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Highly enantioselective α -cyanation with 4-acetylphenyl cyanate

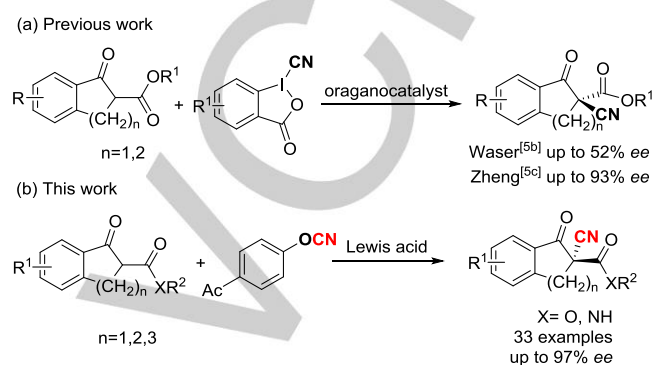
Jia-Shen Qiu,^{†[a]} Yao-Feng Wang,^{†[a]} Gui-Rong Qi,^[a] Pran Gopal Karmaker,^[a] Hong-Quan Yin,^[a] and Fu-Xue Chen^{*[a]}

Dedicated to the 80th birthday occasion of Professor Yao-Zhong Jiang.

Abstract: A highly effective asymmetric version of α -cyanation of β -keto esters and amides has been developed with Lewis acid catalyst. Thus, using 10 mol% of the tridentate bisoxazoline-zinc(II) complex as the catalyst, a series of chiral nitriles containing a quaternary carbon center have been achieved in excellent enantioselectivities up to 97% ee and up to 95% yield in the presence of 4 Å MS at room temperature. For the first time, the mild active 4-acetylphenyl cyanate was used instead of cyano-hyperiodate as the cationic cyano source in the catalytic asymmetric α -cyanation reaction.

Asymmetric incorporation of cyano group into organic molecules has ever been a hot topic in asymmetric synthesis community as the thus obtained nitriles have attractive bioactivities,^[1] and diverse functional transformations in organic synthesis as well.^[2] There are methodologies such as nucleophilic substitution and addition with anionic cyanide affording aliphatic nitriles^[4] and cyanohydrins^[3], respectively. Recently, we disclosed a new protocol to synthesize α -nitriles from active hydrogen substitution with cyano-hyperiodate as the electrophile.^[5a] Following closely, Waser reported the first asymmetric version yet with moderate enantioselectivity using cinchona alkaloid organocatalysts.^[5b] In the same year, Zheng and coworkers documented their solution with high enantioselectivity up to 93% ee using cinchonidine-based PTC after careful screening the structure of cation cyano reagents and optimization of reaction conditions (Scheme 1a).^[5c] Up to date, cyano-hyperiodates^[6,7] have exhibited good capacity but usually suffered a bad solubility in the solvent as well as the moderate enantioselectivity for most substrates. Herein, we report our methodology of the enantioselective α -cyanation for wide β -keto esters and amides featuring in bearing five- or six-membered rings (Scheme 1b).

In the racemic reaction, we knew it could be catalyzed by Lewis acid.^[5a] Together with the knowledge of the good solubility and mild reactivity of cyanate,^[8,9] we preferred phenylcyanate as the cyano source to develop the asymmetric version with transition metal complex as the catalyst. Initially, a model reaction of β -keto ester **1d**^[10] and 4-acetyl phenylcyanate (**C2**) was carried out in the presence of bisoxazoline-based zinc complex. As shown in Table 1, bidentate bisoxazoline ligand **L1**



Scheme 1. Asymmetric α -cyanation with (a) hyperiodate and (b) cyanate.

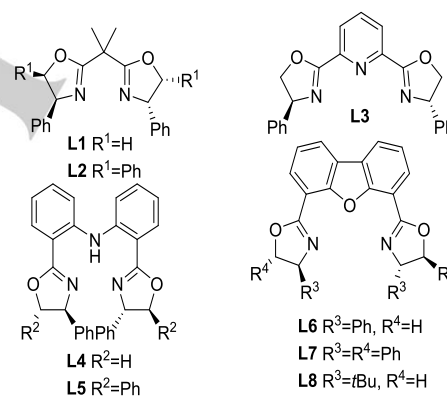


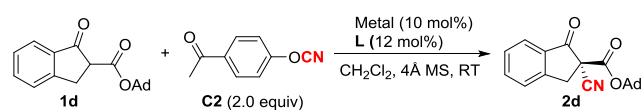
Figure 1. Bisoxazoline ligands evaluated in this study.

and **L2** had good catalytic activity but low enantioselectivity (Table 1, entries 1 and 2). While rigid tridentate bisoxazoline (PyBox, **L3**) gave racemic mixture, flexible tridentate **L4** yielded 21% ee (entry 4 vs 3). Moreover, a second chiral center in the ligand **L5** greatly increased the enantioselectivity to 65% ee (entry 5). Delightedly, 81% ee was obtained using tridentate dibenzofuran bisoxazoline (DBFOX/Ph, **L6**) as the ligand (entry 6).^[11] However, another chiral center in **L7** decreased both catalytic activity and enantioselectivity (entry 7). Instead of the phenyl ring with *t*Bu in the bisoxazoline structure **L8** resulted in completely lost of enantioselectivity (entry 8), indicating a possible strong π - π interaction between the catalyst and reactants.^[12] While other late transition metals exhibited inferior results (entries 9 and 10), Zn(BF₄)₂·6H₂O achieved the highest catalytic capacities in 91% yield and 89% ee (entry 11). In addition, neither changing the catalyst loading nor the ratio between metal and ligand afforded any further improvements in enantioselectivity (entries 12 and 13).

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Table 1. Optimization of the catalyst.^[a]

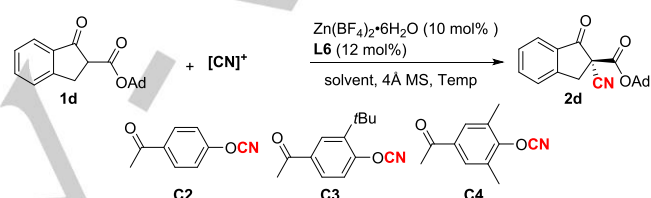
Entry ^[a]	L	Metal	Yield [%] ^[b]	ee [%] ^[c]
1	L1	Zn(OTf) ₂	95	11
2	L2	Zn(OTf) ₂	72	15
3	L3	Zn(OTf) ₂	83	0
4	L4	Zn(OTf) ₂	83	21
5	L5	Zn(OTf) ₂	78	-65
6	L6	Zn(OTf) ₂	83	81
7	L7	Zn(OTf) ₂	60	71
8	L8	Zn(OTf) ₂	95	0
9	L6	Cu(OTf) ₂	–	5
10	L6	Ni(ClO ₄) ₂ ·6H ₂ O	10	-4
11	L6	Zn(BF ₄) ₂ ·6H ₂ O	91	89
12 ^[d]	L6	Zn(BF ₄) ₂ ·6H ₂ O	78	67
13 ^[e]	L6	Zn(BF ₄) ₂ ·6H ₂ O	78	88

[a] Reaction conditions: **1d** (0.05 mmol), **C2** (0.1 mmol, 2.0 equiv), Metal (0.005 mmol, 10 mol%) and **L** (0.006 mmol, 12 mol%), CH₂Cl₂ (1.0 mL), 4 Å MS (25 mg), RT, 24 h, argon. [b] Isolated yield. [c] Determined by HPLC analysis on Chiralpak AS-H. [d] Zn(BF₄)₂·6H₂O (0.0025 mmol, 5 mol%), **L6** (0.003 mmol, 6 mol%). [e] **L6** (0.011 mmol, 22 mol%). Ad=adamantyl, OTf=triflate.

To further optimize the catalyst performance in terms of yield and enantioselectivity, solvent and structure of cyanates were investigated with results listed in Table 2. Polar solvent like THF destroyed the catalytic activity thoroughly (entry 1). Among chlorinated alkane solvents, CH₂Cl₂ gave both higher yield and enantioselectivity than others (entry 5 vs entries 3-4). Other three cyanates **C1**, **C3**, and **C4** were used instead but produced inferior results (entries 6-8). However, higher or lower temperature other than room temperature (RT, entries 9-10) as well as higher concentration corroded the catalyst efficiency significantly (entry 11). Variation of the preparation of the catalyst decreased the yield obviously (entry 12). Without 4 Å molecular sieves (MS) the reaction rate was nearly doubled but with bad enantioselectivity (entry 13).^[13]

With the optimal reaction conditions in hand, the substrate structure effect was investigated (Table 3). First, steric ester (**2d** vs **2a-c**) is necessary for excellent enantioselectivity, which is in agreement with Zheng and Waser.^[5b,5c] This phenomenon is

also true in the six-membered ring substrate (**2p** vs **2m-2o**). In the case of **2d**, the catalyst efficiency was further optimized to 91% yield and 92% ee using 0.2 mL toluene to prepare the catalyst and adding the rest of 0.8 mL dichloromethane to retain the same concentration before addition of the cyanate reagent. For 3',4',5'-substituted substrates, electron-withdrawing group (**2e**) gave higher enantioselectivity than electron-donating ones (**2f-2i**). Noteworthy, substrates bearing six-membered ring were readily converted into corresponding nitriles with excellent enantioselectivity and yield (**2p-2t**), which were not suitable in the organocatalysis.^[5b,5c] The absolute configuration (*R*-) of both five- and six-membered ring was established by the single crystal X-ray analysis of **2t** and **2g**.^[14] In addition, the other enantiomer (*S*-**2p**) was prepared on gram-scale in excellent enantioselectivity (-94% ee) and 93% yield using reduced catalyst loading of 2 mol% with (*R,R*)-**L6** (Scheme 2).

Table 2. Optimization of reaction conditions.^[a]

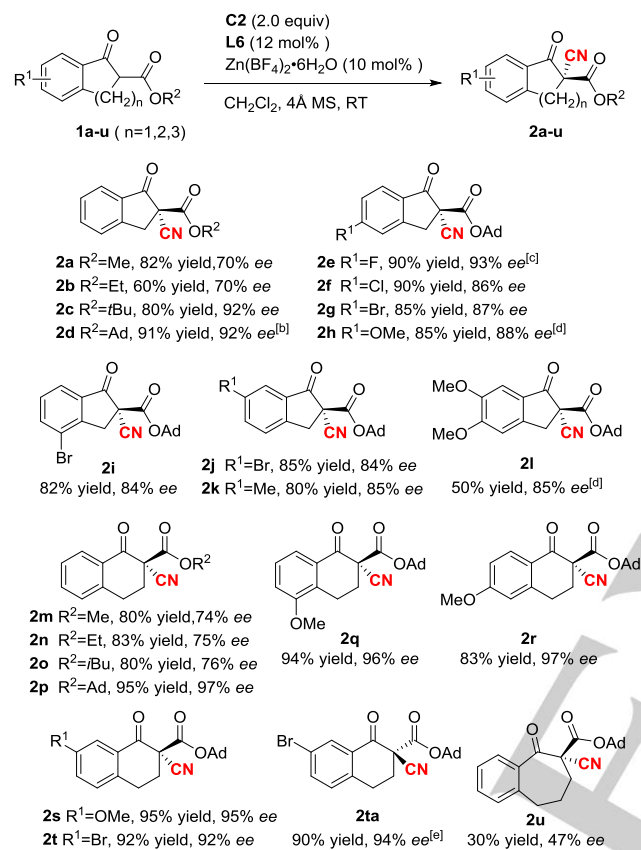
Entry	[CN] ⁺	Solvent	Temp [°C]	Yield [%] ^[b]	ee [%] ^[c]
1	C2	THF	RT	–	0
2	C2	toluene	RT	83	86
3	C2	DCE	RT	53	83
4	C2	CHCl ₃	RT	67	78
5	C2	CH ₂ Cl ₂	RT	91	89
6	C1	CH ₂ Cl ₂	RT	10	32
7	C3	CH ₂ Cl ₂	RT	83	83
8	C4	CH ₂ Cl ₂	RT	40	80
9	C2	CH ₂ Cl ₂	35	–	27
10	C2	CH ₂ Cl ₂	0	61	60
11 ^[d]	C2	CH ₂ Cl ₂	RT	83	65
12 ^[e]	C2	CH ₂ Cl ₂	RT	75	87
13 ^[f]	C2	CH ₂ Cl ₂	RT	78	43

[a] Reaction conditions: **1d** (0.05 mmol), cyanates (0.1 mmol, 2.0 equiv), Zn(BF₄)₂·6H₂O (0.005 mmol, 10 mol%) and **L6** (0.006 mmol, 12 mol%), solvent (1.0 mL), 4 Å MS (25 mg), 24 h, argon. [b] Isolated yield. [c] Determined by HPLC analysis on Chiralpak AS-H. [d] CH₂Cl₂ (0.5 mL). [e] Prepared the catalyst at 35 °C. [f] In the absence of 4 Å MS. Ad=adamantyl, OTf=triflate, DCE=1,2-dichloroethane.

This protocol has a wide scope of substrates with cyclic β-keto amides as well. Aromatic five- and six-membered amides (**3a-k**) with electron-withdrawing and electron-donating group

were well tolerated, providing products **4a** to **4k** in high enantioselectivities and good yields (Table 4), showing similar substituent effects with the esters.

Table 3. Structure effect of β -keto esters in the asymmetric α -cyanation.^[a]



[a] Reaction conditions: **1a-u** (0.05 mmol), **C2** (0.1 mmol, 2.0 equiv), Zn(BF₄)₂·6H₂O (0.005 mmol, 10 mol%), **L6** (0.006 mmol, 12 mol%), CH₂Cl₂ (1.0 mL), 4Å MS (25 mg), RT, 24 h, argon. [b] Using toluene (0.2 mL) to prepare the catalyst. [c] Using toluene (0.5 mL) to prepare the catalyst. [d] Reaction time 48 h. [e] (*R,R*)-**L6** was used instead. Ad=adamantyl



Scheme 2. Gram-scale reaction.

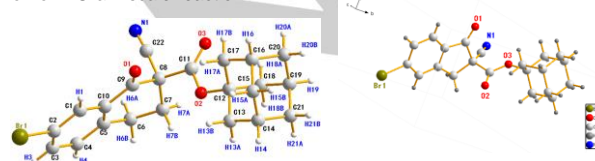
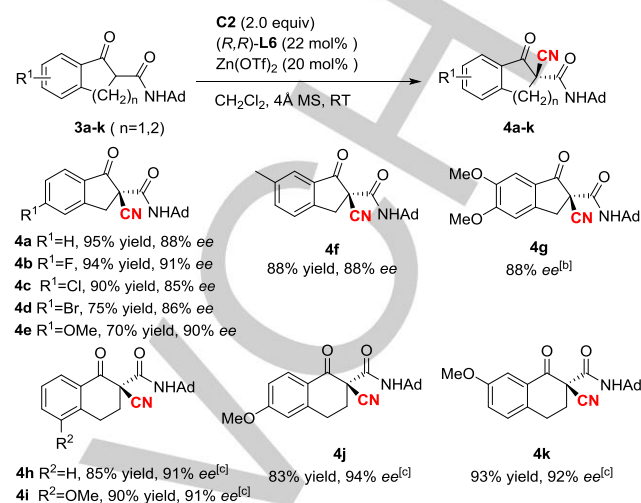
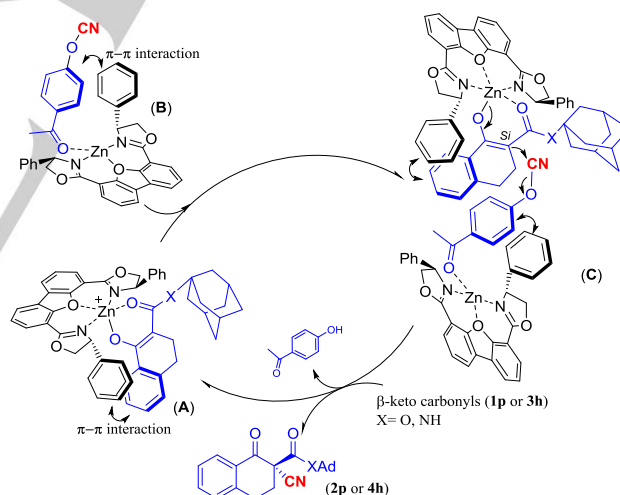


Figure 2. The X-ray structure of product **2t** (left) and **2g** (right).

Table 4. Asymmetric α -cyanation of β -keto amides.^[a]



[a] Reaction conditions: **3a-k** (0.05 mmol), **C2** (0.1 mmol, 2.0 equiv), Zn(OTf)₂ (0.001 mmol, 20 mol%) and **L6** (0.0011 mmol, 22 mol%), CH₂Cl₂ (1.0 mL), 4Å MS (12.5 mg), RT, 24 h, argon. Yield is isolated yield and ee value was determined by HPLC analysis on Chiralpak AD-H.^[15] The absolute configuration of (*S*)-**4** was determined by analogue comparison with esters. [b] Decompose on silica gel column. [c] Catalyst loading (10 mol%).



Scheme 3. Proposed mechanism for the formation of **2p** or **4h**.

In an effort to get insight into the mechanism, controlled experiments were carried out, and a significant positive non-linear effect (NLE) was observed.^[15] Together with the experimental observations (Table 1, entry 6 vs 8) and *in situ* ¹³C NMR studies at 3 °C, which showed the carbon signal of carbonyl group (1.66 ppm) shifted downfield greatly than the carbon of OCN moiety (0.85 ppm) in the case of **C2** as the cyanate reagent while carbon of OCN shifted by 0.45 ppm using **C1** as the cyanate source,^[15] a plausible mechanism was proposed in Scheme 3. Both cyanate reagent and carbonyl

substrate were activated by the zinc-complex,^[16] one in the pattern of Lewis acid catalysis (**B**) and the other in the form of zinc enolate (**A**), respectively. In the stereoselectivity-determining step, the LUMO-lowered cyano cation approaching the enolate plane from *Si* face got the transition state (**C**) arranged very effectively as a result of π - π interactions between substrate and cyanate and the ligand.

In summary, a highly enantioselective α -cyanation of cyclic β -keto carbonyls has been developed using readily available 4-acetylphenyl cyanate as the cationic cyano source for the first time by Lewis acid catalysis. Both five- and six-membered esters and amides were converted into the corresponding α -nitriles in excellent yields and up to 97% ee under mild conditions. This α -cyanation protocol enables the convenient preparation of nitriles with quaternary carboncenter.

Acknowledgements

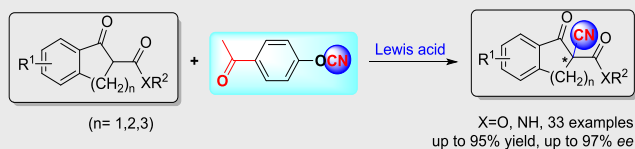
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Keywords: asymmetric catalysis • cyanation • enantioselectivity • nitrile • Lewis acid

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Layout 2:

COMMUNICATION



Jia-Shen Qiu,[†] Yao-Feng Wang,[†] Gui-Rong Qi, Pran Gopal Karmaker, Hong-Quan Yin, and Fu-Xue Chen*

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Highly enantioselective α -cyanation
with 4-acetylphenyl cyanate

A highly enantioselective α -cyanation of cyclic β -keto esters and amides has been developed with 4-acetylphenyl cyanate as the cationic cyano source in excellent yields and up to 97% ee.