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Catalytic asymmetric alkylation of α-cyanocarboxylates and acetoacetates using a phase-transfer catalyst

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ABSTRACT

The catalytic asymmetric alkylation of α-cyanocarboxylates and acetoacetates with an alkyl halide was performed under phase-transfer conditions to afford compounds which have a chiral quaternary carbon with up to 97% and 94% ee, respectively. As applications of this method, chiral 2-oxindole derivatives and a β-lactam derivative were synthesized.

1. Introduction

The stereoselective formation of a chiral carbon with all-carbon substituents is important, because a number of naturally occurring bioactive compounds and pharmaceuticals have a chiral quaternary carbon.[1] In order to create an all-carbon quaternary center stereoselectively, an asymmetric C–C bond-forming reaction needs to be developed. Although asymmetric alkylation is thought to be a useful and straightforward method for achieving this purpose, the steric repulsion between the carbon substituents makes the reaction difficult and challenging. Since a Merck research group reported the alkylation of phenylindanone derivative under phase-transfer conditions,[2] development of chiral phase-transfer catalysts (PTC) and the reactions using them has been studied extensively. As a result, several examples of alkylation, which afford an all-carbon quaternary center, have been reported[3] but the most commonly studied are the asymmetric alkylations of protected glycine derivatives.[4] In order to develop a general method for the synthesis of the compounds that have an all-carbon quaternary center, we chose substrates with an acidic methane to form a carbanion under phase-transfer conditions. It was found that the substitution reaction of α-cyanocarboxylates[5] and acetoacetates with an alkyl halide proceeded stereoselectively in the presence of a chiral PTC. Herein, we report these results in detail.

2. Results and discussion

Prior to asymmetric alkylation, commercially available ethyl 2-cyanopropanoate was tested for the reaction with benzyl bromide in satd Na_2CO_2 aqueous solution/toluene using achiral tetrabutylammonium iodide as a PTC. It was found that ethyl 2-benzyl-2-cyanopropanoate was obtained in 70% yield, but the reaction did not proceed without PTC. Thus we carried out the screening of chiral catalysts in the system (Table 1). Among the chiral phase-transfer catalysts, such as cinchonidine-derived catalysts **1a–c**,[2,6] binaphthyl derivative **2a**,[7] and tartrate-derived bis-ammonium salt **3**,[8] catalyst **2a** gave a higher ee and faster reaction rate. In the phase-transfer alkylation using catalyst **2a**, the reaction rate and ee were improved further (32% ee) by using Cs_2CO_3 as a base in ether solvent. Other solvents such as toluene, CH_2Cl_2, $CHCl_3$, and AcOEt were also investigated, but the results were inferior to the reaction using diethyl ether as a solvent. Thus we next examined the influence of the ester group on the selectivity (Table 2). The reaction was carried out using 5 mol % of catalyst **2a** and benzyl bromide (1.2 equiv) in ether/satd Cs_2CO_3 aqueous solution at room temperature. The result was that bulky ester groups tended to give high enantioselectivity, the ee went up to 73% when *t*-butyl or diisopropylmethyl ester was employed. With these results, we next investigated the influence of the base on the selectivity and the yield using 2-cyanopropanoic acid *t*-butyl ester as a substrate (Table 3). Since the substrate with a *t*-butyl ester was more reluctant to hydrolysis, a base stronger than Cs_2CO_3 was tested. The results showed that KOH and CsOH increased the reaction rate and gave higher enantioselectivity. By using a solid base, it became possible to lower the reaction temperature. When the reaction was run at −60 °C, 93% ee and an acceptable reaction rate were obtained even in the presence of 1 mol % of the catalyst (entry 5). Next the reaction with various alkyl halides was investigated (Table 4). Alkyl halides with a functional group were also revealed to react in high yields with high enantioselectivities. It was also found that the products with an opposite configuration were obtained by changing the order of introduction of alkyl substituent at the α-position of cyanoacetate (entries 3 and 9). Binaphthyl-derived spiro quaternary ammonium salt **2b** was found to enhance enantioselectivity further. The absolute configurations of compounds **5d** and **6** were determined by derivatization to the corresponding α,α-disubstituted-α-cyanoacetic acids and comparison of the specific rotations with the literature values.[9]

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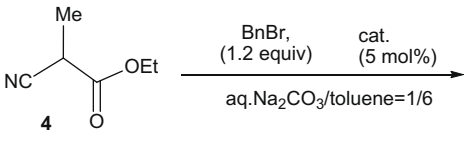
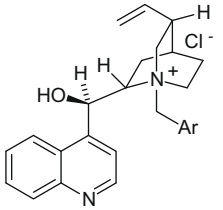
Table 1
Catalyst screening for the phase-transfer asymmetric benzylation of **4**

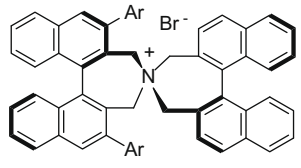




1a: Ar = phenyl

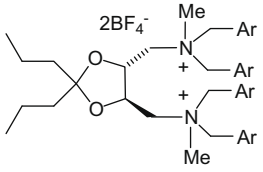
1b: Ar = 9-anthracenyl

1c: Ar = 4-(trifluoromethyl)benzyl



2a: Ar = 3,4,5-trifluorophenyl

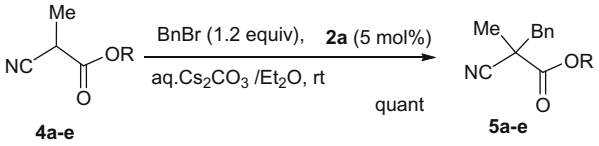
2b: Ar = 3,5-trifluoromethylphenyl



3: Ar = 4-methylphenyl

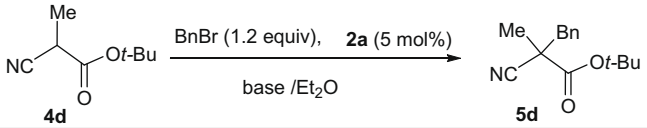
Cat.	Time (d)	%ee
1a	7	12
1b	12	16
1c	12	17
2a	4	28
3	12	3

Table 2
Effect of ester group on the enantioselectivity



Entry	Compound	R	Time (d)	%ee of **5**
1	**4a**	Et	1.5	32
2	**4b**	Me	1	15
3	**4c**	*i*-Pr	1.5	51
4	**4d**	*t*-Bu	7	73
5	**4e**	–CH(*i*Pr)$_2$	7	73

Table 3
Effect of base on the phase-transfer benzylation of **4d** in the presence of **2a**



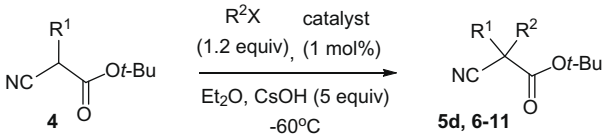
Entry	Base	Temp (°C)	Time (h)	Yield (%)	ee of **5d** (%)
1	aq Cs_2CO_3[a]	rt	168	Quant	73
2	Cs_2CO_3	−40	48	37	73
3	KOH	−40	2	99	87
4	CsOH	−40	2	Quant	89
5[b]	CsOH	−60	72	98	93

[a] A saturated aqueous solution was used.
[b] 1 mol % of **2a** was used.

As an application of the present method, we next carried out the synthesis of 3,3-disubstituted 2-oxindoles. 2-Oxindoles bearing a chiral quaternary center at the 3-position have received increasing attention due to their unique biological activities and their potential as intermediates to synthesize bioactive natural products.[10] Thus we chose 2-bromophenylcyanoacetate **12** as a substrate, and investigated the allylation. In Table 5, the base and temperature effects on the yield and ee are shown. The reaction did not proceed at −60 °C, while the ee did not increase under −10 °C. When Et_2O solvent was used in the reaction, reaction rate and ee decreased. In order to determine the absolute configuration of **13** and to confirm the availability of the chiral adduct, compound **13** was transformed to β-lactam **16** whose specific rotation was reported (Scheme 1).[11] After reduction of the allyl and bromo groups with HCO_2NH_4 catalyzed by Pd/C, the cyano group was reduced with $NaBH_4$ in the presence of $CoCl_2$[12] and the subsequent protection of the thus-produced amino group with CbzCl afforded compound **15**. Next, β-lactam **16** was synthesized by the subsequent removal of both the *t*-butyl and CBz groups followed by intramolecular condensation with dipyridyl disulfide[13] and PPh_3 in 90% yield from **15**.[14] By comparing the specific rotation of **16** thus obtained with that of the reported one, the absolute configuration of **16** was determined to be (*R*). Therefore compound **13** was found to have an (*R*)-configuration. Next, conversion of **13** to oxindoles was investigated (Scheme 2). Treatment of **13** with TFA followed by amidation of the resulting carboxylic acid with benzyl amine gave **17** in 88% yield. The copper-mediated intramolecular aryl amination[15] of **17** afforded 3,3-disubstituted chiral oxindole **18** in quantitative yield. The cyano group of **18** was shown to convert to a carboxyl group by treatment with alkaline hydrogen peroxide.[16]

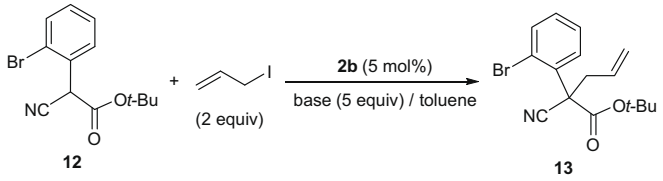
We then investigated the chiral phase-transfer-catalyzed alkylation of acetoacetates. Also in this case, catalysts **2a** and **2b** gave higher enantioselectivity than cinchonidine-derived catalysts **1a–c** (Table 6). In the reaction of entry 5, changing the base from KOH to CsOH gave almost the same result (y. 93%, 63% ee). Thus, further optimization of the reaction was carried out using KOH as a base (Table 7), and the results showed that the less polar sol-

Table 4
Catalytic enantioselective phase-transfer alkylation of **4** with various alkyl halides



Entry	R^1	R^2X	Cat.	Time (h)	Yield (%)	Product	%ee (config.)
1	Me	BnBr	**2a**	72	98	**5d**	93(*R*)
2	Me	BnBr	**2b**	72	96	**5d**	97(*R*)
3	Me	CH_2=$CHCH_2I$	**2a**	72	Quant	**6**	89(*R*)
4	Me	CH_2=$CHCH_2I$	**2b**	72	90	**6**	92(*R*)
5	Me	2-(Bromomethyl)pyridine	**2a**	72	Quant	**7**	70
6	Me	ICH_2CO_2Et	**2a**	96	Quant	**8**	76
7	Me	ICH_2CO_2Et	**2b**	96	97	**8**	85
8	Me	$BrCH_2CO_2tBu$	**2a**	96	Quant	**9**	92
9	Allyl	MeI	**2a**	120	81	**6**	67(*S*)
10	Allyl	BnBr	**2a**	72	Quant	**10**	91
11	Allyl	BnBr	**2b**	72	Quant	**10**	>99
12	Allyl	ICH_2CO_2Et	**2a**	96	Quant	**11**	80
13	Allyl	ICH_2CO_2Et	**2b**	96	Quant	**11**	90

Table 5
Phase-transfer allylation of **12** catalyzed by **2b**

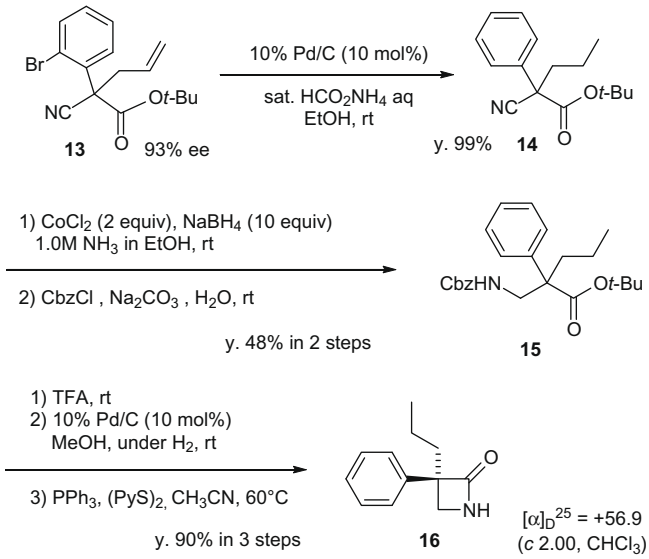


Entry	Base	Temp (°C)	Time	Yield (%)	ee (%)
1	KOH	rt	2 h	Quant	85
2	CsOH	rt	2 h	Quant	87
3	Cs_2CO_3	rt	7 d	7	89
4	CsOH	−10	1 d	Quant	93
5[a]	CsOH	−10	1 d	Quant	93
6	CsOH	−60	7 d	0	—

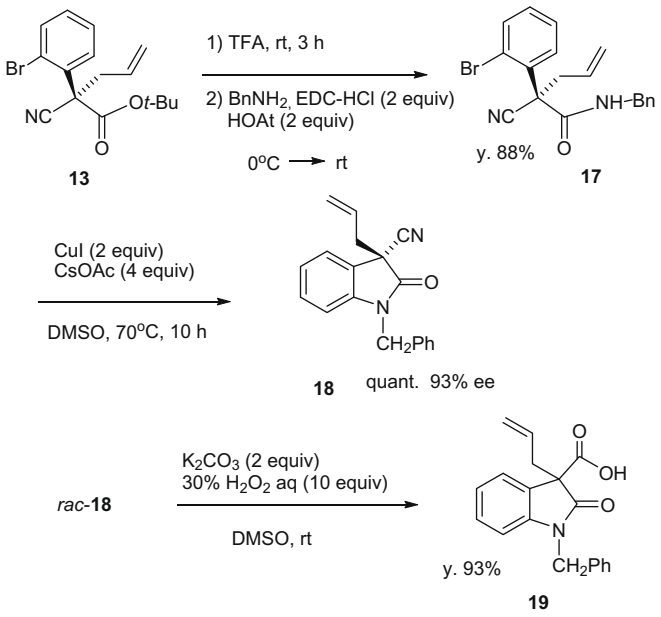
[a] 1 mol % of catalyst was used.

vent tended to give higher ee (entries 1–8). When the reaction was run at −60 °C in mesitylene containing 10% toluene which was added to lower the freezing point of mesitylene, the ee value was improved to 94% (entry 14). Based on these results, the reactions with other electrophiles were examined (Table 8).

Although mesitylene containing 10% toluene gave the best result in the case of benzylation, the solvent was not always suited for the other alkylations. When allyl iodide was subjected to the reaction using the solvent, starting material was recovered due to the reaction of allyl iodide with mesitylene (entry 4).[17] In the case of the reaction with allyl iodide and/or ethyl iodoacetate, Et_2O gave better results than mesitylene/toluene = 9/1(entries 6 and 8). The absolute configuration of **21a** was determined as follows (Scheme 3); since the specific rotation of ethyl ester derivative **23** was reported,[18] ethyl ester **22** was subjected to the present reaction. As a result, compound **23** with an (*R*)-configuration was obtained with 66% ee. Product **23** was then converted to

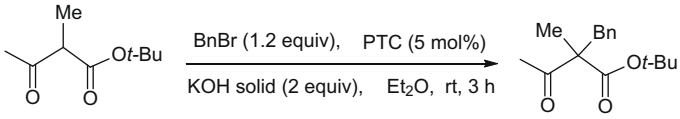


Scheme 1. Synthesis of β-lactam **16**.



Scheme 2. Synthesis of 2-oxindole derivatives.

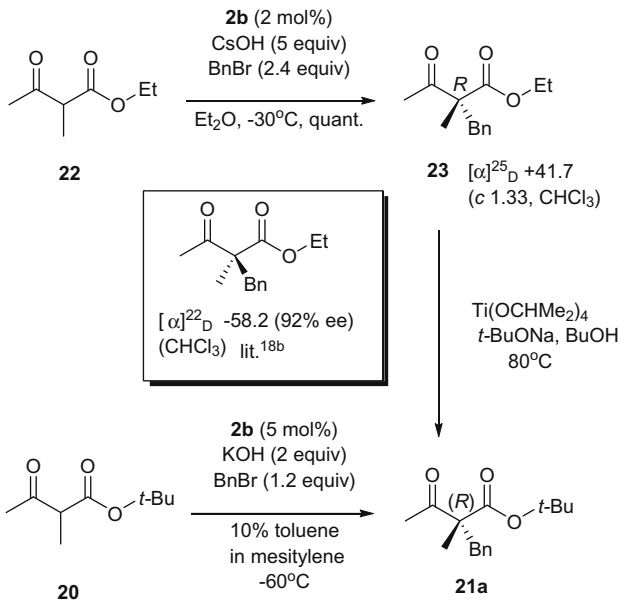
Table 6
Phase-transfer benzylation of **20** catalyzed by **1a**–**2b**



20 **21**

Entry	PTC	Yield (%)	ee of **21** (%)
1	**1a**	62	0
2	**1b**	66	6
3	**1c**	76	8
4	**2a**	60	38
5	**2b**	92	64

the *t*-butyl ester **21a**. The absolute configuration of **21a** prepared from **20** was determined by comparison of the retention time of chiral HPLC analysis with that of **21a** prepared from **23**. The other products **21b** and **21c** were assigned to be (*R*) based on the assumption that the same stereocontrol had occurred.



Scheme 3. Determination of the absolute configuration of **21a**.

3. Conclusion

In conclusion, we have performed the catalytic asymmetric alkylation of α-cyanocarboxylates and acetoacetates using PTC, and it was demonstrated that synthetic cyanocarboxylates with a chiral quaternary carbon center were converted to an oxindole and a β-lactam derivative. The present method is straightforward in constructing an all-carbon quaternary center and is thought to provide facile access to the more complex compounds which have such a stereocenter. Further application of this method to the synthesis of bioactive natural products is now under investigation.

4. Experimental

4.1. General

Unless otherwise specified, reagents were purchased from commercial suppliers and used without further purification. Dehydrated toluene, DMSO, THF, CH_2Cl_2, EtOH, and MeOH were purchased from commercial suppliers. Al CsOH used was anhydrous salt. Moisture-sensitive reactions were carried out under an atmosphere of Ar. ^1H and ^{13}C NMR spectra ware recorded on a 500 MHz (125 MHz for ^{13}C) or a 400 MHz (100 MHz for ^{13}C) spectrometer. All melting points were uncorrected.

4.2. General procedure for the asymmetric phase-transfer alkylation of α-cyanocarboxylates

A solution of *tert*-butyl 2-cyanopropanoate or *tert*-butyl 2-cyanopent-4-enoate (0.1 mmol) in Et_2O (2.4 ml) was cooled at −60 °C. The PTC (**2a** or **2b**) (0.001 mmol), alkyl halide (0.12 mmol), and CsOH (75 mg, 0.5 mmol) were added to the solution. The reaction mixture was vigorously stirred for the time indicated in Table 4 and then diluted with Et_2O. The organic layer was washed with H_2O and brine, dried over $MgSO_4$, and the solvents were removed by evaporation. The residue was chromatographed on silica gel (AcOEt/hexane) to give the corresponding 2-cyanocarboxylate.

4.3. (*R*)-*tert*-Butyl 2-cyano-2-methyl-3-phenylpropanoate 5d

Colorless oil; $[\alpha]_D^{25} = -14.7$ (*c* 2.00, $CHCl_3$) (97% ee); ^1H NMR ($CDCl_3$) δ 1.42 (9H, s), 1.57 (3H, s), 2.98–3.01 (1H, d, *J* = 13.7 Hz), 3.17–3.21 (1H, d, *J* = 13.4 Hz), 7.30–7.33(5H, m); ^{13}C NMR ($CDCl_3$) δ 24.1, 28.4, 44.3, 46.7, 83.1, 121.9, 128.5, 129.2, 130.9, 135.2, 169.2; HR-FAB MS: calcd for $C_{15}H_{20}NO_2$ $[M+H]^+$: 246.1493, found: 246.1494. The ee was determined by HPLC analysis (Daicel CHIRALCEL OJ, 2-propanol/hexane = 1:400).

4.4. (*R*)-*tert*-Butyl 2-cyano-2-methylpent-4-enoate 6

Colorless oil; $[\alpha]_D^{25} = +2.2$ (*c* 1.67, $CHCl_3$) (92% ee); ^1H NMR ($CDCl_3$) δ 1.50 (9H, s), 1.54 (3H, s), 2.47 (1H, dd, *J* = 13.8, 7.4 Hz), 2.64 (1H, dd, *J* = 13.8, 7.2 Hz), 5.22–5.26 (2H, m), 5.82 (1H, m); ^{13}C NMR ($CDCl_3$) δ 22.7, 27.8, 42.1, 44.2, 83.9, 120.0, 120.7, 130.9, 167.8; HR-FAB MS: calcd for $C_{11}H_{18}NO_2$ $[M+H]^+$: 196.1407, found: 196.1321. The ee was determined by HPLC analysis (Daicel CHIRALCEL OJ-H, 2-propanol/hexane = 1:400).

4.5. *tert*-Butyl 2-cyano-2-methyl-3-pyridin-2-ylpropanoate 7

Colorless oil; $[\alpha]_D^{25} = +8.4$ (*c* 3.45, CH_2Cl_2) (92% ee); ^1H NMR ($CDCl_3$) δ 1.48 (9H, s) 1.65 (3H, s), 3.21 (1H, d, *J* = 14.6 Hz), 3.45 (1H, d, *J* = 14.6 Hz), 7.19 (1H, ddd, *J* = 7.6, 4.8, 1.2 Hz), 7.27 (1H, m), 7.64 (1H, td, *J* = 7.6, 2.0 Hz), 8.54 (1H, ddd, *J* = 4.9, 2.1, 0.8 Hz); ^{13}C NMR ($CDCl_3$) δ 23.6, 27.7, 44.3, 44.9, 83.6, 120.3, 122.3, 123.8, 136.4, 149.1, 155.2, 168.0; HR-FAB MS: calcd for $C_{14}H_{19}N_2O_2$ $[M+H]^+$: 247.1440, found: 247.1449. The ee was determined by HPLC analysis (Daicel CHIRALCEL OJ-H, 2-propanol/hexane = 1:4).

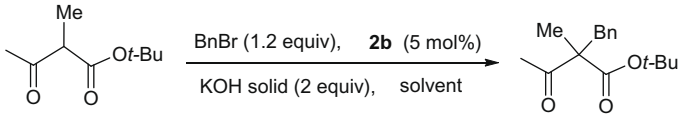
4.6. 1-*tert*-Butyl 4-ethyl 2-cyano-2-methylbutanedioate 8

Colorless oil; $[\alpha]_D^{25} = +15.6$ (*c* 2.00, $CHCl_3$) (85% ee); ^1H NMR ($CDCl_3$) δ 1.28 (3H, t, *J* = 7.2 Hz), 1.52 (9H, s), 1.63 (3H, s), 2.77 (1H, d, *J* = 17.1 Hz), 2.98 (1H, d, *J* = 17.1 Hz), 4.20 (2H, q, *J* = 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 14.1, 23.7, 27.7, 41.2, 41.6, 61.4, 84.1, 120.0, 167.4, 168.7; HR-FAB MS: calcd for $C_{12}H_{20}NO_4$ $[M+H]^+$: 242.1332, found: 242.1411. The ee was determined by HPLC analysis (Daicel CHIRALCEL OJ-H, 2-propanol/hexane = 1:200).

4.7. Di-*tert*-butyl 2-cyano-2-methylbutanedioate 9

Colorless oil; $[\alpha]_D^{25} = +19.3$ (*c* 7.50, $CHCl_3$) (92% ee); ^1H NMR ($CDCl_3$) δ 1.47 (9H, s), 1.51 (9H, s), 1.60 (3H, s), 2.69 (1H, d, *J* = 16.8 Hz), 2.89 (1H, d, *J* = 16.8 Hz); ^{13}C NMR ($CDCl_3$) δ 23.7,

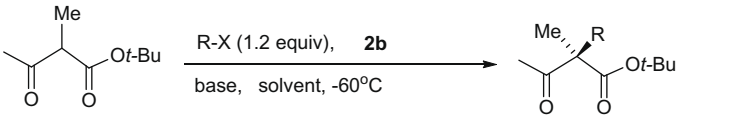
Table 7
Phase-transfer benzylation of **20** catalyzed by **2b** in various solvents



20 **21**

Entry	Solvent	Temp (°C)	Time (h)	Yield (%)	ee of **21** (%)
1	Et_2O	rt	3	92	64
2	TBME	rt	3	32	53
3	THF	rt	3	85	28
4	CH_2Cl_2	rt	3	85	9
5	CH_3CN	rt	3	92	0
6	Toluene	rt	3	80	68
7	Xylene	rt	3	90	71
8	Mesitylene	rt	3	Quant	69
9	Et_2O	−60	72	75	64
10	Toluene	−60	72	56	74
11	Xylene	−30	72	95	84
12	10% Toluene in xylene	−40	72	84	85
13	Mesitylene	−50	72	75	82
14	10% Toluene in mesitylene	−60	72	85	94

Table 8
Phase-transfer alkylation of **20** catalyzed by **2b**



20

21a: R = CH_2Ph
21b: R = $CH_2CH{=}CH_2$
21c: R = CH_2CO_2Et

Entry	R–X	Solvent	**2b** (mol %)	Base	Time (h)	Yield (%)	ee of **21** (%)
1		Mesitylene/toluene = 9/1	5	KOH	72	85	94
2	BnBr	Et_2O	5	KOH	72	75	64
3		Et_2O	1	CsOH	72	89	80
4		Mesitylene/toluene = 9/1	5	KOH	72	0	–
5	$CH_2{=}CHCH_2I$	Et_2O	5	KOH	72	65	68
6		Et_2O	1	CsOH	72	84	78
7	ICH_2CO_2Et	Mesitylene/toluene = 9/1	5	KOH	96	70	23
8		Et_2O	1	CsOH	72	100	80

27.7, 28.0, 41.4, 42.6, 82.3, 83.9, 120.0, 167.5, 167.8; HR-FAB MS: calcd for $C_{14}H_{24}NO_4$ $[M+H]^+$: 270.1694, found: 270.1709. The ee was determined by HPLC analysis (Daicel CHIRALCEL OJ-H, 2-propanol/hexane = 1:800).

4.8. *tert*-Butyl 2-benzyl-2-cyanopent-4-enoate 10

Colorless oil; $[\alpha]_D^{25} = -18.1$ (*c* 1.74, $CHCl_3$) (99% ee); ^1H NMR ($CDCl_3$) δ 1.29 (9H, s), 2.47 (1H, dd, *J* = 13.6, 6.8 Hz), 2.63 (1H, dd, *J* = 13.7, 7.8 Hz), 2.96 (1H, d, *J* = 13.4 Hz), 3.09 (1H, d, *J* = 13.4 Hz), 5.17–5.21 (2H, m), 5.78 (1H, m) 7.19–7.30 (5H, m); ^{13}C NMR ($CDCl_3$) δ 27.7, 41.7, 42.5, 84.2, 119.0, 120.8, 127.7, 128.4, 130.1, 130.7, 134.3, 166.9; HR-FAB MS: calcd for $C_{17}H_{22}NO_2$ $[M+H]^+$: 272.1621, found: 272.1662. The ee was determined by HPLC analysis (Daicel CHIRALCEL OD, 2-propanol/hexane = 1:800).

4.9. 1-*tert*-Butyl 4-ethyl 2-cyano-2-prop-2-en-1-ylbutanedioate 11

Colorless oil; $[\alpha]_D^{25} = +13.9$ (*c* 2.38, $CHCl_3$) (90% ee); ^1H NMR ($CDCl_3$) δ 1.25 (3H, t, *J* = 7.1 Hz), 1.48 (9H, s), 2.50 (1H, dd, *J* = 13.7, 7.3 Hz), 2.62 (1H, dd, *J* = 13.9, 7.3 Hz), 2.72 (1H, d, *J* = 17.1 Hz), 2.96 (1H, d, *J* = 16.8 Hz), 4.16 (2H, q, *J* = 7.3 Hz), 5.20–5.26 (2H, m), 5.80 (1H, m); ^{13}C NMR ($CDCl_3$) δ 14.1, 27.7, 40.0, 41.2, 45.9, 61.4, 84.3, 118.5, 121.3, 130.0, 166.6, 168.7; HR-FAB MS: calcd for $C_{14}H_{22}NO_4$ $[M+H]^+$: 268.1560, found: 268.1545. The ee was determined by HPLC analysis (Daicel CHIRALCEL OJ-H, 2-propanol/hexane = 1:100).

4.10. *tert*-Butyl (2-bromophenyl)cyanoacetate 12

To a stirred solution of 2-bromophenylacetonitrile (4.02 ml, 30 mmol) in DMF (100 ml) was added NaH (60% in oil) (1.32 g, 33 mmol) slowly at 0 °C. After 5 min di-*tert*-butyl dicarbonate (10.3 ml, 45 mmol) was added, and the solution was stirred for 6 h at room temperature in Ar atmosphere. Then water was added and the mixture was extracted with CH_2Cl_2. The combined organic layer was washed with brine and dried over $MgSO_4$. After the solvent was removed by evaporation, the residue was chromatographed on silica gel (AcOEt/hexane = 1/16) to give **12** (8.8 g) in 99% yield. Colorless oil: ^1H NMR ($CDCl_3$) δ 1.48 (9H, s), 5.13 (1H,

s), 7.26 (1H, dt, J = 1.5, 8.0 Hz), 7.40 (1H, dt, J = 1.0, 7.6 Hz), 7.57–7.63 (2H, m); ^{13}C NMR ($CDCl_3$) δ 27.7, 44.4, 85.0, 115.5, 123.9, 128.3, 129.9, 130.6, 130.7, 133.4, 162.8; HR-FAB MS: calcd for $C_{13}H_{15}BrNO_2$ $[M+H]^+$: 296.0286, found 296.0283.

4.11. (*R*)-*tert*-Butyl 2-(2-bromophenyl)-2-cyanopent-4-enoate 13

To a solution of **12** (29.6 mg, 0.1 mmol) in toluene (2.4 ml) cooled at −10 °C were added PTC **2b** (1.1 mg, 0.001 mmol) and allyl iodide (18 μl, 0.2 mmol), then CsOH (75 mg, 0.5 mmol) was added to the solution. The reaction mixture was stirred vigorously for 1d and diluted with H_2O. The mixture was extracted with CH_2Cl_2 and the combined organic layer was washed with brine and dried over $MgSO_4$. After the solvent was removed by evaporation, the residue was chromatographed on silica gel (AcOEt/hexane = 1/16) to give **13** in quantitative yield. Colorless oil; $[\alpha]_D^{25} = -9.2$ (c 2.00, $CHCl_3$) (93% ee); ^{1}H NMR ($CDCl_3$) δ 1.48 (9H, s), 3.11 (1H, dd, J = 7.6, 14.0 Hz), 3.27 (1H, dd, J = 6.8, 14.0 Hz), 5.19–5.26 (2H, m), 5.78 (1H, m), 7.24 (1H, dt, J = 1.6, 7.6 Hz), 7.37 (1H, dt, J = 1.2, 8.0 Hz), 7.55 (1H, dd, J = 1.4, 8.0 Hz), 7.64 (1H, dd, J = 1.6, 8.0 Hz); ^{13}C NMR ($CDCl_3$) δ 27.6, 39.7, 54.8, 84.7, 117.7, 120.7, 122.8, 127.7, 129.6, 130.1, 130.8, 133.9, 134.7, 165.2; HR-FAB MS: calcd for $C_{16}H_{19}O_2NBr$ $[M+H]^+$: 336.0630, found: 336.0584. The ee was determined by HPLC analysis (Daicel CHIRALCEL OJ-H, 2-propanol/hexane = 1:100).

4.12. *tert*-Butyl 2-cyano-2-phenylpentanoate 14

To a solution of **13** (3.36 g, 10 mmol) in EtOH (25 ml) were added 10% Pd/C (1.06 g) and satd HCO_2NH_4 aq (25 ml) under Ar atmosphere. The solution was stirred for 1 d at room temperature, and then filtered through a pad of Celite. The filtrate was evaporated to remove EtOH, and the remaining aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with brine and dried over $MgSO_4$. After the solvent was removed by evaporation, the residue was chromatographed on silica gel (AcOEt/hexane = 1/6) to give **14** (2.57 g) in 99% yield. Colorless oil: ^{1}H NMR ($CDCl_3$) δ 0.97 (3H, t, J = 7.3 Hz), 1.39–1.52 (11H, m), 2.03 (1H, m), 2.31 (1H, m), 7.36–7.41 (3H, m), 7.53 (2H, d, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$) δ 13.8, 18.9, 27.6, 40.0, 55.0, 84.1, 118.9, 125.9, 128.5, 129.0, 135.2, 166.5; HR-FAB MS: calcd for $C_{16}H_{22}NO_2$ $[M+H]^+$: 260.1651, found: 260.1659.

4.13. *tert*-Butyl 2-(benzyloxycarbonylaminomethyl)-2-phenylpentanoate 15

To a solution of **14** (2.57 g, 10 mmol) in EtOH (25 ml) was added 2.0 M NH_3 in EtOH (25 ml). Then a mixture of $NaBH_4$ (3.75 g, 100 mmol) and $CoCl_2$ (2.57 g, 20 mmol) was added slowly to the solution. The reaction mixture was stirred for 1d at room temperature and quenched with 1 M aq HCl. After the precipitate was removed by filtration, the filtrate was evaporated off. Then AcOEt was added to the residue and extracted with 1 M aq HCl. The combined aqueous layer was neutralized with $NaHCO_3$ and extracted with AcOEt. The combined organic layer was washed with brine and dried over $MgSO_4$. After the solvent was removed by evaporation, H_2O (20 ml), Na_2CO_3 (2.07 g, 20 mmol), and CbzCl (0.88 ml, 6.2 mmol) were added and the solution was stirred for 1 d at room temperature. The reaction mixture was extracted with CH_2Cl_2 and the combined organic layer was washed with brine and dried over $MgSO_4$. After the solvent was removed by evaporation, the residue was chromatographed on silica gel (AcOEt/hexane = 1/10→1/8) to give **15** (1.91 g) in 48% yield. Colorless oil: ^{1}H NMR ($CDCl_3$) δ 0.92 (3H, t, J = 7.1 Hz), 1.26–1.27 (2H, m), 1.42 (9H, s), 1.89–1.95 (2H, m), 3.62 (1H, dd, J = 4.6, 13.9 Hz), 3.82 (1H, dd, J = 7.8, 13.7 Hz), 4.89 (1H, br s), 5.28 (2H, s), 7.22–7.33 (10H, m); ^{13}C NMR ($CDCl_3$) δ 14.8, 17.9, 27.9, 36.9, 45.9, 55.5, 66.4, 81.5, 126.5, 126.9, 128.0, 128.0, 128.4, 128.5, 136.6, 140.9, 156.3, 173.9; HR-FAB MS: calcd for $C_{24}H_{32}NO_4$ $[M+H]^+$: 398.2331, found: 398.2308.

4.14. (*R*)-3-Phenyl-3-propylazetidin-2-one 16

Compound **15** (397 mg, 1.0 mmol) was dissolved in TFA (5 ml), and the solution was stirred for 12 h at room temperature. The reaction mixture was evaporated, and the residue was dissolved in MeOH (5 ml). Then, 10% Pd/C (106 mg, 0.10 mmol) was added to the solution and stirred for 1 d under H_2 atmosphere. The reaction mixture was filtered through a pad of Celite, and the filtrate was evaporated. Then MeCN (20 ml) was added, and PPh_3(315 mg, 1.2 mmol) and 2,2'-dipyridyl disulufide (264 mg, 1.2 mmol) were added to the solution. The reaction mixture was stirred for 4d at 60 °C under an Ar atmosphere. After being diluted with H_2O, the solution was extracted with CH_2Cl_2. The combined organic layer was washed with brine and dried over $MgSO_4$. After the solvent was removed by evaporation, the residue was chromatographed on silica gel (AcOEt/hexane = 1/4→1/2→1/0) to give **16** (170 mg) in 90% yield. Colorless oil: $[\alpha]_D^{25} = +56.9$ (c 2.00, $CHCl_3$) (93% ee), ^{1}H NMR ($CDCl_3$) δ 0.89 (3H, t, J = 7.6 Hz), 1.28 (1H, m), 1.44 (1H, m), 1.95 (2H, m), 3.50 (1H, d, J = 5.6 Hz), 3.59 (1H, d, J = 4.8 Hz), 5.76 (1H, br s), 7.26 (1H, m), 7.33–7.36 (2H, m), 7.40–7.43 (2H, m), ^{13}C NMR ($CDCl_3$) δ 14.2, 18.3, 39.9, 48.4, 64.7, 126.6, 127.0, 128.4, 140.0, 172.2; HR-FAB MS: calcd for $C_{12}H_{16}NO$ $[M+H]^+$: 190.1232, found: 190.1223.

4.15. (*R*)-*N*-Benzyl-2-(2-bromophenyl)-2-cyanopent-4-enamide 17

Compound **13** (34 mg, 0.1 mmol) was dissolved in TFA (1.0 ml) and stirred at room temperature for 12 h under an Ar atmosphere. The TFA was then removed by evaporation and CH_2Cl_2 (1.0 ml) was added. The solution was cooled to 0 °C and EDC·HCl (38 mg, 0.2 mmol), 1-hydroxy-7-azabenzotriazole (27 mg, 0.2 mmol), and $BnNH_2$ (16 μl, 0.15 mmol) were added. The reaction mixture was stirred overnight at room temperature under an Ar atmosphere. After the addition of H_2O, the mixture was extracted with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$, and the solvents were removed by evaporation. The residue was chromatographed on silica gel (AcOEt/hexane = 1/4) to give compound **17** in 88% yield. Mp 124 °C (CH_2Cl_2); $[\alpha]_D^{25} = -21.9$ (c 3.07, $CHCl_3$) (93% ee); ^{1}H NMR ($CDCl_3$) δ 3.19–3.30 (2H, m), 4.44 (1H, dd, J = 5.1, 14.8 Hz), 4.54 (1H, dd, J = 6.0, 14.8 Hz), 5.19–5.27 (2H, m), 5.75 (1H, m), 6.13 (1H, br s), 7.24–7.34 (6H, m), 7.39 (1H, t, J = 7.6 Hz), 7.61 (1H, d, J = 7.6 Hz), 7.66 (1H, d, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$) δ 39.6, 44.8, 54.6, 118.4, 121.2, 123.0, 127.9, 128.1, 128.8, 130.3, 130.7, 130.7, 133.2, 135.3, 136.8, 165.3; HR-FAB MS: calcd for $C_{19}H_{18}ON_2Br$ $[M+H]^+$: 369.0619, found: 369.0592; Anal. Calcd for $C_{19}H_{17}ON_2Br$: C, 61.80; H, 4.64; N, 7.59. Found: C, 61.78; H, 4.54; N, 7.48. The ee was determined by HPLC analysis (Daicel CHIRALCEL OJ-H, 2-propanol/hexane = 1:20).

4.16. (*R*)-1-Benzyl-3-cyano-3-(prop-2-en-1-yl)-1,3-dihydroindol-2-one 18

To a solution of compound **17** (44 mg, 0.11 mmol) in DMSO (1.1 ml) were added CuI (42 mg, 0.2 mmol) and CsOAc (106 mg, 0.5 mmol). The mixture was stirred for 10 h at 70 °C under an Ar atmosphere. After the addition of Et_2O, the organic layer was washed with H_2O and brine, and dried over $MgSO_4$. The solvent was removed by evaporation and the residue was chromatographed on silica gel (AcOEt/hexane = 1/7) to give the compound **18** in quantitative yield. Mp 122 °C (CH_2Cl_2); $[\alpha]_D^{25} = +27.3$ (c 5.81, $CHCl_3$) (93% ee); ^{1}H NMR

($CDCl_3$) δ 2.83 (1H, dd, J = 8.4, 13.6 Hz), 3.05 (1H, dd, J = 6.4, 13.2 Hz), 4.81 (1H, d, J = 15.6 Hz), 5.02 (1H, d, J = 15.6 Hz), 5.18–5.22 (2H, m), 5.65 (1H, m), 6.78 (1H, d, J = 7.6 Hz), 7.11 (1H, t, J = 7.6 Hz), 7.26–7.33 (6H, m), 7.41 (1H, d, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 41.1, 44.6, 46.4, 110.1, 116.7, 122.2, 123.6, 124.5, 124.7, 127.4, 128.1, 128.9, 129.0, 130.3, 134.7, 142.2, 170.1; HR-FAB MS: calcd for $C_{19}H_{17}ON_2$ $[M+H]^+$: 289.1351, found: 289.1337; Anal. Calcd for $C_{19}H_{16}ON_2$: C, 79.14; H, 5.59; N, 9.72. Found: C, 79.02; H, 5.52; N, 9.75. The ee was determined by HPLC analysis (Daicel CHIRALCEL IA, 2-propanol/hexane = 1:10).

4.17. 3-Allyl-1-benzyl-2-oxo-2,3-dihydro-1*H*-indole-3-carboxylic acid 19

To a solution of **18** (290 mg, 1.0 mmol) in DMSO (10 ml) were added K_2CO_3 (280 mg, 2.0 mmol) and 30% aq H_2O_2 (1.02 ml, 10 mmol) at 0 °C. The solution was stirred for 1 d at room temperature, then diluted with H_2O, and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$, and the solvents were removed by evaporation. The residue was chromatographed on silica gel (AcOEt/hexane = 1/1) to give the compound **19** (286 mg) in 93% yield.

Mp 199–200 °C (AcOEt); ^{1}H NMR ($CDCl_3$) δ 2.88 (1H, dd, J = 13.4, 8.0 Hz), 2.97 (1H, dd, J = 13.4, 6.3 Hz), 4.84 (1H, d, J = 15.6 Hz), 4.94–5.07 (3H, m), 5.45 (1H, m), 6.73 (1H, d, J = 7.8 Hz), 7.09 (1H, m), 7.19 (1H, dt, J = 7.6, 1.2 Hz), 7.22–7.31 (5H, m), 7.70 (1H, m); ^{13}C NMR ($CDCl_3$) δ 43.3, 44.2, 58.8, 109.1, 119.9, 123.3, 126.7, 127.4, 127.9, 128.6, 128.9, 131.1, 135.5, 142.1, 169.3, 176.5; HR-FAB MS: calcd for $C_{19}H_{18}NO_3$ $[M+H]^+$: 308.1287, found: 308.1284.

4.18. General procedure for the asymmetric phase-transfer alkylation of acetoacetates

A solution of *tert*-butyl 2-methyl-3-oxobutanoate (0.1 mmol) in Et_2O or 10% toluene in mesitylene (2.4 ml) was cooled at −60 °C. Next, PTC **2b** (0.001 mmol), alkyl halide (0.12 mmol), and then base (0.4 mmol) were added to the solution. The reaction mixture was vigorously stirred for the time indicated in Table 7 and quenched with 1 M aq HCl. After the solution was diluted with AcOEt, organic layer was washed with H_2O and brine, and dried over $MgSO_4$. The solvents were removed by evaporation and the residue was chromatographed on silica gel (AcOEt/hexane) to give the corresponding 2-substituted acetoacetates.

4.19. *tert*-Butyl 2-benzyl-2-methyl-3-oxobutanoate 21a

Colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.17 (3H, s), 1.37 (9H, s), 2.10 (3H, s), 2.98 (1H, d, J = 14 Hz) 3.15 (1H, d, J = 13.6 Hz), 7.04–7.19 (5H, m); ^{13}C NMR ($CDCl_3$) δ 19.1, 26.4, 27.8, 40.2, 61.3, 82.0, 126.7, 128.1, 130.3, 136.7, 171.5, 205.5; HR-FAB MS: calcd for $C_{16}H_{23}O_3$ $[M+H]^+$: 263.1569, found: 263.1637. The ee was determined by HPLC analysis (Daicel CHIRALCEL IA, AcOEt/hexane = 1:11).

4.20. *tert*-Butyl 2-acetyl-2-methylpent-4-enoate 21b

Colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.23 (3H, s), 1.41 (9H, s), 2.11 (3H, s), 2.39–2.45 (1H, m), 2.52–2.58 (1H, m), 5.03–5.04 (2H, m), 5.56–5.66 (1H, m); ^{13}C NMR ($CDCl_3$) δ 19.2, 26.5, 28.2, 39.6, 60.3, 82.2, 119.1, 133.2, 171.9, 205.7; HR-FAB MS: calcd for $C_{12}H_{21}O_3$ $[M+H]^+$: 213.1412, found: 213.1475. The ee was determined by HPLC analysis (Daicel CHIRALCEL AD-H, 2-propanol/hexane = 1:500).

4.21. 1-*tert*-Butyl 4-ethyl 2-acetyl-2-methylbutanedioate 21c

Colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.25 (3H, t, J = 7.2 Hz), 1.461 (9H, s), 1.455 (3H, s), 2.24 (3H, s), 2.81 (1H, d, J = 16.8 Hz), 2.87 (1H, d, J = 16.4 Hz), 4.11 (2H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 13.7, 19.6, 25.7, 27.3, 39.5, 57.7, 60.2, 81.7, 170.3, 170.5, 204.4; HR-FAB MS: calcd for $C_{13}H_{23}O_5$ $[M+H]^+$: 259.1467, found: 259.1531. The ee was determined by HPLC analysis (Daicel CHIRALCEL IA, AcOEt/hexane = 1:25).

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