		97[e]	4.0/1	94/80
3	$CH_3CH_2CH_2CH_2$ (**3b**)	90[f]	3.8/1	95/95
4	$CH_3CH_2CH_2$ (**3c**)	99	4.6/1	94/93
5	CH_3CH_2 (**3d**)	99	4.6/1	95/−
6	CH_3 (**3e**)	99	6.7/1	93 (*S*)/−
7		99[e]	6.5/1	93 (*S*)/−
8	$(CH_3)_2CH$ (**3f**)	99	5.4/1	96/−
9		80[e]	7.5/1	96/−
10	$CH_2{=}CHCH_2CH_2$ (**3g**)	99	3.3/1	92/89
11	$CH_2{=}CHCH_2$ (**3h**)	99	6.2/1	92/81
12	$(CH_3)_2CHCH_2CH_2$ (**3i**)	99	3.8/1	95/93
13	$(CH_3)_3SiCH_2CH_2$ (**3j**)	96	5.1/1	95 (*S*)/93
14		72[e]	5.8/1	97 (*S*)/90
15	*p*-Br−$PhCH_2CH_2$ (**3k**)	99	3.7/1	95 (*S*)/91 (*S*)
16	Ph (**3l**)	89	2.2/1	18/−

[a] Unless otherwise specified, the reaction was carried out with 2 equiv of *t*-butyl propiolate in the presence of 1 mol % of (*S*)-**1i** and 1.2 equiv of Cs_2CO_3 in toluene under the given reaction conditions. [b] Isolated yield. [c] Determined by ^1H NMR analysis. [d] Enantiopurity of the adducts **4a**−**k** was determined by HPLC analysis using a chiral column. [e] Catalytic use (0.5 equiv) of Cs_2CO_3 at −40 °C for 16−24 h. [f] At −40 °C for 20 h.

94% ee was finally attained when the lower temperature was employed with (*S*)-**1i** in combination with the use of *t*-butyl propiolate (entries 10−12). The amount of Cs_2CO_3 base can be reduced to 0.2 equiv without decreasing the yield and enantioselectivity (entries 12, 13, 16, and 17).

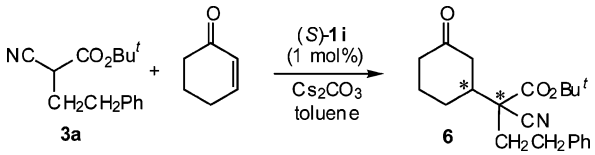
With the optimal condition at hand, we further studied the generality of the asymmetric conjugate addition to *t*-butyl propiolate using various *t*-butyl α-substituted-α-cyanoacetates as shown in Table 2, where excellent enantioselectivity is observable in the catalytic enantioselective synthesis of polyfunctional molecules with an all-carbon quaternary stereocenter. Among α-substituted-α-cyanoacetates, both α-(*prim*-alkyl)- and α-(*sec*-alkyl)-α-cyanoacetates exhibited high enantioselection. However, use of α-phenyl-α-cyanoacetate **3l** resulted in the low enantioselectivity for **4l** (entry 16). Catalytic Cs_2CO_3 (0.5 equiv) is also employable (entries 2, 7, 9, and 14). Although the observed *E*/Z selectivity is moderate, these (*E*)- and (*Z*)-**4a**−**k** can be easily separated by simple column chromatography.

The absolute configuration of the conjugate adduct (*E*)-**4e** was firmly determined to be *S* by conversion to the known dimethyl ester **5** with the sequence of (i) catalytic hydrogenation (catalyst Pd/C, H_2, MeOH); (ii) acid hydrolysis (CF_3CO_2H/CH_2Cl_2); and (iii) methylation (CH_2N_2/ether).[8] The absolute configuration of other conjugate adducts, (*E*)-**4j**, (*E*)-**4k**, and (*Z*)-**4k** was also determined by X-ray crystallographic analysis (Table 2).



5

This approach is also applicable to the asymmetric conjugate addition of *t*-butyl α-(2-phenylethyl)-α-cyanoacetate (**3a**) to 2-cyclohexenone with Cs_2CO_3 in the presence of a catalytic amount (1 mol %) of the catalyst (*S*)-**1i** in toluene at 0 °C for 2 h to afford the corresponding conjugate adduct **6** in 99% yield (diastereomeric ratio, 85:15; 91% ee for the major diastereomer).



In conclusion, we succeeded in designing a new, chiral phase transfer catalyst of type (*S*)-**1i** to realize a general and useful procedure for the asymmetric conjugate addition of various *t*-butyl α-alkyl-α-cyanoacetates to *t*-butyl propiolate.

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Supporting Information Available: Experimental details and physical characterization data of the catalysts and all new compounds including the X-ray analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

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