DOI: 10.1002/adsc.201200237

Catalytic Asymmetric Synthesis of 2-Alkyleneoxetanes through [2+2] Annulation of Allenoates with Trifluoromethyl Ketones

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Received: March 7, 2012; Revised: March 20, 2012; Published online: ■■ ■■, 0000

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201200237.

Abstract: The first example of a β-isocupreidine (β-ICD)-catalyzed highly enantioselective [2+2] annulation of allenoates with trifluoromethyl ketones has been disclosed, allowing the synthesis of optically active 2-alkyleneoxetanes in moderate to good yields along with good to high enantioselectivities and high diastereoselectivities. Further transformations of the cycloadducts have been also disclosed to afford biologically interesting 6-trifluoromethyl-5,6-dihydropyran-2-ones and trifluoromethyl β-keto acids in good yields.

Keywords: allenoates; 5,6-dihydropyran-2-ones; enantioselective [2+2] annulation; β-isocupreidine; β-keto acids; oxetanes; trifluoromethyl ketones

Chiral oxetanes represent important motifs in a number of natural products and biologically active compounds.[1] However, in contrast to their homologous heterocycles, such as oxiranes,[2] tetrahydrofurans[3] and tetrahydropyrans,[4] the synthetic approaches to enantiomerically enriched oxetanes are few in number and generally require multistep processes.[1,5] Among the different synthetic routes, the formal [2+2] cycloaddition[5c,d,6] is certainly one of the most powerful methods for the construction of the strained four-membered ring.

Recently, an elegant synthesis of 2-alkyleneoxetanes involving a new DABCO-catalyzed regioselective [2+2] cycloaddition of trifluoromethyl ketones with allenoates was described by Ye[6a] and Miller.[6b] While the synthetic potential of this transformation is self-evident, its enantioselective version remains, to the best of our knowledge, unknown to date. In connection with our ongoing project that deals with the catalytic potential of the *Cinchona* alkaloid-derived amides,[7,8] we became interested in examining the reaction of allenoates with trifluoromethyl ketones in the presence of a chiral tertiary amine catalyst. Herein, we report the first example of the catalytic enantioselective [2+2] cycloaddition between allenoates and trifluoromethyl ketones to give enantioenriched 2-alkyleneoxetanes in good yields and good to high *ee* values.

We initiated our studies by examining the reaction of allenoate **1a** and trifluoromethylketone **2a** in the presence of various nitrogen-containing chiral organocatalysts (20 mol%) (Figure 1) in THF (Table 1). First, quinidine, quinine and cinchonine were used as the catalysts in this [2+2] cycloaddition reaction of **1a** with **2a** in THF at 0 °C for 2 days, but unfortunately, no product was observed and nearly all the starting materials were recovered (Table 1, entries 1–3). Using **LB1** as the catalyst afforded *E*-oxetane **3aa**[9a] in 25% yield along with 21% *ee* in THF at 0 °C for 3 days (Table 1, entry 4). Gratifyingly, it was found that β-isocupreidine (β-ICD) was the more effective catalyst in this reaction, giving **3aa** in 85% yield and 68% *ee* within 2 days (Table 1, entry 5). Catalyst **LB2** synthesized from β-ICD by protecting the OH group with *tert*-butyl(diphenyl)chlorosilane (TBDPSCl) could not catalyze this reaction under the standard conditions, suggesting that the C-6′-OH group of β-ICD is very critical for the reaction (Table 1, entry 6). Another *Cinchona* alkaloid-derived catalyst **LB3** was also examined in this reaction, affording **3aa** in 48% yield and 37% *ee* within 3 days (Table 1, entry 7). Next, a solvent screening using β-ICD (20 mol%) as the catalyst disclosed that solvents such as toluene, CH_2Cl_2, CH_3CN and Et_2O were not suitable media for this reaction, affording merely traces of product (Table 1, entries 8–11). Employing allenoates **1b** and **1c** with more sterically bulky substituents, **3ba** was obtained in higher yield (90%) but with lower enantiomeric excess (31% *ee*) for allenoate **1b** bearing a *tert*-butyl

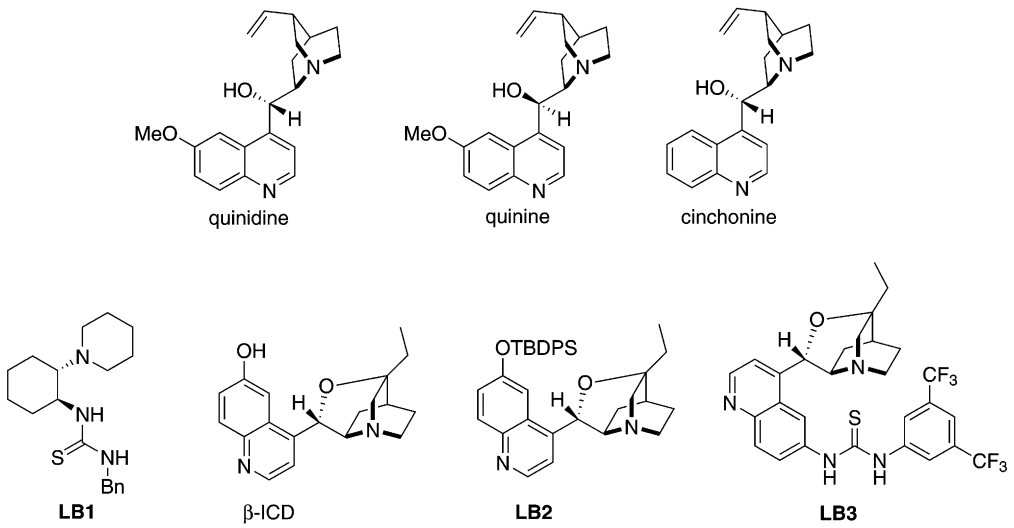
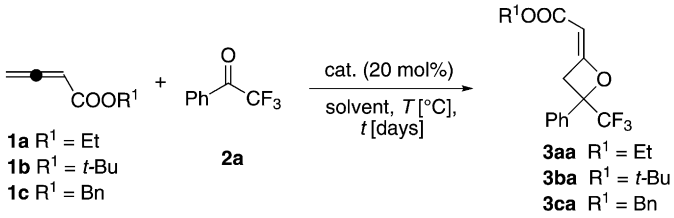


Figure 1. Screening of chiral nitrogen-containing catalysts for the asymmetric [2+2]cycloaddition.

Table 1. Optimization of the reaction conditions in the asymmetric [2+2]cycloaddition of **1** with **2a**.[a]



1a R^1 = Et
1b R^1 = *t*-Bu
1c R^1 = Bn

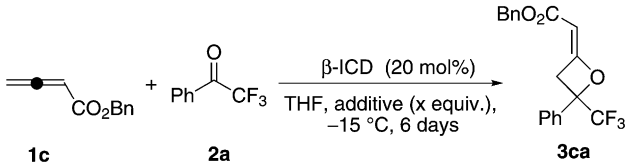
2a

3aa R^1 = Et
3ba R^1 = *t*-Bu
3ca R^1 = Bn

Entry	Catalyst	R^1	Temp. T [°C]	Solvent	Time t [days]	Yield [%][b] **3**	*ee* [%][c] **3**
1	quinidine	Et	0	THF	2	NP[f]	-
2	cinchonine	Et	0	THF	2	NP[f]	-
3	quinine	Et	0	THF	2	NP[f]	-
4	**LB1**	Et	0	THF	3	25	21
5	β-ICD	Et	0	THF	2	85	68
6	**LB2**	Et	0	THF	3	NP	-
7	**LB3**	Et	0	THF	3	48	37
8	β-ICD	Et	0	toluene	3	trace	-
9	β-ICD	Et	0	CH_2Cl_2	3	trace	-
10	β-ICD	Et	0	CH_3CN	3	trace	-
11	β-ICD	Et	0	Et_2O	3	trace	-
12	β-ICD	*t*-Bu	0	THF	2	90	31
13	β-ICD	Bn	0	THF	2	85	72
14	β-ICD	Bn	r.t.	THF	2	70	60
15	β-ICD	Bn	−10	THF	4	84	73
16	β-ICD	Bn	−20	THF	7	20	81
17	***β-ICD***	***Bn***	***−15***	***THF***	***6***	***80***	***80***
18[d]	β-ICD	Bn	−15	THF	8	61	78
19[e]	β-ICD	Bn	−15	THF	6	77	80

[a] The reaction was carried out on a 0.1-mmol scale, and the ratio of **1**/**2a** was 1.0/2.0.
[b] Isolated yield of *E*-**3** with $E:Z > 20:1$.
[c] Determined by chiral HPLC.
[d] The catalyst loading was 10 mol%.
[e] The catalyst loading was 40 mol%.
[f] NP = no product.

Table 2. Additives screening for asymmetric [2+2] cycloaddition of **1c** with **2a**.[a]



1c **2a** **3ca**

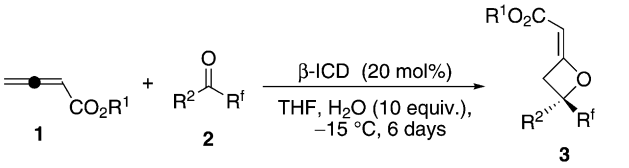
Entry	Additive	x	Yield [%][b]	*ee* [%][c]
1	CH_3OH	0.2	69	72
2	Ph_2CHOH	0.2	71	74
3	Ph_3COH	0.2	59	75
4	2-naphthalenemethanol	0.2	43	76
5	9-anthracenemethanol	0.2	70	76
6	H_2O	1	80	83
7	H_2O	5	78	90
8	***H_2O***	***10***	***74***	***96***
9	PhOH	0.2	48	77
10	benzoic acid	0.2	NP	-
11	aniline	0.2	65	80

[a] The reaction was carried out on a 0.1-mmol scale, and the ratio of **1c**/**2a** was 1.0/2.0.
[b] isolated yield of *E*-**3ca** with $E:Z > 20:1$.
[c] Determined by chiral HPLC.

ester group (Table 1, entry 12), while **3ca** was obtained with good yield (85% yield) and higher enantiomeric excess (72% *ee*) for allenoate **1c** bearing a benzyl ester group (Table 1, entry 13), suggesting that allenoate **1c** is the optimal substrate for this reaction. Further screening of temperatures and catalyst loadings (Table 1, entries 14–19) revealed that carrying out the reaction in the presence of 20 mol% β-ICD in THF at −15 °C for 6 days represented the optimal reaction conditions, affording the desired product *E*-oxetane **3ca**[9b] in 80% yield with 80% *ee* value (Table 1, entry 17).

The original optimal reaction conditions described above are obviously not adequate for the asymmetric version of this [2+2] annulation reaction, thus additive effects were further investigated in this reaction and the results are summarized in Table 2. Adding 0.2 equiv. methanol as the additive to the catalytic system resulted in lower yield and *ee* value of **3ca** (Table 2, entry 1). When employing other more sterically bulky alcohols such as diphenylmethanol, triphenylmethanol, 2-naphthalenemethanol and 9-anthracenemethanol as the additives, also no improvements in the yield and *ee* value were observed (Table 2, entries 2–5). However, when we turned to examine the additive effect of 1 equiv. water in this reaction, a tiny increase of the *ee* value (from 80% to 83%) with the same yield (80%) as that without the addition of H_2O was observed in this reaction (Table 2, entry 6 *vs.* Table 1, entry 17). Upon increasing the employed amount of water to 5 equiv. and 10 equiv., we were pleased to find that the *ee* value of **3ca** was increased from 83% to 96% also along with good yields (Table 2, entries 7 and 8). Moreover, other additives such as phenol, benzoic acid and aniline were also tested, giving the corresponding [2+2] annulation product **3ca** in 0–65% yields with 77–80% *ee* values (Table 2, entries 9–11). Therefore, the best reaction conditions have been identified as using 20 mol% of β-ICD as the catalyst, 10 equiv. H_2O as the additive and carrying out the reaction in THF at −15 °C for 6 days.

Table 3. Substrate scope of the asymmetric [2+2] cycloaddition of allenoates **1** with various trifluoromethyl ketones **2** catalyzed by β-ICD.[a]

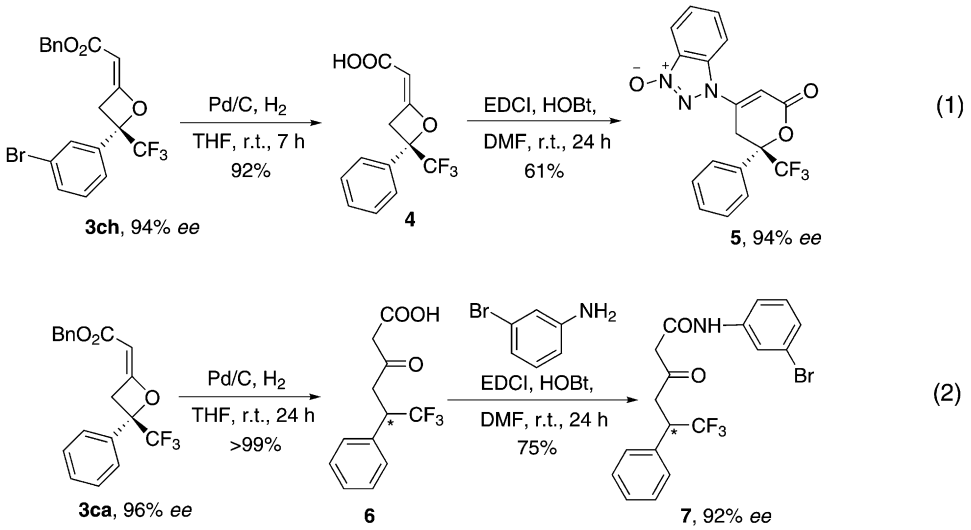


1 **2** **3**

Entry	R^1	R^2/R^f	Product, yield [%][b]	*ee* [%][c]
1	**1c**, Bn	**2a**, Ph/CF_3	**3ca**, 74	96
2	**1c**, Bn	**2b**, 4-MeC_6H_4/CF_3	**3cb**, 82	93
3	**1c**, Bn	**2c**, 3-MeC_6H_4/CF_3	**3cc**, 73	92
4	**1c**, Bn	**2d**, 3,5-$Me_2C_6H_3$/CF_3	**3cd**, 79	94
5	**1c**, Bn	**2e**, 4-MeOC_6H_4/CF_3	**3ce**, 87	93
6	**1c**, Bn	**2f**, 2-MeOC_6H_4/CF_3	**3cf**, 70	92
7	**1c**, Bn	**2g**, 4-BrC_6H_4/CF_3	**3cg**, 81	95
8	**1c**, Bn	**2h**, 3-BrC_6H_4/CF_3	**3ch**, 80	94
9	**1c**, Bn	**2i**, 4-ClC_6H_4/CF_3	**3ci**, 85	90
10	**1c**, Bn	**2j**, 4-FC_6H_4/CF_3	**3cj**, 76	92
11	**1c**, Bn	**2k**, 2-thienyl/CF_3	**3ck**, 68	90
12	**1c**, Bn	**2l**, pentyl/CF_3	**3cl**, 66	72
13[d]	**1a**, Et	**2a**, Ph/CF_3	**3aa**, 68	78
14[d]	**1b**, *t*-Bu	**2a**, Ph/CF_3	**3ba**, 73	85
15	**1c**, Bn	**2m**, Ph/CF_2CF_3	**3cm**, 75	85
16	**1c**, Bn	**2n**, Ph/CF_2Br	NP[e]	-
17	**1c**, Bn	**2o**, Ph/CFH_2	NP[e]	-

[a] The reaction was carried out on a 0.1-mmol scale, and the ratio of **1**/**2** was 1.0/2.0.
[b] Isolated yields *E*-**3** with $E:Z > 20:1$.
[c] Determined by chiral HPLC.
[d] The reactions were carried out at 0 °C for 7 days.
[e] NP = no product.

With these optimal reaction conditions in hand, we subsequently turned our attention to examine the substrate scope of this interesting asymmetric [2+2] annulation reaction with respect to a variety of trifluoromethyl ketones and allenoates. The results of these experiments are summarized in Table 3. As can be seen from Table 3, 2,2,2-trifluoroacetophenone **2a** and a variety of trifluoromethyl ketones **2b**–**2j** having electron-rich or electron-poor aromatic groups as R^2 or trifluoromethyl ketone **2k** bearing a heteroaromatic group such as 2-thienyl as R^2 could react with elec-

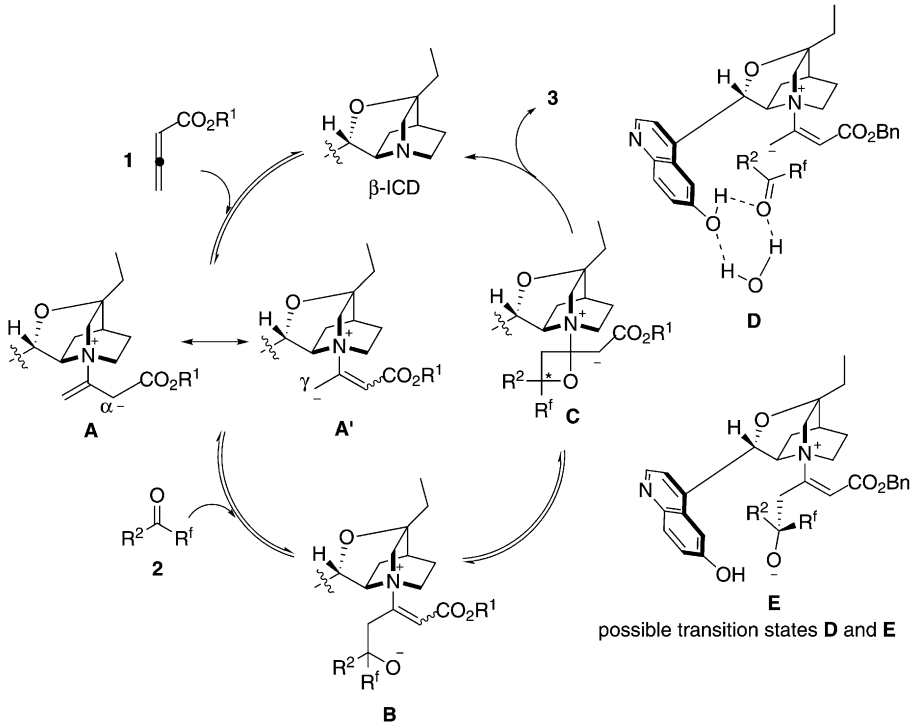


Scheme 1. Further transformations of the obtained [2+2] annulation products **3ch** and **3ca.**

tron-deficient allene **1c** smoothly to give the corresponding [2+2] cycloaddition products **3ca**–**3ck** in moderate to good yields along with 90–95% enantiomeric excesses (Table 3, entries 1–11). When R^2 is an alkyl group, such as pentyl, the corresponding [2+2] cycloaddition product **3cl** was also obtained in 66% yield and 72% *ee* value (Table 3, entry 12). Since [2+2] cycloaddition products **3aa** and **3ba** from the reaction of **2a** with ethyl buta-2,3-dienoate **1a** and *tert*-butyl buta-2,3-dienoate **1b** were obtained in low yields under the standard conditions in this reaction; increasing the temperature to 0 °C and prolonging the reaction time to 7 days are required for the formation of **3aa** and **3ba** in 68–73% yields and 78–85% *ee* values (Table 3, entries 13 and 14). In the case of pentafluoroethyl ketone **2m**, the desired product was obtained in similar yield, affording **3cm** in 75% yield and 85% *ee* (Table 3, entry 15). However, in the cases of difluoromethylated ketone **2n** and monofluoromethylated ketone **2o**, no [2+2] cycloaddition product was provided under the standard conditions (Table 3, entries 16 and 17).

To illustrate the synthetic utility of the thus obtained, optically active [2+2] cycloaddition product **3**, further transformations of **3ch** and **3ca** were performed. As shown in Scheme 1, upon hydrogenation of **3ch** with Pd/C in THF for 5 h, the corresponding product **4** was produced in 92% yield,[10] which could be further transformed to the 6-trifluoromethyl-5,6-dihydropyran-2-one **5** in 61% yield with the *ee* value being retained during the reaction with *N*-ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI) (3.0 equiv.) and 1-hydroxy *N*-hydroxybenzotriazole (HOBt) (4.0 equiv.) in *N*,*N*-dimethylformamide (DMF) [Scheme 1, Eq. (1)]. Since 5,6-dihydropyran-2-ones (α,β-unsaturated δ-lactones) are widely present in a number of natural and unnatural compounds which possess potent biological activities,[11,12] and in view of the wide application of fluorinated compounds in pharmaceuticals, agrochemistry and materials,[13] the 6-trifluoromethyl-5,6-dihydropyran-2-one **5** synthesized from 2-alkyleneoxetane **3ch** should be useful in organic synthesis. The absolute configuration of products **3** was unambiguously assigned as the *S*-configuration on the basis of the X-ray crystallographic analysis of the transformation product **5** (see Figure S1 in the Supporting Information for the details).[14] A plausible mechanism for the formation of product **5** from compound **4** is also outlined in the Supporting Information (see Scheme S1 in the Supporting Information for the details).[15,16] Treatment of **3ca** with Pd/C under H_2 in THF for 24 h gave the ring-opened β-keto acid **6** quantitatively, which could be further transformed to the desired amide **7** in 75% yield and 92% *ee* from the reaction with *meta*-bromoaniline (2.0 equiv.) in the presence of EDCI (3.0 equiv.) and HOBt (4.0 equiv.) in DMF, suggesting the hydrogenolysis of a benzylic bond with retention of optical activity in this novel case [Scheme 1, Eq. (2)].

Mechanistically, the reaction of trifluoromethyl ketones **2** with allenoates **1** in the presence of a chiral tertiary amine catalyst (β-ICD) can take place through the processes shown in Scheme 2.[6,17] The nucleophilic addition of β-ICD to allenoate **1** produces the enolate intermediate **A**, which is in resonance with the allylic carbanion **A′**. The γ-addition of **A′** to trifluoromethyl ketone gives the α,β-unsaturated ester **B**, which undergoes an intramolecular Michael addition to give the ring-closed zwitterion **C**. The elimination of catalyst from **C** affords the product and regenerates β-ICD. A possible transition state model **D** using β-ICD as the catalyst is also shown in Scheme 2. We hypothesized that the trifluoromethyl ketone



Scheme 2. A plausible catalytic cycle for the asymmetric [2+2] annulation.

would be activated by both C-6′-OH of β-ICD and H_2O through three hydrogen bonds, which could be stabilized as a six-membered ring. Then the zwitterion homoenolate may preferentially add to the trifluoromethyl ketone from the *Re* face in a pseudo-intramolecular manner, thus leading to intermediate **E**, which after cyclization and elimination events would provide the *S*-oxetane **3**.

In summary, we have developed the first asymmetric organocatalytic formal [2+2] cycloaddition of trifluoromethyl ketones and allenoates using β-isocupreidine (β-ICD) as a catalyst to afford *S*-configured 2-alkyleneoxetanes in moderate to good yields along with good to high diastereoselectivities and enantioselectivities. Furthermore, useful transformations of the corresponding 2-alkyleneoxetanes have been also demonstrated, which provide a straightforward approach to the optically active and biologically interesting trifluoromethyldihydropyranone and ring-opened trifluoromethyl β-keto acid.

Experimental Section

General Methods

^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz or 300 and 75 MHz, respectively. Low- and high-resolution mass spectra were recorded by the EI or ESI method. The used organic solvents were dried by standard methods when necessary. Optical rotations were determined at 589 nm (sodium D line) by using a Perkin–Elmer-341 MC digital polarimeter; $[\alpha]_D$ values are given in units of 10 $deg^{-1}cm^2g^{-1}$. Chiral HPLC was performed on a Shimadzu SPD-10 A *vp* series with chiral columns [Chiralpak AD-H, OD-H, OJ-H, AS-H and Phenomenex Lux 5μ Cellulose-2 columns 4.6× 250 mm (Daicel Chemical Ind., Ltd.)]. Commercially obtained reagents were used without further purification. All these reactions were monitored by TLC with silica gel-coated plates. Flash column chromatography was carried out by using silica gel at increased pressure.

General Procedure for β-ICD-Catalyzed [2+2] Annulation of Allenoates 1 with Trifluoromethyl Ketones 2

Allenoate **1** (0.1 mmol), trifluoromethyl ketone **2** (0.2 mmol), β-ICD (0.02 mmol), and THF (0.5 mL) were added into a Schlenk tube. The reaction mixture was stirred at −15 °C for 6 days, the solvent was removed under reduced pressure, and the residue was purified by flash column chromatography (PE/EA = 20/1 ~ 10/1).

General Procedure for the Synthesis of 4 and 5

Compound **3ch** (43 mg, 0.10 mmol) was stirred in anhydrous tetrahydrofuran (5.0 mL) in the presence of 10% palladium on carbon (11.0 mg) under an atmosphere of hydrogen for 5 h. After removal of the catalyst through Celite, the filtrate was concentrated under reduced pressure and the crude product was chromatographed on silica gel (elution with petroleum ether/EtOAc = 1:4) to give compound **4**.

Compound **4** (26 mg, 0.10 mmol) was added to a solution of N-ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI) (58 mg, 0.30 mmol) and 1-hydroxybenzotriazole (HOBt) (54 mg, 0.40 mmol) in *N*,*N*-dimethylformamide (DMF) (2.0 mL). The resulted mixture was stirred for 24 h at room temperature. Then, the solvent was removed from the flask under reduced pressure. The resulting residue was diluted with EtOAc, washed with saturated NaCl solution twice, and extracted by EtOAc. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was chromatographed on silica gel (elution with petroleum ether/EtOAc = 2:1) to give compound **5**.

Supporting Information

Experimental procedures, chiral HPLC traces, and spectroscopic data for all new compounds, X-ray crystal structures and CIF data for **5** are available in the Supporting Information.

Acknowledgements

We thank the Shanghai Municipal Committee of Science and Technology (11JC1402600), National Basic Research Program of China (973)-2010CB833302, the Fundamental Research Funds for the Central Universities and the National Natural Science Foundation of China for financial support (21072206, 20872162, 20672127, 20732008, 21121062 and 20702013).

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