Organic & Biomolecular Chemistry

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DOI: 10.1039/C7OB01782K

Journal Name

COMMUNICATION

Enantioselective Electrophilic Cyanation of *β*-keto Amides Catalysed by Cinchona Organocatalyst

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

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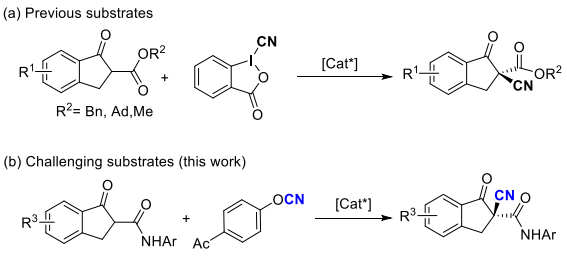
An operationally simple protocol for the enantioselective electrophilic α-cyanation of *β*-keto amides catalyzed by cinchona-derived catalysts has been demonstrated. The resulting products could be obtained with good to high enantioselectivities (up to 88% ee) and with excellent yields (up to 94%) by employing the gentle active 4-acetylphenyl cyanate as the cationic cyano source in the catalytic asymmetric α-cyanation reaction.

The enantioselective introduction of a cyano group into various substrates has received considerable research interest because it was discovered to be an important functional group among natural products, pharmaceuticals, materials, agrochemicals as well as multipurpose intermediate with diverse transformations.[1] There are several successful examples of asymmetric nucleophilic addition of cyano reagents to sp^2-hybridized electrophiles bearing C=O, C=N, and C=C bonds.[2]

In the last decade, significant achievements have been made in nucleophilic addition of cyanide to electrophiles in which, e.g., preparations of chiral nitriles and cyanohydrins are realized by the extensively studied enantioselective 1,2-addition of imines, ketones and aldehydes,[2] and conjugated hydrocyanation of α,β-unsaturated carbonyls[3] with diverse nucleophilic cyanide precursors.[4] However, as an alternative method, electrophilic cyanation reaction of sp^3 carbon has been less explored in previously studied reports compared to nucleophilic ones.[5] On the other hand, α-functionalization of carbonyl compounds have been developed a large numbers of interesting synthetic building blocks and molecules.[6] A variety of transformations, specifically through the electrophilic reaction corridor, such as α-fluorination,[7] halogenation,[8] hydroxylation,[9] arylation,[10] trifluoromethylation,[7b,11] trifluoro-methylthiolation,[12] and azidation.[13] Recently, our group disclosed the racemic *α*- cyanation of *β*-keto carbonyls with cyanohyperiodine reagent.[14a] Subsequently in the same year, Waser[15a] and Zheng[15b] individually reported their asymmetric versions with moderate to good *ee* values using alkaloid-based organocatalysts. A third interesting example came from Feng and Liu's group by an amazing hydrogen-bond network using their featuring *N,N*′-dioxide organocatalysts.[15c-d] They all used synthesized hypervalent iodine(III) reagents which have been vastly used in many organic transformations (Scheme 1a).[6c,16] Considering the activity of hypervalent iodine(III) reagent, we selected mild aromatic cyanate as the cyano source affording excellent enantioselectivities using Lewis acid catalysis.[14b] However, β-keto amides are still the problematic substrates suffering either high catalyst loading, or low enantioselectivity or even no conversion. Compared with the β-keto esters,[15e] the α-functionalization of β-keto amides has been much less investigated,[7f,14b,17a-b] possibly due to the lower acidity of the α-hydrogen, although the amide group is useful for further manipulation.[17] Inspired by these above literature survey as well as our illimitable interest in the asymmetric synthesis, we became interested in developing a novel protocol for the asymmetric *α*-cyanation reaction of *β*-keto amides (**1**) using mild active 4-acetylphenyl cyanate (**2b**) as the electrophilic cyano transfer reagent (Scheme 1b).



Scheme 1 Asymmetric electrophilic α-cyanation reaction of β-keto amides

Results and Discussion

To optimize the catalyst performance, initially the model substrate of racemic β-ketoamide (**1a**) was selected to be

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[a] *Electronic Supplementary Information (ESI) available: experimental procedure, characteristics of compounds, copies of spectra, CCDC 1563576. See DOI: 10.1039/x0xx00000x*

treated with 4-acetylphenyl cyanate (**2b**) in the presence of 4 Å molecular sieve (MS) in CH_2Cl_2 at 0 °C under an argon atmosphere, using a variety of easily accessible cinchona derived organocatalysts of different nature (Figure 1). Table 1 presents an outline of the most significant results obtained in a detailed screening of the catalysts and reaction parameters.

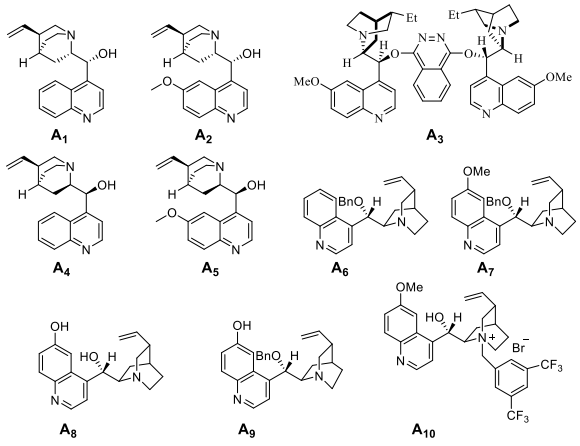


Figure 1 Cinchona-derived catalysts evaluated in this study.

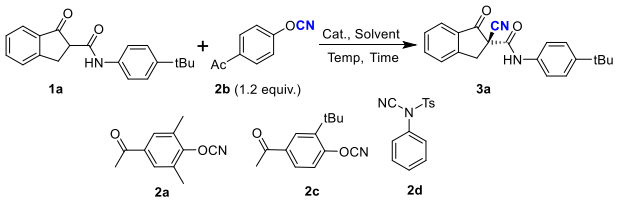
We were pleased to observe the formation of the desired product **3a** with 41% ee albeit 27% yield (Table 1, entry 1) when using a simple chinchona alkaloid $\mathbf{A_1}$ as the catalyst bearing a free-OH group. This result suggested that the basic moiety and H-bond donating group in the natural cinchona organocatalyst could work cordially in this electrophilic cyanation reaction. Next, we examined other naturally existed pseudo-isomers $\mathbf{A_2}$, cinchonine $\mathbf{A_4}$, quinidine ($\mathbf{A_5}$), and the symmetric dimmer $\mathbf{A_3}$. To our delight, $\mathbf{A_4}$ gave the promising highest 54% ee of **3a** and comparable low yield of 32% (entry 4 vs entries 2-3 and 5). Subsequently, some structurally modified cinchona derivatives were screened as the catalyst but affording inferior results. Either blocking the 9-OH groups by benzyl in $\mathbf{A_6}$, $\mathbf{A_7}$ and $\mathbf{A_9}$ or free 6-OH in $\mathbf{A_8}$ resulted in bad catalyst performance (entries 6-9), whereas use of $\mathbf{A_{10}}$ as the PTC catalyst produced **3a** with negligible enantioselectivity and lower yield with opposite configuration (entry 10). These data indicate a possible H-bond raised by free 9-OH is the key for good enantioselectivity for cinchonine in this reaction.

Prompted by this result, then the effect of solvent was investigated. However, other solvents such as toluene, THF, acetonitrile and chloroform are not suitable for this reaction because of their inferior enantioselectivity and or low yield (Table 1, entries 11-14). CH_2Cl_2 is the suitable solvent for this catalytic reaction. Subsequently, decreasing the reaction temperature to –20 °C furnished the product with a little better result 57% ee (entry 15). Further lowering the reaction temperature to –40 °C, the product **3a** was isolated in 74% ee (entry 16). However, performing the reaction at –78 °C led to a slight drop in the both yield and ee value (entry 17).

Decreasing the catalyst loading to 10 mol% in the model reaction, **3a** was yielded in comparable enantioselectivity and a little lower yield (entry 18 vs 16). Continuously lowering the amount of catalyst loading to 5 mol% gave a step-wise lowered yield but the same ee value (entry 19). Further decreasing the catalyst loading to 1 mol% eroded the catalyst capacity significantly (entry 20). To retain the catalyst efficiency, increasing the amount of cyano reagent **2b** from 1.2 equiv. to 5 equiv. improved the enantioselectivity from 73% ee to 82% ee at 5 mol% of catalyst loading (entry 21 vs 19). Interestingly, prolongation of reaction time from 12 h to 36 h increased both the enantioselectivity of **3a** from 82% to 88% ee and yield from 58% to 94% (entry 22 vs 21, for more details, see Figure S1 and Table S1 in ESI).

Therefore, the natural occurring $\mathbf{A_4}$ is the suitable catalyst. And the optimal catalyst efficiency was achieved in CH_2Cl_2 at –40 °C at 5 mol% of catalyst loading with excellent 94% yield and high enantioselectivity (88% ee) for the model substrate. The chemical yield of **3a** is a simple factor of reaction time and equivalence of the cationic cyano reagent **2b**. However, other three cationic cyano reagents (**2a**, **2c** and **2d**) were also screened but unfortunately found giving no desired product under this condition. In addition, 4 Å MS (5 mg) is essential as either absence or higher or lower of it was unbeneficial to this protocol.

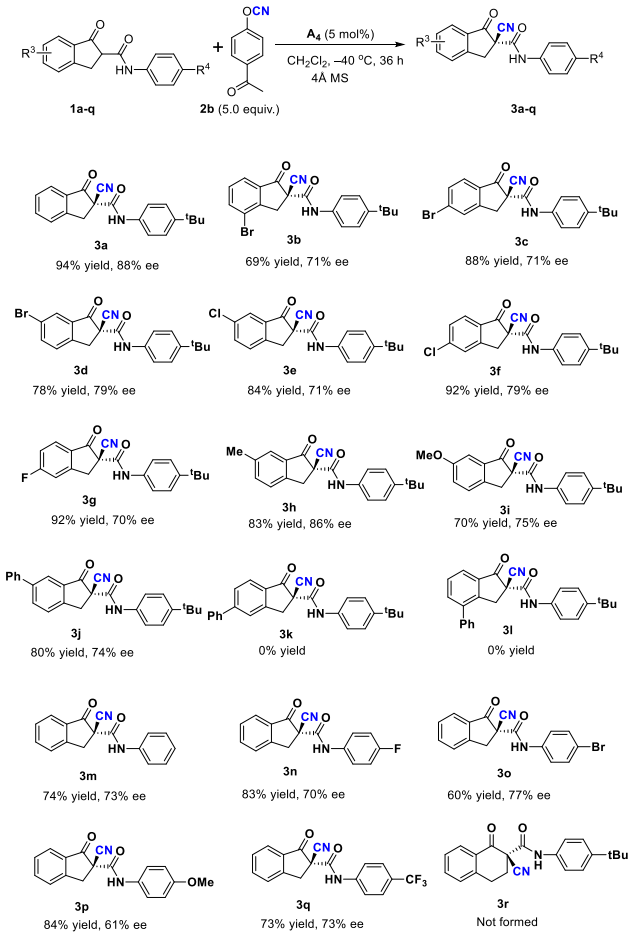
Table 1 Identification of the optimal organocatalyst and the reaction conditions for the asymmetric α-cyanation of **1a**.[a]



Entry	Cat. (mol%)	Solvent	Temp (°C)	Time (h)	Yield (%)[b]	ee (%)[c]
1	$\mathbf{A_1}$ (20)	CH_2Cl_2	0	12	27	–41
2	$\mathbf{A_2}$ (20)	CH_2Cl_2	0	12	23	–9
3	$\mathbf{A_3}$ (20)	CH_2Cl_2	0	12	31	7
4	$\mathbf{A_4}$ (20)	CH_2Cl_2	0	12	32	54
5	$\mathbf{A_5}$ (20)	CH_2Cl_2	0	12	39	0
6	$\mathbf{A_6}$ (20)	CH_2Cl_2	0	12	49	–15
7	$\mathbf{A_7}$ (20)	CH_2Cl_2	0	12	52	0
8	$\mathbf{A_8}$ (20)	CH_2Cl_2	0	12	42	–3
9	$\mathbf{A_9}$ (20)	CH_2Cl_2	0	12	38	–9
10	$\mathbf{A_{10}}$ (20)	CH_2Cl_2	0	12	43	–7
11	$\mathbf{A_4}$ (20)	Toluene	0	12	24	39
12	$\mathbf{A_4}$ (20)	THF	0	12	27	41
13	$\mathbf{A_4}$ (20)	CH_3CN	0	12	27	39
14	$\mathbf{A_4}$ (20)	$CHCl_3$	0	12	21	51
15	$\mathbf{A_4}$ (20)	CH_2Cl_2	-20	12	30	57
16	$\mathbf{A_4}$ (20)	CH_2Cl_2	-40	12	40	74
17	$\mathbf{A_4}$ (20)	CH_2Cl_2	-78	12	37	65
18	$\mathbf{A_4}$ (10)	CH_2Cl_2	–40	12	30	73
19	$\mathbf{A_4}$ (5)	CH_2Cl_2	–40	12	25	73
20	$\mathbf{A_4}$ (1)	CH_2Cl_2	–40	12	18	63
21[d]	$\mathbf{A_4}$ (5)	CH_2Cl_2	–40	12	58	82
22[d]	$\mathbf{A_4}$ (5)	CH_2Cl_2	–40	36	94	88

[a] Reaction Conditions: **1a** (0.1 mmol), **2b** (0.12 mmol, 1.2 equiv.), catalyst (20 mol%), 4Å MS (5 mg), solvent (1.0 mL) at 0 °C, 12 h under argon atmosphere, unless otherwise indicated; [b] Isolated yield; [c] Enantiomeric excess (ee) was determined by chiral HPLC analysis on Chiralpak AD-H. [d] **2b** (0.5 mmol, 5.0 equiv.).

Table 2 Substrate scope and limitation of the asymmetric α-cyanation.[a]



[a] All reactions were performed on the scale of 0.1 mmol of the substrate with 4Å MS (5 mg) in CH_2Cl_2 (1 mL) at –40 °C for 36 h under argon atmosphere. The results are listed with isolated yields and ee values determined by Chiral HPLC analysis on Chiralpak AD-H.

Under the optimized reaction conditions of **1a**, the substrate scope of this protocol with some differently substituted β-keto amides **1b**-**1r** was subsequently explored. As shown in Table 2, good yields and moderate to high enantioselectivities were obtained in the α-cyanation of indanone-derived β-keto amides. The electron-withdrawing substituent such as Cl, F and Br in the benzene ring at 4,5,6-positions affected the yield and enantioselectivity slightly by affording the products with a little lower but almost the same ee values (**3b**-**3g**). On the other hand, electron-donating substituent such as 6-Me, 6-MeO and 6-Ph gave higher enantioselectivity with good yield (**3h**, **3i**, **3j**) while β-keto amides **3k** and **3l** bearing 4- and 5-Ph had no conversion indicating that the nature of substituent and its position had complex and ambient influence on the catalyst performance.

Moreover, substituent at the amide side also affected the catalytic outcomes. Aniline-derived substrates containing 4'-MeO, 4'-F, 4'-Br, 4'-CF_3, 4'-H groups could be converted into the corresponding products **3m**-**3q** in good yields (60-84%) and moderate 61-77% ee while substrate bearing six-membered ring (**1r**) was not suitable for this protocol.[15a-b]

The absolute configuration (*S*) of the stereogenic carboncenter in the cyanated product **3c** was determined by X-ray structure analysis of the single crystal **3c** with 98% ee after simple recrystallization (Figure 2). Other products' absolute configurations were established by analogue.

Based on the absolute configuration of product **3c** and the above experimental observations, a plausible mechanism was proposed in Figure 3. On one hand, the catalyst acts as a Bronsted base to activate the substrate through enolate in which a larger planar moiety is consolidated by H-bond around the prochiral C=C bond by restricting free rotation of exocyclic C_α-C single bond. On the other hand, C_9-OH of cinchonine connects the acetyl group of the cyano reagent by a second H-bond thus activating the *O*-CN bond. This two hydrogen bonds network warranted the arrangement of the most stable conformation in the transition state, governing the *Si* face attack in favour of the formation of (*S*)-enantiomers.

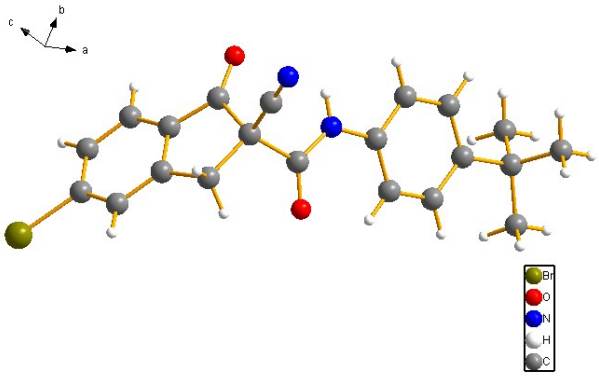


Figure 2 The X-ray structure of product **3c**.

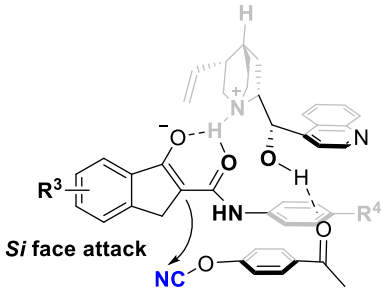


Figure 3 Possible model of the reaction transition-state.

Conclusion

In summary, we have developed a facile enantioselective α-cyanation of β-keto amides. The readily available of catalyst, mild reaction conditions, and the highly functionalized nitrile products with a chiral quaternary carbon center, all make this transformation more practical. The corresponding products could be obtained with good to excellent enantioselectivities (up to 88% ee) and high yields (up to 94%) using the mild active 4-acetylphenyl cyanate as the cationic cyano source.

Acknowledgment

The authors are grateful of financial support from NSFC (21572020).

References

1 (*a*) D. R. Buckle, B. C. C. Cantello, H. Smith and B. A. J. Spicer, *Med. Chem.* 1977, **20**, 265; (*b*) Z. Rappoport, *Chemistry of the cyano group,* Interscience, New York, 1970; (*c*) F. F. Fleming*, Nat. Prod. Rep.*, 1999, **16**, 597; (*d*) A. Kleemann, J. Engel, B. Kutscher and D. Reichert, *Pharmaceutical substances: syntheses, patents, applications*, Thieme, Stuttgart, 1999; (*e*) R. C. Larock, *Comprehensive organic transformations: a guide to functional group preparations*, Wiley-VCH, New York, 1999; (*f*) J. S. Miller and J. L. Manson, *Acc. Chem. Res*., 2001, **34**, 563; (*g*) F. F. Fleming, L. Yao, P. C. Ravikumar, L. Funk and B. C. Shook, *J. Med. Chem*., 2010, **53**, 7902.

2 For some selected reviews on addition of cyanide to electrophiles: (*a*) N. Kurono and T. Ohkuma, *ACS Catal*., 2016, **6**, 989; (*b*) H. Pellissier, *Adv. Synth. Catal*., 2015, **357**, 857; (*c*) M. North, D. L. Usanov and C. Young, *Chem. Rev*., 2008, **108**, 5146; (*d*) F.-X. Chen, X. Liu, X. Feng, B. Qin, H. Zhou and G. Zhang, *Synthesis*, 2004, 2266.

3 J. Wang, X. Liu and X. Feng, *Chem. Rev*., 2011, **111**, 6947.

4 For some selected examples, see: (*a*) Y.-F. Wang, W. Zeng, M. Sohail, J. Guo, S. Wu and F.-X. Chen, *Eur. J. Org. Chem*., 2013, 4624; (*b*) J. Zhang, X. Liu and R. Wang, *Chem. Eur. J.*, 2014, **20**, 4911; (*c*) Y. Liu, S. Shirakawa and K. Maruoka, *Org. Lett*., 2013, **15**, 1230; (*d*) H. Kawai, S. Okusu, E. Tokunaga, H. Sato, M. Shiro and N. Shibata, *Angew. Chem., Int. Ed.,* 2012, **51**, 4959; (*e*) B. A. Provencher, K. J. Bartelson, Y. Liu, B. M. Foxman and L. Deng, *Angew. Chem., Int. Ed*., 2011, **50**, 10565; (*f*) N. Kurono, N. Nii, Y. Sakaguchi, M. Uemura and T. Ohkuma, *Angew. Chem., Int. Ed.,* 2011, **50**, 5541; (*g*) Y. Tanaka, M. Kanai and M. Shibasaki, *J. Am. Chem. Soc*., 2008, **130**, 6072; (*h*) T. Mita, K. Sasaki, M. Kanai and M. Shibasaki, *J. Am. Chem. Soc*., 2005, **127**, 514; (*i*) G. M. Sammis, H. Danjo and E. N. Jacobsen, *J. Am. Chem. Soc*., 2004, **126**, 9928; (*j*) J. Wang, W. Li, Y. Liu, Y. Chu, L. Lin, X. Liu and X. Feng, *Org. Lett*., 2010, **12**, 1280; (*k*) G. M. Sammis and E. N. Jacobsen, *J. Am. Chem. Soc*., 2003, **125**, 4442; (*l*) C. Mazet and E. N. Jacobsen, *Angew. Chem., Int. Ed*., 2008, **47**, 1762.

5 (*a*) M. Wakselman, E. Guibe-Jampel, A. Raoult and W. D. Busse, *J. Chem. Soc., Chem. Commun*., 1976, 21; (*b*) R. E. Murray and G. Zweifel, *Synthesis*, 1980, **150**; (*c*) D. Kahne and D. B. Collum, *Tetrahedron Lett.,* 1981, **22**, 5011; (*d*) W. A. Davis and M. P. Cava, *J. Org. Chem*., 1983, **48**, 2774; (*e*) D. Enders, V. N. Pathak and P. Weuster, *Chem. Ber*., 1992, **125**, 515; (*f*) R. W. Stephens and L. A. Domeier, *Synth. Commun*., 1991, **21**, 2025; (*g*) K. Buttke and H. J. Niclas, *Synth. Commun*., 1994, **24**, 3241; (*h*) T. V. Hughes, S. D. Hammond and M. P. Cava*, J. Org. Chem*., 1998, **63**, 401; (*i*) T. V. Hughes and M. P. Cava, *J. Org. Chem*., 1999, **64**, 313; (*j*) Y.-Q. Wu, D. C. Limburg, D. E. Wilkinson and G. S. Hamilton, *Org. Lett*., 2000, **2**, 795; (*k*) P. Anbarasan, H. Neumann and M. Beller, *Chem. Eur. J*., 2010, **16**, 4725; (*l*) R. Akula, Y. Xiong and H. Ibrahim, *RSC Adv*., 2013, **3**, 10731.

6 (*a*) G. Guillena and D. J. Ramon, *Tetrahedron: Asymmetry*, 2006, **17**, 1465; (*b*) A. M. R. Smith and K. K. Hii, *Chem. Rev.,* 2011, **111**, 1637; (*c*) J. P. Brand, D. F. Gonzalez, S. Nicolai and J. Waser, *Chem. Commun*., 2011, **47**, 102; (*d*) E. A. Merritt and B. Olofsson, *Synthesis*, 2011, 517.

7 (*a*) P. M. Pihko, *Angew. Chem., Int. Ed*., 2006, **45**, 544; (*b*) J.-A. Ma and D. Cahard, *Chem. Rev*., 2008, **108**, PR1; (*c*) S. Lectard, Y. Hamashima and M. Sodeoka, *Adv. Synth. Catal*., 2010, **352**, 2708; (*d*) T. Furuya, A. S. Kamlet and T. Ritter*, Nature*, 2011, **473**, 470; (*e*) G. Valero, X. Companyó and R. Rios, *Chem. Eur. J*., 2011, **17**, 2018; (f) L.-S. Zheng, Y.-L. Wei, K.-Z. Jiang, Y. Deng, Z.-J. Zheng and L.-W. Xu, *Adv. Synth. Catal.,* 2014, **356**, 3769.

8 (*a*) H. Ibrahim and A. Togni, *Chem. Commun*., 2004, 1147; (*b*) S. France, A. Weatherwax and T. Lectka, *Eur. J. Org. Chem*., 2005, 475; (*c*) M. Oestreich, *Angew. Chem., Int. Ed*., 2005, **44**, 2324.

9 (*a*) M. R. Acocella, O. G. Mancheño, M. Bella and K. A. Jørgensen, *J. Org. Chem*., 2004, **69**, 8165; (*b*) P. Y. Toullec, C. Bonaccorsi, A. Mezzetti and A. Togni, *Proc. Natl. Acad. Sci. U. S. A.*, 2004, **101**, 5810; (*c*) M. Lu, D. Zhu, Y. Lu, X. Zeng, B. Tan, Z. Xu and G. Zhong, *J. Am. Chem. Soc*., 2009, **131**, 4562; (*d*) A. M. R. Smith, D. Billen and K. K. Hii, *Chem. Commun*., 2009, 3925.

10 (*a*) E. A. Merritt and B. Olofsson, *Angew. Chem., Int. Ed*., 2009, **48**, 9052; (*b*) A. Bigot, A. E. Williamson and M. J. Gaunt, *J. Am. Chem. Soc*., 2011, **133**, 13778.

11 (*a*) T. Umemoto and S. Ishihara, *J. Am. Chem. Soc*., 1993, **115**, 2156; (*b*) J.-A. Ma and D. Cahard, *J. Org. Chem*., 2003, **68**, 8726; (*c*) P. Eisenberger, S. Gischig and A. Togni, *Chem. Eur. J*., 2006, **12**, 2579; (*d*) I. Kieltsch, P. Eisenberger and A. Togni, *Angew. Chem., Int. Ed.,* 2007, **46**, 754.

12 (*a*) X. Shao, X. Wang, T. Yang, L. Lu and Q. Shen, *Angew. Chem*., *Int. Ed.,* 2013, **52**, 3457; (*b*) X. Wang, T. Yang, X. Cheng and Q. Shen, *Angew. Chem., Int. Ed*., 2013, **52**, 12860; (*c*) Q.-H. Deng, C. Rettenmeier, H. Wadepohl and L. H. Gade, *Chem. Eur. J*., 2014, **20**, 93; (*d*) X.-L. Zhu, J.-H. Xu, D.-J. Cheng, L.-J. Zhao, X.-Y. Liu and B. Tan, *Org. Lett*., 2014, **16**, 2192.

13 (*a*) Q.-H. Deng, T. Bleith, H. Wadepohl and L. H. Gade, *J. Am. Chem. Soc*., 2013, **135**, 5356; (*b*) M. V. Vita and J. Waser, *Org. Lett*., 2013, **15**, 3246.

14 (*a*) Y.-F. Wang, J.-S. Qiu, Y. Gao, F. Lu, P. G. Karmaker and F.-X. Chen, *Org. Biomol. Chem*. 2015, **13**, 365; (*b*) J.-S. Qiu, Y.-F. Wang, G.-R. Qi, P. G. Karmaker, H.-Q. Yin and F.-X. Chen, *Chem. Eur. J.,* 2017**, 23***,* 1775; (*c*) J.-S. Qiu, D. Wu, P. G. Karmaker, G. Qi, P. Chen, H.-Q. Yin and F.-X. Chen, *Org. Lett.*, 2017, **19**, 4018.

15 (*a*) R. Chowdhury, J. Schörgenhumer, J. Novacek and M. Waser, *Tetrahedron Lett*. 2015, **56**, 1911; (*b*) M. Chen, Z.-T. Huang and Q.-Y. Zheng, *Org. Biomol. Chem*., 2015, **13**, 8812; (*c*) B.-W. Ma, X.-B. Li, L.-L. Lin, X.-M. Feng and X.-H. Liu, *J. Org. Chem.,* 2017, **82**, 701; (*d*) X.-H. Liu, L.-L. Lin and X.-M. Feng, *Acc. Chem. Res.,* 2011, **44**, 574; (e) T. Govender, P. I. Arvidsson, G. E. M. Maguire, H. G. Kruger and T. Naicker, *Chem. Rev.* 2016, **116**, 9375; (f) J. Schörgenhumer and M. Waser, *Org. Chem. Front.*, 2016, **3**, 1535.

16 For selected reviews of hypervalent iodine reagents, see: (*a*) V. V. Zhdankin and P. J. Stang, *Chem. Rev*., 2002, **102**, 2523; (*b*) T. Wirth, *Angew Chem. Int. Ed.,* 2005, **44**, 3656–3665; (*c*) Y. Li, D. P. Hari, M. V. Vita and J. Waser, *Angew. Chem. Int. Ed*., 2016, **55**, 4436; (*d*) M. V. Vita, P. Caramenti and J. Waser, *Org. Lett*., 2015, **17**, 5832; (*e*) R. Frei, T. Courant, M. D. Wodrich and J. Waser, *Chem. Eur. J.,* 2015, **21**, 2662.

17 (*a*) C. De Fusco, S. Meninno, C. Tedesco and A. Lattanzi, *Org. Biomol. Chem*., 2013, **11**, 896; (*b*) S.-J. Jia and D.-M. Du, *Chin. Chem. Lett.,* 2014, **25**, 1479; (*c*) C. Yin, W. Cao, L. Lin, X. Liu and X. Feng, *Adv. Synth. Catal.,* 2013, **355**, 1924; (*d*) C. Pan, X. Zeng, Y. Guan, X. Jiang, L. Li and H. Zhang, *Synlett,* 2011, 425.

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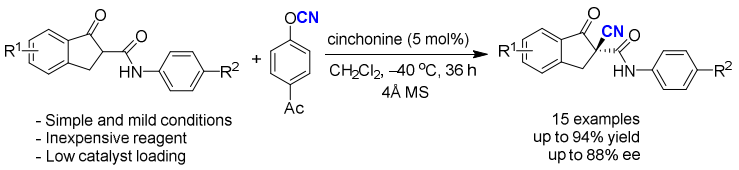
Abstract



Enantioselective Electrophilic Cyanation of *β*-keto Amides Catalysed by Cinchona Organocatalysts