Organic bases-promoted enantioselective electrophilic cyanation of β-keto esters by chiral phase-transfer catalysts

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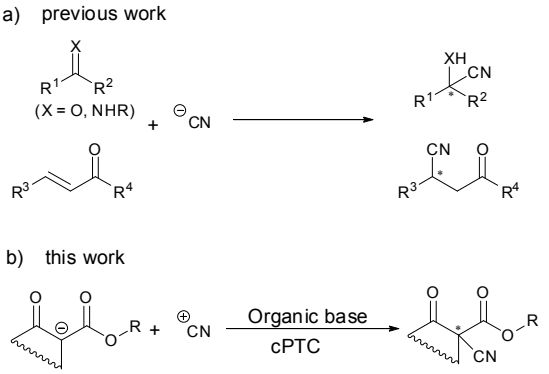
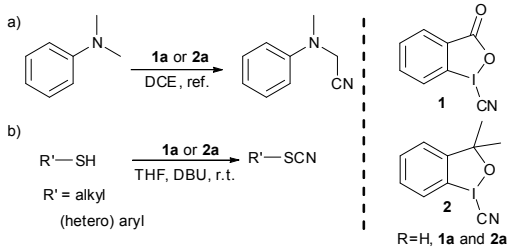
The highly enantioselective cyanation of β-keto esters using hypervalent iodine (III) as electrophilic cyanating reagents induced by cinchona alkaloid-based chiral quaternary ammonium salt was demonstrated. Organic bases, especially DMAP, in the chiral phase-transfer catalysis were used to obtain high ees.

Nitriles or cyano-containing compounds are one of the most fundamental motifs in natural products, agrochemicals and synthetic drugs due to their fascinating bioactivities.[1] Moreover, as an intriguing intermediate in organic synthesis, cyano-group is prone to be converted into carboxylic acid, amide, aldehyde, ketone, amine and tetrazole.[2] In this context, increasing attention has been focused on synthesizing nitriles by transition metal-catalyzed cyanation[3] of aryl halides with novel cyanating reagents[4], such as safe and combined cyanation sources[5], to furnish aryl nitriles. However, to the best of our knowledge, most preparations of chiral nitriles are realized by the extensively studied asymmetric 1,2-addition of imines/ketones[6] or 1,4-addition of α,β-unsaturated carbonyls[7] with nucleophilic cyanating reagents such as TMSCN and KCN (Scheme 1, eqn. (a)). The electrophilic cyanating ones are reactive enough and easy to handle while rarely employed in asymmetric reactions. Very recently, Chen[8] demonstrated the racemic α-cyanation of β-keto carbonyls and Waser[9] completed asymmetric ones in moderate ee. So herein we would like to report the highly enantioselective cyanation of β-keto esters catalyzed by chiral phase-transfer catalysts (cPTC) (Scheme 1, eqn. (b)).

To achieve umpolung of CN^-, *N*-[10], *O*-[11] and *S*-[12]centered cyanating reagents were developed from ClCN, which have been applied in many mild reactions. Meanwhile hypervalent iodine, especially the 1,2-benziodoxole or benziodoxlone motifs featured with bench stability, derivatived reagents such as –CN,[13] -N_3,[14] -CF_3,[15] -CF_2SO_2Ph,[16] alkynylation[17] and -SCF_3,[18] also could reverse polarity and improve their reactivity. To our surprise, **1** or **2** are scarcely studied except the cyanation of tertiary anilines reported by Zhdankin[13] (Scheme 2, eqn. (a)) and thios by Waser[19] (Scheme 2, eqn. (b)).



Scheme 1 Enantioselective cyanation processes



Scheme 2 Reactions involved 1,2-benziodoxole **1** and **2**

We envisioned that enantioselective cyanation of nucleophiles may be feasible under mild reaction conditions. Recently, cPTC catalyzed asymmetric thiotrifluorometylation and alkynylation of β-keto esters by Shen[18b] or Waser[17h] were accomplished in moderate to good enantioselectivity. However, more functionalizations deserve attempts considering that cPTC are readily prepared and modified[20]. In this communication, it was found by serendipity that organic bases was crucial for high ees in the chiral phase-transfer catalysis.

We began our preliminary studies with the racemic of β-keto ester **3a** with **1a** or **2a**, respectively. Compared with no reaction occurring when **2a** was employed, the cyanation of **3a** with **1a** went smoothly especially in dipolar aproton solvents, e.g. NMP, DMSO, up to 92% yield. Next, we turned to the investigation of asymmetric

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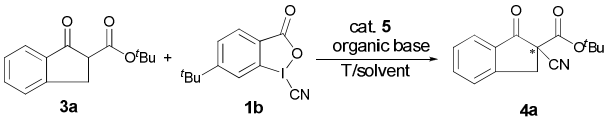
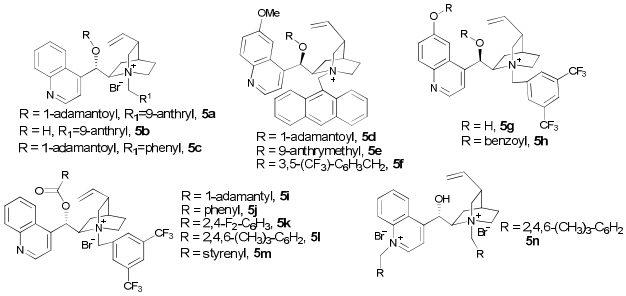
one. With **5a** (10 mol %) as the phase-transfer catalyst, Cs_2CO_3 (4 equiv.) as the base and **1a** being cyanating reagent, the reaction was carried out at low temperature of -40 °C, providing **4a** of 21% ee after consumption of substrate **3a** (Table S1, entry 1). To further improve the enantioselectivity, the temperature was lowered to -78 °C, only to furnish the product in a lower ee of 15% (Table S1, entry 2), which was presumably due to the poor solubility of **1a** in THF. Then **1b** was employed, and resulted with a higher ee of 35% (Table S1, entry 3). However, other inorganic bases such as KOH and K_2HPO_4 were not suitable for this reaction with inferior enantioselectivity or chemical reactivity (Table S1, entries 4-5). To our disappointment, cyanation transfer reagents with other substitutions failed to increase the ees (Table S1, entries 9-14).

Table 1. Further optimization of asymmetric cyanation of β-keto esters with organic base [a]



3a 1b 4a

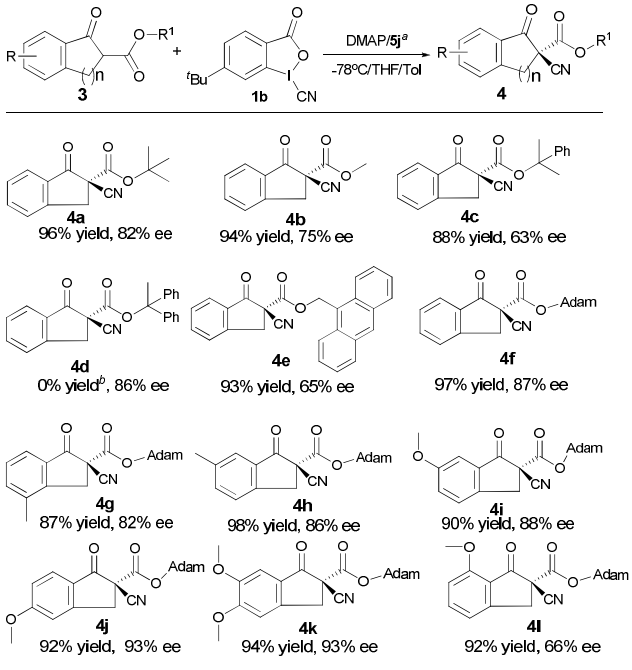
Entry	Cat.5	Org. base	Conv.[b] (%)	Ee[c] (%)
1	**5a**	DBU[d]	100	0
2	**5a**	N^iPr_3	100	63
3	**5a**	NEt_3	100	62
4	**5a**	TMEDA[d]	100	65
5	**5a**	DABCO[d]	100	67
6	**5a**	diisopropylamine	100	46
7	**5a**	*N*,*N*-dimethylaniline	0	-
8[e]	**5a**	Py	100	64
9	**5a**	DMAP[d]	100	75
10	**5a**	*N*,*N*-dimethylpyridin-2-amine	0	-
11	**5b**	DMAP	100	0
12	**5c**	DMAP	100	45
13	**5d**	DMAP	100	-57
14	**5e**	DMAP	100	-3
15	**5f**	DMAP	100	-5
16	**5g**	DMAP	100	-5
17	**5h**	DMAP	100	-11
18	**5i**	DMAP	100	74
19	**5j**	DMAP	100	75
20	**5k**	DMAP	100	68
21	**5l**	DMAP	100	67
22	**5m**	DMAP	100	65
23[f]	**5j**	DMAP	100(96)[g]	82
24[f]	**5n**	DMAP	100	-35
25[f]	**-**	DMAP	100	24

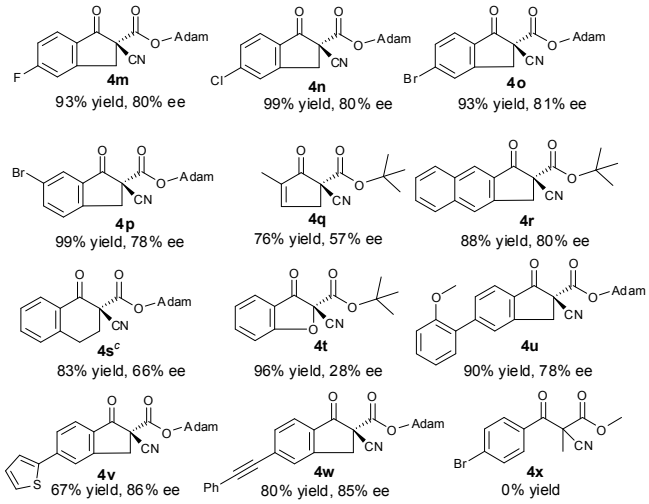


[a]Unless otherwise noted, the reaction was performed with **3a** (0.05 mmol), **1b** (0.055 mmol) and organic base (0.055 mmol) in the presence of catalyst (10 mol%) in THF/Tol (0.1 mL : 0.7 mL) for 1 h. [b]The conv. was determined by crude NMR. [c]The enantiomeric excess was determined by HPLC analysis of the product **3a** using a chiral column (DAICEL Chiralcel AS-H) with hexane/2-propanol (85:15) as the eluent. [d]DBU = 1,8-Diazabicyclo[5.4.0]undec-7-ene, TMEDA = Tetramethylethylenediamine, DABCO = 1,4-Diazabicyclo[2.2.2]octane, DMAP = 4-dimethylaminopyridine. [e] 8h. [f]THF/Tol (0.3 mL : 0.6 mL). [g]Isolated yield.

Generally, chiral phase-transfer catalysts induced asymmetric reactions were conducted mostly with inorganic bases as proton bounders,[21] while we were glad to find that organic ones were better alternatives (Table 1). As the reaction with DBU yielded the racemic product, TEA or DIPEA of less bacisity were utilized, furnishing more enantioriched products of 63% and 62% ee (Table 1, entries 1-3). The diamines helped improve the ee values slightly, but secondary amines did not (Table 1, entries 4-6). The cyanation failed with *N*,*N*-dimethylaniline as base, while became slack using pyridine (Table 1, entries 7-8). To our delight, DMAP was chosen as the best base in this system, offering **4a** of 75% ee, which may be attributed to the strong nucleophilicity when compared with that of *N*,*N*-dimethylpyridin-2-amine (Table 1, entries 9-10).

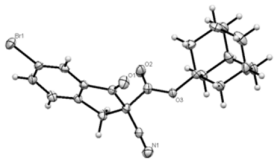
Then, we further investigated the phase-transfer catalysts. It was found that a bulky group at the quinuclidine nitrogen atom was necessary and the secondary alcohol of C-9 must be protected to be the corresponding ester (Table 1, entries 11-15). In sharp contrast, the cinchonine-derived catalysts were better than that of quinine with respect to enantioselectivity (Table 1, entries 13, 16-17). When 3,5-ditrifluoromethylbenzyl was installed onto the quinuclidine nitrogen, the ee was kept (Table 1, entries 18-22). After careful screening of solvents, we finally got the product with 82% ee and 96% yield (Table 1, entry 23). The doubly quaternized catalyst[22] provided an opposite result of 35% *ee* (Table 1, entry 24). As control experiments, stoichiometric tertiary aimine was needed to complete the reaction, only to result inferior enantioselectivity when cinchonine used (Table 1, entry 25). Very recently, Waser unveiled that Lewis base DBU may activate **1a** when synthesizing thiocyanates.[19] In this system, organic base presumably also interact with cyanating reagents meanwhile enhancing the nucleophilicity of **3a** by deprotonation, furnishing products of different ees varying with more than their pK_a.





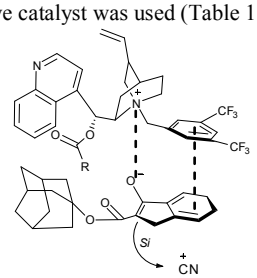
Scheme 3 [a]reaction conditions: **3** (0.2 mmol), **1b** (0.022 mmol) and organic base (0.022 mmol) in the presence of 10 mol% of catalyst in THF/Tol (0.6 mL : 0.3 mL) at -78 ^{o}C for 1 h-8 h; the yield was isolated yield; the enantiomeric excess was determined by HPLC analysis of the product using a chiral column; Adam means 1-admantanyl. [b]Conv. is 100%, but it couldn't be purified due to its instability. [c]6 day.

With the optimized conditions in hand, the effects of R^1 groups of β-keto esters on ee were investigated firstly (Scheme 3, **4a-4f**). Though the reaction of keto ester **3a** with *tert*-butyl gave a higher enantionselectivity than that of **3b**, **3c** with more bulky group did not promote ee, all being in excellent yields. Then other alcohols-derived esters by transesterification were checked, and the one of 1-adamantene alcohol gave a higher ee value of 87% in 97% yield (Scheme 3, **4f**). Compared with **3h**, **3g** substituted with 4-methyl group on phenyl of it resulted in lower enantioselectivity and chemical reactivity in 82% *ee* and 87% yield respectively, which was probably due to the steric hindrance of substitutions (Scheme 3, **4g-4h, 4l**). In general, electron-donating groups have a positive effect on enantioselectivity of **4** than electron-withdrawing ones (Scheme 3, **4i-4p**), obtaining up to 93% *ee*. When less rigid motif **3q** was employed, the *ee* of cyanating product decreased dramatically to 57%, while more rigid one **3r** gave almost result. Moreover, other motifs furnished poor yield or enantioselctivity, especially the acyclic substrate **3x** took no reactions (Scheme 3, **4s-4t, 4x**). Heterocycle, alkyne and other functional groups were all tolerated well (Scheme 3, **4u-4w**). The absolute configuration (*S*) of the stereogenic carboncenter in the cyanating products **4** was determined by the X-ray structure of **4p** over 99% *ee* after recrystallizaiton (for more see †ESI).



Scheme 3 The X-ray structure of product **4p**.

Though the precise mechanism was unclear now, we may get some clues from the experiments and literatures. The C9-hydroxy group was protected by acyl chloride to ensure the high enantioselectivity, which may help to break the potential mismatched interaction between hydroxyl and carbonyl group of substrate **3**. However, the bulky protecting groups, such as 1-adamantoyl group were not crucial, which was different from that by Jørgensen.[23] We deduced that the enolate of **3** residue in the groove between quinoline and the 3,5-ditrifluoromethylbenzene systems[24] which presumably interacted with the phenyl group of indanone. This may be accounted by the fact that the electron-donating groups other than electron-withdrawing ones could enhance the enantioselectivity. With the *Re* face of the enolate blocked by the PTC, the electrophilic cyanating agent would attack from the *Si* face. So the opposite enantiomer was easy to obtain when quasienantioselective catalyst was used (Table 1, entry 13).



Scheme 4 Possible model of the reaction transition-state.

To conclude, we reported the enantioselective electrophilic cyanation of β-keto esters with hypervalent iodine (III) as the cyanating reagents induced by the cinchonine-based chiral phase-transfer catalysts. The asymmetric reaction is operated very conveniently and insensitive to air/water with organic base, furnishing better reactivity and enantioselectivity than that with inorganic base. Further study about the asymmetric cyanation of other nucleophiles is ongoing.

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