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Asymmetric Catalysis

# Highly Enantioselective α-Cyanation with 4-Acetylphenyl Cyanate

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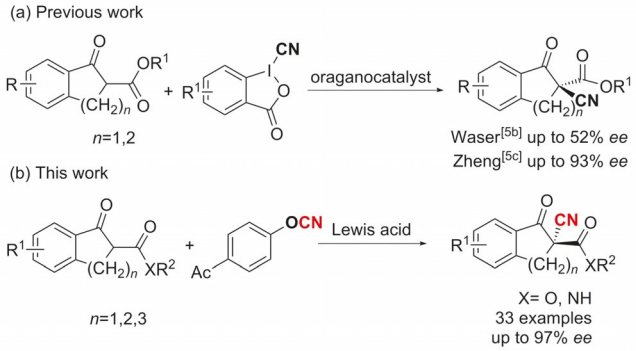
*Dedicated to Professor Yao-Zhong Jiang on the occasion of his 80th birthday*

**Abstract:** A highly effective asymmetric version of α-cyanation of β-keto esters and amides was developed with a Lewis-acid catalyst. Thus, by using 10 mol% of a tridentate bisoxazoline–zinc(II) complex as the catalyst, a series of chiral nitriles containing a quaternary carbon center were obtained in excellent enantioselectivities (up to 97% enantiomeric excess) and up to 95% yield in the presence of 4 Å molar sieve at room temperature. For the first time, mild and active 4-acetylphenyl cyanate was used instead of cyano-hyperiodinate as the cationic cyano source for catalytic asymmetric α-cyanation.

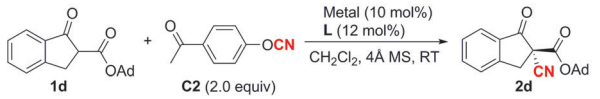



**Scheme 1.** Asymmetric α-cyanation with: a) hyperiodinate, and b) cyanate.

Asymmetric incorporation of cyano groups into organic molecules has always been a hot topic in the asymmetric synthesis community because the resulting nitriles show attractive bioactivity[1] and are useful for diverse functional transformations in organic synthesis as well.[2] There are methodologies for their synthesis, such as nucleophilic substitution or addition with anionic cyanides, affording cyanohydrins[3] and aliphatic nitriles,[4] respectively. Recently, we disclosed a new protocol to synthesize α-nitriles from active hydrogen substitution with cyano-hyperiodinate as the electrophile.[5a] Following closely, Waser and co-workers reported the first asymmetric version with moderate enantioselectivity with cinchona alkaloid organocatalysts.[5b] In the same year, Zheng and co-workers documented their study with high enantioselectivities of up to 93% enantiomeric excess (*ee*) by using a cinchonidine-based phase-transfer catalyst (PTC) after carefully screening the structure of cation cyano reagents and optimizing the reaction conditions (Scheme 1 a).[5c] Cyano-hyperiodinates[6,7] exhibited good capacity but usually suffer from low solubility in the solvent and afford only moderate enantioselectivities for most substrates. Herein, we report our methodology for the enantioselective α-cyanation for β-keto esters and amides bearing five- or six-membered rings (Scheme 1 b).

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

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




| Entry | 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** | $Ni(ClO_4)_2{\cdot}6H_2O$ | 10 | −4 |
| 11 | **L6** | $Zn(BF_4)_2{\cdot}6H_2O$ | 91 | 89 |
| 12[d] | **L6** | $Zn(BF_4)_2{\cdot}6H_2O$ | 78 | 67 |
| 13[e] | **L6** | $Zn(BF_4)_2{\cdot}6H_2O$ | 78 | 88 |

[a] Reaction conditions: **1 d** (0.05 mmol), **C2** (0.1 mmol, 2.0 equiv), metal (0.005 mmol, 10 mol%), and **L** (0.006 mmol, 12 mol%), $CH_2Cl_2$ (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] $Zn(BF_4)_2{\cdot}6H_2O$ (0.0025 mmol, 5 mol%), **L6** (0.003 mmol, 6 mol%); [e] **L6** (0.011 mmol, 22 mol%); Ad = adamantyl, OTf = triflate.

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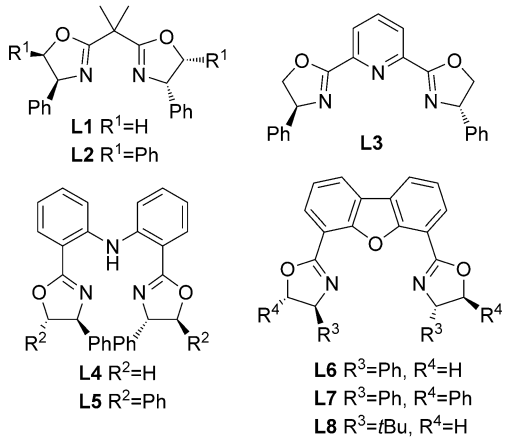


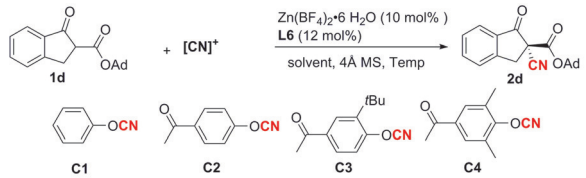

**Figure 1.** Bisoxazoline ligands evaluated in this study.

line ligands **L1** and **L2** (Figure 1) showed good catalytic activity but low enantioselectivity (Table 1, entries 1 and 2). Although rigid tridentate bisoxazoline (PyBox, **L3**) afforded a racemic mixture, flexible tridentate **L4** afforded 21% *ee* (entry 4 vs. 3). Moreover, a second chiral center in the ligand **L5** greatly increased the enantioselectivity to 65% *ee* (entry 5). 81% *ee* was obtained by using tridentate dibenzofuran bisoxazoline (DBFOX/Ph, **L6**) as the ligand (entry 6).[11] However, adding another chiral center in **L7** decreased both catalytic activity and enantioselectivity (entry 7). Containing *t*Bu instead of a phenyl ring in the bisoxazoline structure, **L8** resulted in complete loss of enantioselectivity (entry 8), indicating a possible strong π–π interaction between catalyst and reactants.[12] Although other late transition metals exhibited inferior results (entries 9 and 10), $Zn(BF_4)_2{\cdot}6H_2O$ achieved the highest catalytic performance with 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).

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 solvents such as THF severely inhibited the catalytic activity (entry 1). Among chlorinated alkane solvents, $CH_2Cl_2$ afforded both higher yield and enantioselectivity than others (entry 5 vs. entries 3 and 4). Three other cyanates (**C1**, **C3**, and **C4**) were used but produced inferior results (entries 6–8). However, temperatures higher or lower than room temperature (entries 9 and 10) as well as higher concentration (entry 11) decreased the catalyst efficiency significantly. Variation of the preparation of the catalyst decreased the yield severely (entry 12). Without 4 Å molecular sieves (MS), the reaction rate was nearly doubled, but with inferior enantioselectivity (entry 13).[13]

With the optimal reaction conditions in hand, the substrate-structure effect was investigated (Table 3). First, a steric ester (**2d** vs. **2a**–**2c**) is necessary for excellent enantioselectivity, which is in agreement with studies by Zheng[5b] and co-workers and Waser[5c] and co-workers. This phenomenon is also true for six-membered ring substrates (**2p** vs. **2m**–**2o**). In the case

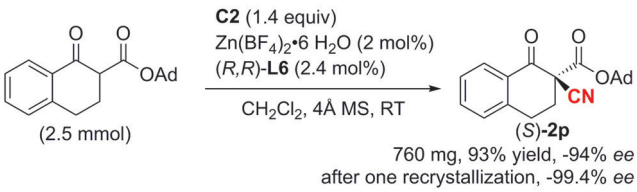
**Table 2.** Optimization of reaction conditions.[a]




| Entry | [CN]+ | Solvent | T [°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** | $CH_2Cl_2$ | RT | 91 | 89 |
| 6 | **C1** | $CH_2Cl_2$ | RT | 10 | 32 |
| 7 | **C3** | $CH_2Cl_2$ | RT | 83 | 83 |
| 8 | **C4** | $CH_2Cl_2$ | RT | 40 | 80 |
| 9 | **C2** | $CH_2Cl_2$ | 35 | – | 27 |
| 10 | **C2** | $CH_2Cl_2$ | 0 | 61 | 60 |
| 11[d] | **C2** | $CH_2Cl_2$ | RT | 83 | 65 |
| 12[e] | **C2** | $CH_2Cl_2$ | RT | 75 | 87 |
| 13[f] | **C2** | $CH_2Cl_2$ | RT | 78 | 43 |

[a] Reaction conditions: **1d** (0.05 mmol), cyanates (0.1 mmol, 2.0 equiv), $Zn(BF_4)_2{\cdot}6H_2O$ (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] $CH_2Cl_2$ (0.5 mL); [e] catalyst prepared at 35 °C; [f] in the absence of 4 Å MS; DCE = 1,2-dichloroethane.

of **2d**, the catalyst efficiency was further optimized to 91% yield and 92% *ee* by using 0.2 mL toluene to prepare the catalyst and adding 0.8 mL $CH_2Cl_2$ to retain the same concentration before addition of the cyanate reagent. For 3′,4′,5′-substituted substrates electron-withdrawing groups (**2e**) afforded higher enantioselectivity than electron-donating ones (**2f**–**2l**). Notably, substrates bearing six-membered rings, which were not suitable for organocatalysis,[5b,c] were readily converted into the corresponding nitriles with excellent enantioselectivities and yields (**2p**–**2t**). The absolute configuration *R* of both five- and six-membered rings was established by single-crystal X-ray analysis of **2t** and **2g** (Figure 2).[14] In addition, the other enantiomer (*S*)-**2p** was prepared on a gram-scale in excellent enantioselectivity (−94% *ee*) and 93% yield by using a reduced catalyst loading of 2 mol% with (*R*,*R*)-**L6** (Scheme 2).




**Scheme 2.** Gram-scale reaction.

This protocol has a wide scope of substrates, in which cyclic β-keto amides are suitable as well. Aromatic five- and six-membered amides (**3a**–**3k**) with electron-withdrawing and electron-donating groups were well tolerated, affording products

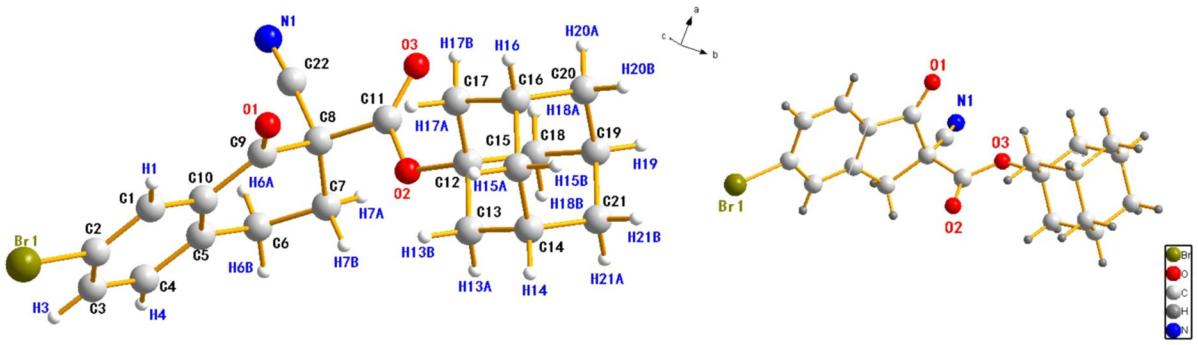
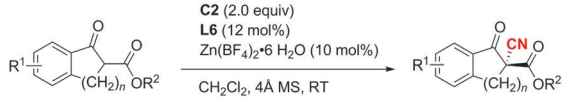
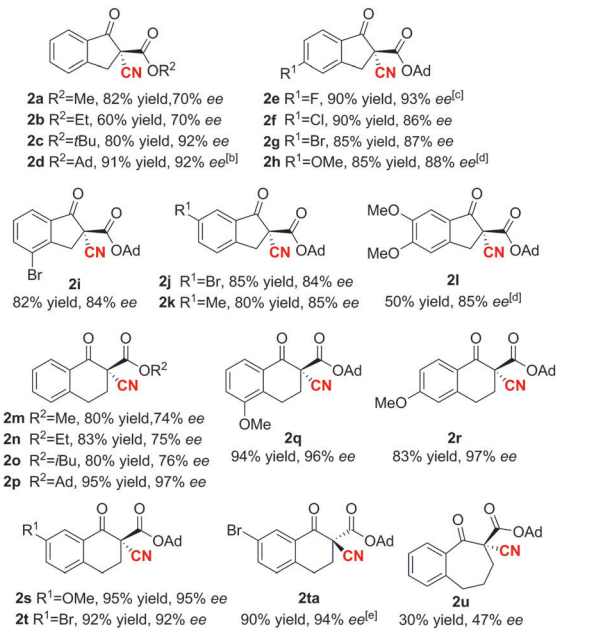



**Figure 2.** The X-ray structure of products **2t** (left) and **2g** (right).

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

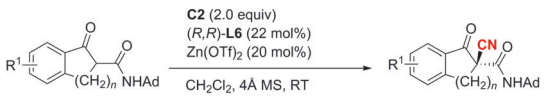



**1a-u** ( *n*=1,2,3) → **2a-u**

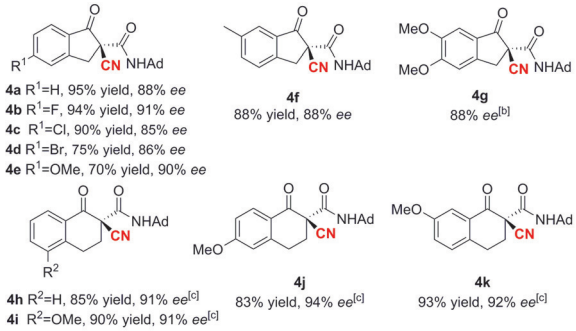



[a] Reaction conditions: **1a–u** (0.05 mmol), **C2** (0.1 mmol, 2.0 equiv), $Zn(BF_4)_2{\cdot}6H_2O$ (0.005 mmol, 10 mol%), and **L6** (0.006 mmol, 12 mol%), $CH_2Cl_2$ (1.0 mL), 4 Å MS (25 mg), RT, 24 h, argon; [b] toluene (0.2 mL) used to prepare the catalyst; [c] toluene (0.5 mL) used to prepare the catalyst; [d] reaction time 48 h; [e] (*R*,*R*)-**L6** was used instead.

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




**3a-k** ( *n*=1,2) → **4a-k**

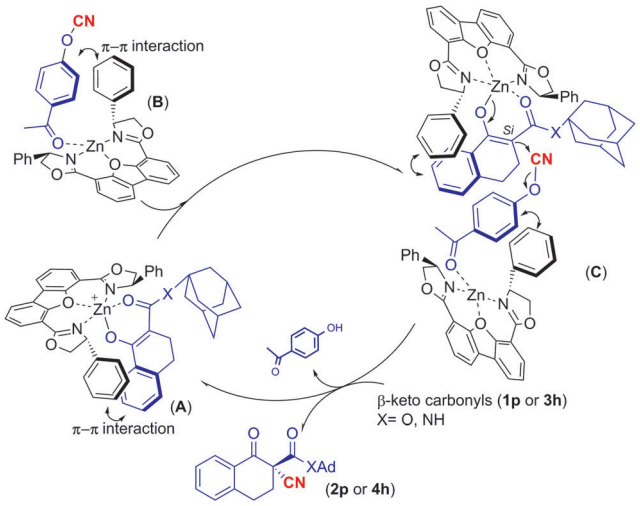



[a] Reaction conditions: **3a–k** (0.05 mmol), **C2** (0.1 mmol, 2.0 equiv), $Zn(OTf)_2$ (0.001 mmol, 20 mol%), and **L6** (0.0011 mmol, 22 mol%), $CH_2Cl_2$ (1.0 mL), 4 Å MS (12.5 mg), RT, 24 h, argon. Yield is isolated yield, and *ee* value was determined by HPLC analysis on Chiralpak AD-H.[15] The absolute configuration of (*S*)-**4** was determined by analogue comparison with esters; [b] decomposed on silica gel column; [c] catalyst loading (10 mol%).

**4a–4k** in high enantioselectivities and good yields (Table 4), and showing similar substituent effects concerning the esters.

In an effort to obtain insight into the mechanism, controlled experiments were performed, and a significant positive nonlinear effect was observed.[15] In situ $^{13}C$ NMR studies at 3 °C showed that the carbon signal of the carbonyl group (1.66 ppm) was shifted significantly further downfield than the carbon of the OCN moiety (0.85 ppm) in the case of **C2** as the cyanate reagent, whereas the carbon of the OCN group shifted by 0.45 ppm with **C1** as the cyano source.[15] Combined with the experimental observations (Table 1, entry 6 vs. 8), a plausible mechanism is 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**). In the stereoselectivity-determining step, the LUMO-lowered cyano cation approaching the enolate plane from the *Si* face led to transition state (**C**), arranged very effectively as a result of π–π interactions between substrate, cyanate, and the ligand.

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




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

This α-cyanation protocol enables the convenient preparation of nitriles with quaternary carbon centers.

## *Acknowledgements*

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**Keywords:** asymmetric catalysis · cyanation · enantioselectivity · Lewis acids · nitrile

[1] F. F. Fleming, *Nat. Prod. Rep.* **1999**, *16*, 597 – 606.

[2] a) R. J. H. Gregory, *Chem. Rev.* **1999**, *99*, 3649 – 3682; b) D. Enders, J. P. Shilvock, *Chem. Soc. Rev.* **2000**, *29*, 359 – 373; c) M. X. Wang, *Top. Catal.* **2005**, *35*, 117 – 130.

[3] For selected reviews of cyanohydrins, see: a) D. T. Mowry, *Chem. Rev.* **1948**, *42*, 189 – 283; b) E. A. Colby Davie, S. M. Mennen, Y. Xu, S. J. Miller, *Chem. Rev.* **2007**, *107*, 5759 – 5812; c) M. North, D. L. Usanov, C. Young, *Chem. Rev.* **2008**, *108*, 5146 – 5226; d) U. Hanefeld, *Chem. Soc. Rev.* **2013**, *42*, 6308 – 6568; e) P. Bracco, H. Busch, J. v. Langermannb, U. Hanefeld, *Org. Biomol. Chem.* **2016**, *14*, 6375 – 6389; f) W. Wang, X. Liu, L. Liu, X.-M. Feng, *Eur. J. Org. Chem.* **2010**, 4751 – 4769.

[4] For selected examples of chiral aliphatic nitriles, see: a) G. M. Sammis, E. N. Jacobsen, *J. Am. Chem. Soc.* **2003**, *125*, 4442 – 4443; b) Y. Tanaka, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2010**, *132*, 8862 – 8863; c) P. Bernal, R. Fernández, J. M. Lassaletta, *Chem. Eur. J.* **2010**, *16*, 7714 – 7718; d) J. Yang, S. Wu, F.-X. Chen, *Synlett* **2010**, 2725 – 2728; e) Y.-F. Wang, W. Zeng, M. Sohail, J. Guo, S.-X. Wu, F.-X. Chen, *Eur. J. Org. Chem.* **2013**, 4624 – 4633; f) R.-G. Ren, Z. Wu, Y. Xu, C. Zhu, *Angew. Chem. Int. Ed.* **2016**, *55*, 2866 – 2869; *Angew. Chem.* **2016**, *128*, 2916 – 2919; g) W. Zhang, F. Wang, S. D. McCann, D. Wang, P. Chen, S. S. Stahl, G.-S. Liu, *Science* **2016**, *353*, 1014 – 1018. During revision of this work, we noted a new advance, see: h) F. Wang, D. Wang, X. Wan, L. Wu, P. Chen, G. Liu, *J. Am. Chem. Soc.* **2016**, *138*, 15547 – 15550.

[5] a) Y.-F. Wang, J.-S. Qiu, Y. Gao, F. Lu, P. G. Karmaker, F.-X. Chen, *Org. Biomol. Chem.* **2015**, *13*, 365 – 368; b) R. Chowdhury, J. Schörgenhumer, J. Novacek, M. Waser, *Tetrahedron Lett.* **2015**, *56*, 1911 – 1914; c) M. Chen, Z.-T. Huang, Q.-Y. Zheng, *Org. Biomol. Chem.* **2015**, *13*, 8812 – 8816; d) G. Talavera, J. Peña, M. Alcarazo, *J. Am. Chem. Soc.* **2015**, *137*, 8704 – 8707.

[6] For selected reviews of hypervalent iodine reagents, see: a) V. V. Zhdankin, P. J. Stang, *Chem. Rev.* **2002**, *102*, 2523 – 2584; b) T. Wirth, *Angew. Chem. Int. Ed.* **2005**, *44*, 3656 – 3665; *Angew. Chem.* **2005**, *117*, 3722 – 3731; c) J. P. Brand, D. F. González, S. Nicolai, J. Waser, *Chem. Commun.* **2011**, *47*, 102 – 115; d) Y. Li, D. P. Hari, M. V. Vita, J. Waser, *Angew. Chem. Int. Ed.* **2016**, *55*, 4436 – 4454; *Angew. Chem.* **2016**, *128*, 4512 – 4531. We explored the cinchonidine-catalyzed α-cyanation in $CH_2Cl_2$ up to 59% *ee* for β-keto esters with cyano-hyperiodinate. The solubility of the cyano reagent is a problem in $CH_2Cl_2$: e) Y.-F. Wang, Doctorate thesis, **2014**, pp. 74 – 75; for recent examples, see: f) M. V. Vita, P. Caramenti, J. Waser, *Org. Lett.* **2015**, *17*, 5832 – 5835; g) R. Frei, T. Courant, M. D. Wodrich, J. Waser, *Chem. Eur. J.* **2015**, *21*, 2662 – 2668.

[7] For selected examples of cyanation of aryls with cationic cyano sources, see: a) P. Anbarasan, H. Neumann, M. Beller, *Chem. Eur. J.* **2010**, *16*, 4725 – 4728; b) P. Anbarasan, H. Neumann, M. Beller, *Angew. Chem. Int. Ed.* **2011**, *50*, 519 – 522; *Angew. Chem.* **2011**, *123*, 539 – 542; c) G.-Y. Zhang, J.-T. Yu, M.-L. Hu, J. Cheng, *J. Org. Chem.* **2013**, *78*, 2710 – 2714; d) Z.-B. Shu, W.-Z. Ji, X. Wang, Y.-J. Zhou, Y. Zhang, J.-B. Wang, *Angew. Chem. Int. Ed.* **2014**, *53*, 2186 – 2189; *Angew. Chem.* **2014**, *126*, 2218 – 2221.

[8] K. Buttke, H. J. Niclas, *J. Prakt. Chem.* **1998**, *340*, 669 – 675.

[9] For applications of cyanate reagents, see: a) R. E. Murray, G. Zweifel, *Synthesis* **1980**, *2*, 150 – 151; b) K. Buttke, T. Reiher, H. J. Niclas, *Synth. Commun.* **1992**, *22*, 2237 – 2243; c) K. Buttke, H. J. Niclas, *Synth. Commun.* **1994**, *24*, 3241 – 3248; d) D. C. Koester, M. Kobayashi, D. B. Werz, Y. Nakao, *J. Am. Chem. Soc.* **2012**, *134*, 6544 – 6547.

[10] For selected recent examples of other substitutions of β-ketoesters, see: azidation: a) Q.-H. Deng, T. Bleith, H. Wadepohl, L. H. Gade, *J. Am. Chem. Soc.* **2013**, *135*, 5356 – 5359; b) M. Vita, J. Waser, *Org. Lett.* **2013**, *15*, 3246 – 3249; trifluoromethylation: c) I. Kieltsch, P. Eisenberger, A. Togni, *Angew. Chem. Int. Ed.* **2007**, *46*, 754 – 757; *Angew. Chem.* **2007**, *119*, 768 – 771; d) Q.-H. Deng, H. Wadepohl, L. H. Gade, *J. Am. Chem. Soc.* **2012**, *134*, 10769 – 10772; e) L. Woźniak, J. J. Murphy, P. Melchiorre, *J. Am. Chem. Soc.* **2015**, *137*, 5678 – 5681; f) X.-X. Shao, X.-Q. Wang, T. Yang, L. Lu, Q.-L. Shen, *Angew. Chem. Int. Ed.* **2013**, *52*, 3457 – 3460; *Angew. Chem.* **2013**, *125*, 3541 – 3544; alkynylation: g) T. B. Poulsen, L. Bernardi, J. Alemán, J. Overgaard, K. Jørgensen, *J. Am. Chem. Soc.* **2007**, *129*, 441 – 449.

[11] For selected BOX-metal complex-catalyzed reactions of β-keto carbonyls, see: a) N. Shibata, J. Kohno, K. Takai, T. Ishimaru, S. Nakamura, T. Toru, S. Kanemasa, *Angew. Chem. Int. Ed.* **2005**, *44*, 4204 – 4207; *Angew. Chem.* **2005**, *117*, 4276 – 4279; b) D. S. Reddy, N. Shibata, J. Nagai, S. Nakamura, T. Toru, S. Kanemasa, *Angew. Chem. Int. Ed.* **2008**, *47*, 164 – 168; *Angew. Chem.* **2008**, *120*, 170 – 174; c) T. Bleith, Q.-H. Deng, H. Wadepohl, L. H. Gade, *Angew. Chem. Int. Ed.* **2016**, *55*, 7852 – 7856; *Angew. Chem.* **2016**, *128*, 7983 – 7987.

[12] For seminar discussion and selected reviews of π–π interaction, see: a) S. K. Burley, G. A. Petsko, *Science* **1985**, *229*, 23 – 28; b) J.-Y. Ortholand, A. M. Z. Slawin, N. Spencer, J. F. Stoddart, D. J. Williams, *Angew. Chem. Int. Ed.* **1989**, *28*, 1394 – 1395; *Angew. Chem.* **1989**, *101*, 1402 – 1404.

[13] L. Hong, W. Sun, D. Yang, G. Li, R. Wang, *Chem. Rev.* **2016**, *116*, 4006 – 4123.

[14] We observed that the algebraic signs of optical rotation values of nitriles with five- and six-membered ring are opposite, not in agreement with those in the literature (ref. [5c]). To determine the absolute configuration of five-membered rings, we spent 18 months in cultivating the single crystal from the solution of **2g**. See the Supporting Information (S18 and S51).

[15] See the Supporting Information (S37).

[16] a) A. H. Mermerian, G. C. Fu, *J. Am. Chem. Soc.* **2003**, *125*, 4050 – 4051; b) F.-X. Chen, B. Qin, X. Feng, G. Zhang, Y. Jiang, *Tetrahedron* **2004**, *60*, 10449 – 10460; c) J.-A. Ma, D. Cahard, *Angew. Chem. Int. Ed.* **2004**, *43*, 4566 – 4583; *Angew. Chem.* **2004**, *116*, 4666 – 4683; d) M. Shibasaki, M. Kanai, S. Matsunaga, N. Kumagai, *Acc. Chem. Res.* **2009**, *42*, 1117 – 1127.

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