Advanced Synthesis & Catalysis

## Accepted Article

**Title:** Enantioselective Copper-Catalyzed Radical Ring-Opening Cyanation of Cyclopropanols and Cyclopropanone Acetals

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**To be cited as:** *Adv. Synth. Catal.* 10.1002/adsc.202000202

**Link to VoR:** http://dx.doi.org/10.1002/adsc.202000202

10.1002/adsc.202000202

**Very Important Publication** **COMMUNICATION**

# Enantioselective Copper-Catalyzed Radical Ring-Opening Cyanation of Cyclopropanols and Cyclopropanone Acetals

Lianqian Wu, Lei Wang, Pinghong Chen, Yin-Long Guo,* and Guosheng Liu*

***Abstract:*** *A novel approach for enantioselective cyanation of cyclopropanols and their derivatives through copper-catalyzed radical relay processes has been developed. Various cyclopropanols and cyclopropanone acetals are compatible to the catalytic conditions, providing β-carbonyl nitriles with excellent enantioselectivity. These products can be readily converted to chiral γ-amino acids derivatives and drugs such as (R)-baclofen. Preliminary mechanistic studies have supported a ring-opening process for cyclopropanoxy radicals followed by copper-catalyzed enantioselective cyanation of benzylic radicals to form the C−CN bonds in an enantioselective manner.*

Optically pure organonitriles are found in many bioactive natural products and therapeutics.[1] In addition, organonitriles are an important class of synthons that are essential precursors to highly valuable amines, carboxylic acids and their derivatives.[2] Among them, enantiomerically enriched β-carbonyl nitriles are particularly prominent targets, because they can be transformed into γ-lactams and γ-amino acids, which are widely used as anti-depressant agents and selective agonists of GABA (γ-aminobutyric acids) receptors (Figure 1).[3]

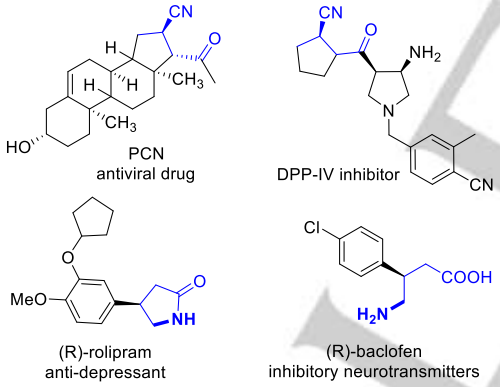
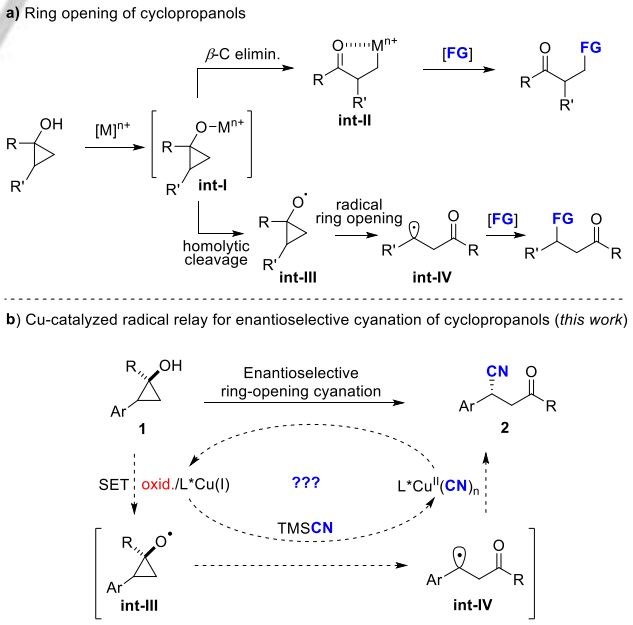



***Figure 1.*** Representative compounds containing or derived from chiral carbonyl nitriles

A variety of methods have been established for asymmetric synthesis of β-carbonyl nitriles, including lewis acid-catalyzed conjugate hydrocyanation of α,β-unsaturated compounds,[4] enzyme catalyzed bioreduction of cyanoacrylates,[5] and nickel-catalyzed cross-coupling of α-halonitriles with organozinc reagents.[6] Despite these progresses, exploration of efficient approaches to access the chiral β-carbonyl nitriles is still in strong demand.

In the last several decades, transition metal-catalyzed ring-opening of cyclopropanols have been extensively studied. The β-carbon elimination of an alkyloxide metal complex **int-I** (M = Rh, Cu, Pd, Co, Ni) involved in these reactions usually occurs preferentially at the less substituted carbon centers, resulting in the formation of the β-functionalized carbonyl products through reductive elimination from **int-II** (Scheme 1a, top). Based on this mechanistic hypothesis, a variety of methods for the synthesis of β-functionalized carbonyl compounds have been developed.[7] Alternatively, the cyclopropanoxide complex **int-I** (M = Ag, Mn, etc) could undergo homolytic cleavage of the M–O bond to generate the cyclopropoxy radical **int-III**, which subsequently gives the carbon-centered radical **int-IV** through a radical ring-opening process at the more substituted carbon centers, thus leading to different β-functionalized carbonyl products (Scheme 1a, bottom).[8] For instance, Zhu and coworkers reported a series of Ag- and Mn-catalyzed ring-opening processes of cyclopropanols and cyclobutanols in conjunction with fluorination, azidation and alkynylation reactions.[8c-8f] Furthermore, Chiba and coworkers reported the sequential Mn-catalyzed ring opening of cyclopropanols and cycloaddition of vinylazides for the synthesis of heterocycles.[8g-8h] However, owing to the highly reactive carbon-centered radical, it is extremely difficult to achieve the stereoselective control of radical speices **int-IV**. Thus far, asymmetric radical ring opening of cyclopropanols has not been reported.




***Scheme 1.*** Transition metal-catalyzed ring opening of cyclopropanols.

As part of our ongoing programs focused on transition metal-catalyzed asymmetric radical transformations (ARTs),[9] we have demonstrated a Cu-catalyzed radical relay process for the asymmetric

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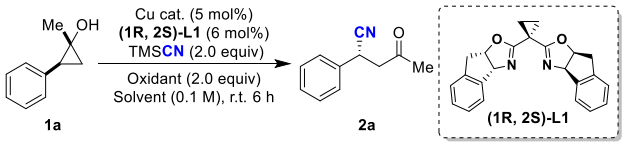
10.1002/adsc.202000202



functionalizations of styrenes,[10]benzylic[11] and allylic C–H bond,[12] in which the *in situ* generated benzylic radicals can be captured by chiral Cu(II) intermediates to construct new chemical bonds with excellent enantioselectivity. We reasoned that, if a L*Cu(I)/oxidant system could be designed to trigger the oxidation of cyclopanols **1** to **int-III**, the generated benzylic radical **int-IV** might be captured by chiral Cu(II) cyanide to give enantiomerically enriched *β-carbonyl nitriles* **2** (Scheme 1b).[13] Herein, we communicates our results as the first asymmetric system for radical ring opening of cyclopropanols .

***Table 1.*** Optimization of the reaction parameters[a,b,c]



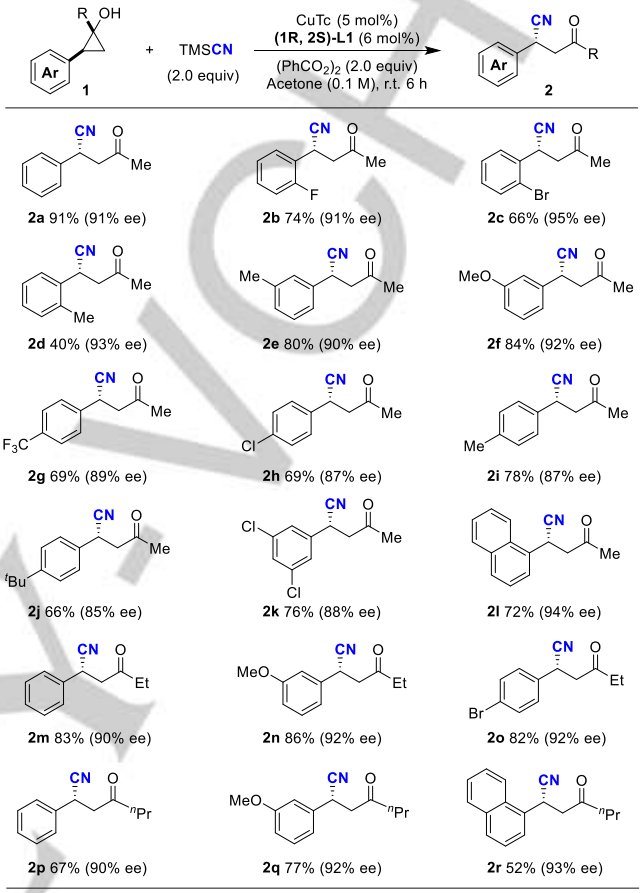

| Entry | Cu cat. | Solvent | Oxidant | **2a** Yield[b] (ee)[c] |
|---|---|---|---|---|
| 1 | $Cu(CH_3CN)_4PF_6$ | $CH_3CN$ | $PhCO_3{}^tBu$ | 0 |
| 2 | $Cu(CH_3CN)_4PF_6$ | $CH_3CN$ | $(^tBuO)_2$ | 0 |
| 3 | $Cu(CH_3CN)_4PF_6$ | $CH_3CN$ | $PhI(OAc)_2$ | 49% (82%) |
| 4 | $Cu(CH_3CN)_4PF_6$ | $CH_3CN$ | SelectFluor | 54% (38%) |
| 5 | $Cu(CH_3CN)_4PF_6$ | $CH_3CN$ | NFSI | 70% (39%) |
| 6 | $Cu(CH_3CN)_4PF_6$ | $CH_3CN$ | BPO | 97% (82%) |
| 7 | $CuBr{\cdot}SMe_2$ | $CH_3CN$ | BPO | 75% (85%) |
| 8 | $CuBr{\cdot}SMe_2$ | Acetone | BPO | 94% (91%) |
| 9 | CuTc | Acetone | BPO | 99% (91%) |

[a] All reactions were run on 0.1 mmol scale; [b] Crude $^1H$ NMR yield with $CF_3$-DMAc as internal standard; [c] Enantiomeric excess (ee) was determined by HPLC on a chiral stationary phase. Cu(Tc) = copper(I)-thiophene-2-carboxylate; BPO = benzoyl peroxide.

On the basis of our mechanistic hypothesis, the initial study was focused on the reaction of cyclopropanol **1a**. First, a series of oxidants were tested in the presence of $[Cu(MeCN)_4]PF_6$ and chiral ligand **(1*R*, 2*S*)-L1** as the catalyst and trimethylsilyl cyanide (TMSCN) as the cyanation reagent. As shown in Table 1, the reaction with $PhCO_3{}^tBu$ and $(^tBuO)_2$ did not proceed with the substrate being quantitatively recovered (entries 1-2). We were delighted to find that, hypervalent iodine $PhI(OAc)_2$ was effective to promote the reaction, and the desired product **2a** was obtained in 49% yield with 82% ee, along with a byproduct benzalacetone (entry 3). Electrophilic fluorination reagents, such as N-fluorobenzenesulfonimide (NFSI) or selectfluor, were also suitable oxidants for this reaction, but gave poor enantioselectivities (38 or 39% ee, entries 4-5). Encouragingly, when benzoyl peroxide (BPO) was used as the oxidant, the reaction provided **2a** in a nearly quantitative yield with good enantioselectivity (82% ee, entry 6). Evaluation of different copper catalysts indicated that enantiomeric excess could be slightly improved to 85% ee by using $CuBr{\bullet}SMe_2$ (entry 7). Solvent screening revealed that the enantiomeric excess was further improved to 91% ee in acetone (entry 8). The best result was obtained in the presence of 5 mol% of CuTc (Tc = thiophene-2-carboxylate) in acetone, in which case **2a** was produced in 99% yield with 91% ee (entry 9). The absolute configuration of the cyanation product **2a** was assigned as an ***R*** isomer based on the comparation of specific rotation with the literature value (see SI).

With the optimized reaction conditions in hand, we next explored the substrate scope of the reaction. As shown in Table 2, cyclopropanols with both electron-rich and electron-deficient aryl groups were compatible to the reaction conditions, furnishing a variety of β-cyano ketones in good to excellent yields (up to 91% yield) with excellent ee values (up to 95%). For instance, when substrates have an *ortho*-substituent in the aryl ring, the reactions exhibited a better enantioselectivities (91-95% ee) to give **2b-2d** in moderate to good yields (40-74%). When a substituent was introduced to the *meta*- or *para*-position of the aryl ring, the reaction performed similarly as **1a** to give the corresponding cyanation products **2e-2j** in 66-84% yields with 85-92% ee. Moreover, a substrate with 3,5-dichlorobenzene ring also proceeded well, providing **2k** in good yield and enantioselectivity. Cyclopropanol bearing a naphthalene ring was also a viable substrate

***Table 2.*** Scope of cyclopropanols.[a,b]




[a] All reactions were run on 0.3 mmol scale; [b] Isolated yields and Enantiomeric excess (ee) values were determined by HPLC on a chiral stationary phase.

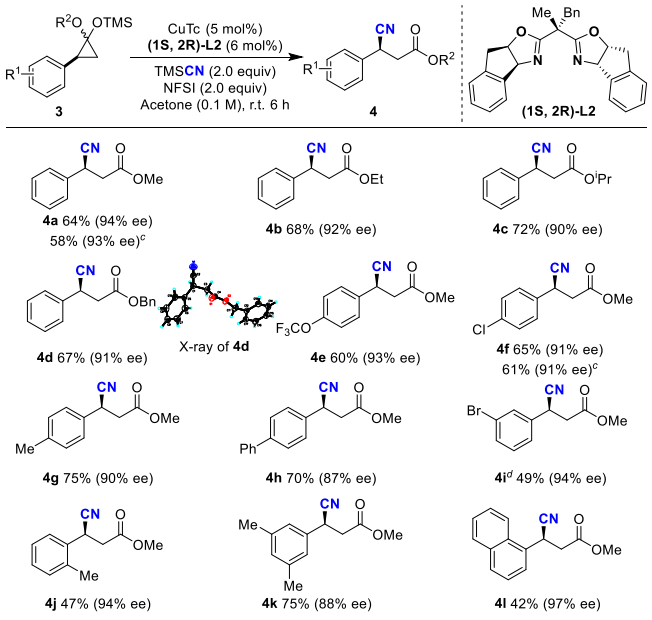
for the reaction, giving **2l** in 72% yield with 94 % ee. Finally, apart from cyclopropanols with a methyl group at the C-1 position, substrates with other aliphatic groups, such as ethyl and *n*-propyl, also reacted smoothly and yielded the target compounds **2m-2r** in good yields (52-86%) with excellent enantioselectivities (90-93% ee). Notably, various functional groups, such as halides, ether and trifluoromethyl group, were tolerated under the reaction conditions.

The aforementioned results confirmed that it was possible to use copper-catalyzed radical relay strategy for the asymmetric cyanation of cyclopropanols via a radical ring-opening process, and β-cyanoketones with various structures could be obtained with good to excellent enantioselectivities. We then turned our attention to investigating the cyanation of cyclopropanone acetals for the efficient synthesis of optically active β-cyanoesters.

The acetal **3a** was initially used for reaction optimization, and it became clear that the previous reaction conditions needed to be slightly modified as follows: (1) for a higher enantioselectivity, bis(oxazoline) **(1*S*, 2*R*)-L2** bearing geminal benzyl and methyl groups should be employed; (2) NFSI should be used as the oxidant as it performed better than BPO (For details, see SI). As shown in Table 3, a large number of cyclopropanone acetals showed excellent reactivities to give β-cyano propanoic esters **4a-4d** in good yields (64-72%) with excellent enantioselectivities (90-94% ee). In general, our protocol accommodated a broad range of cyclopropanone acetals containing electron-poor (**4e-4f**) or electron-rich aryl groups (**4g-4k**), delivering

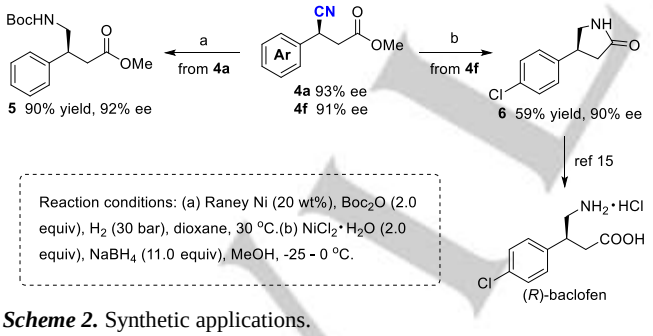
enantiomerically enriched esters with a high level of stereocontrol (87-97% ee). The absolute configuration of **4d** was determined to be ***S*** by X-ray crystallography.[14]

***Table 3.*** Scope of cyclopropanone acetals.[a,b]



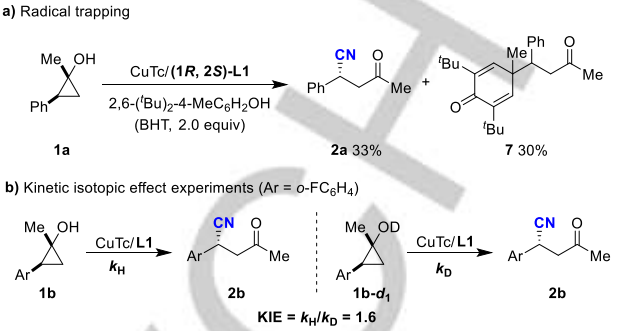

[a] All reactions were run on 0.3 mmol scale; [b] Isolated yields and enantiomeric excess (ee) values were determined by HPLC on a chiral stationary phase; [c] The reaction was run on gram scale with 1 mol% catalyst; [d] Reaction was run on 0.2 mmol scale.

To demonstrate the synthetic utility of this asymmetric cyanation method, the gram-scale reactions of **3a** and **3f** were conducted. The copper catalyst loading could be reduced to 1 mol %, and these reactions proceeded smoothly to afford **4a** and **4f** in 58% yield (93% ee) and 61% yield (91% ee), respectively (Table 3). In addition, selective hydrogenation of **4a** afforded the chiral γ-amino acids derivatives **5** in 90% yield (92% ee).[15] Reductive cyclization of **4f** followed by hydrolysis of the **6** represented a short 3-step synthesis of (R)-baclofen,[16] an inhibitory neurotransmitter as a GABA receptor agonist (Scheme 2).




***Scheme 2.*** Synthetic applications.

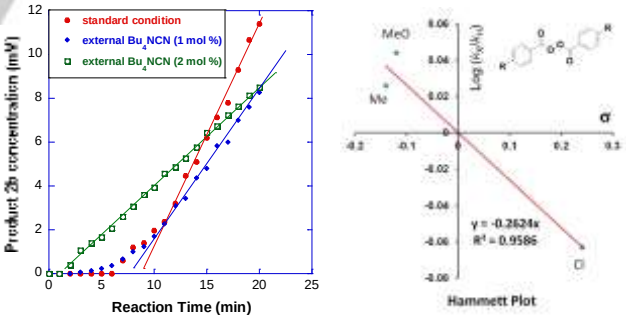
Recently, Dai and coworkers reported copper-catalyzed trifluoromethylation and amination of cyclopropanols, in which β-carbon elimination of the cyclopropanoxide $Cu^{II}$ complex **int-I** was proposed to be responsible for the C–C bond cleavage.[17] In that particular system, radical scavengers such as TEMPO exhibited a negligible effect on the reaction. In contrast, our reaction was completely inhibited by TEMPO (see SI) and the product yield diminished significantly by the addition of 2,6-($^t$Bu)$_2$-4-Me$C_6H_2$OH (BHT). In the latter case, the benzylic radical was captured by BHT to give the product **7** in 30% yield (Scheme 3a). These observations supported a radical ring-opening pathway for our reaction.




***Scheme 3.*** Control experiments and mechanistic studies.

For the radical ring opening of cyclopropanols, previous studies by Depuy and coworkers showed a significant kinetic isotope effect (KIE = $k_H/k_D$ ranged from 3.6 to 6.6) due to direct hydrogen atom abstraction.[18] However, a small kinetic isotopic effect (KIE = 1.6) was obtained by comparing the rates for the individual reactions of **1b** and **1b-$d_1$** (Scheme 3b), indicating that the direct hydrogen atom abstraction process was less likely involved in our reaction.

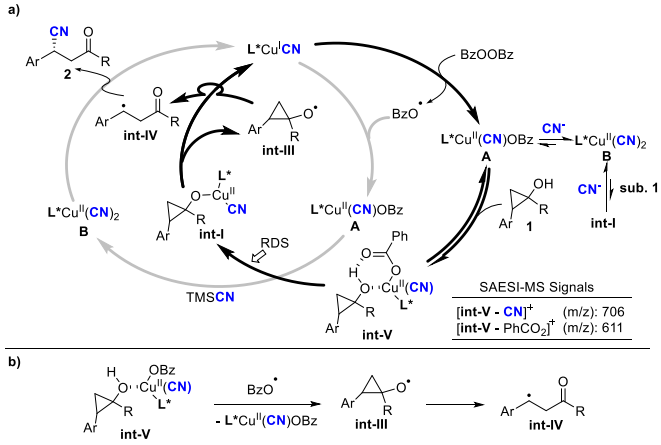
Similar to our previous studies of asymmetric cyanation of alkenes,[10a] a induction period was observed in the reaction of **1b**, which could be shortened by adding 1 mol % $Bu_4NCN$ and eliminated with 2 mol % $Bu_4NCN$. However, the reaction rate was significantly decreased in both cases (Figure 2a), suggesting that the reaction could be inhibited in the presence of excess cyanide. In addition, when the catalytic reaction was monitored by *in situ* SAESI-MS spectroscopy, signals at m/z 706 and 611 were detected (see SI), possibly which were [(**int-V**) - CN] and [(**int-V**) - BzO] (for the structure of **int-V**, see Scheme 4a). Taken together these observations, the complex **int-V** is likely to be involved in the catalytic cycle, and the following O–H bond cleavage from **int-V** partially contributes to the rate-determining step.




***Firure 2***. a) Effect of cyanide on the reaction of **1b** (2 mol% copper catalyst) by adding $Bu_4NCN$ (0-2 mol %) externally (left); b) Electronic effect of aryl acylperoxides (right).

Based on above analysis and our previous studies, [10a] a plausible mechanism for the enantioselective cyanation of cyclopropanols is outlined in Scheme 4a. The reaction is initiated by a (**L***)$Cu^{I}$CN species, which can be oxidized by BPO to give the copper(II) species **A**. Cyclopropanol **1** then coordinates to the copper center of **A**, before intramolecular deprotonation occurs with **int-V** to yield a key intermediate **int-I**.[19] After homolytic cleavage of O–$Cu^{II}$ bond of **int-I**,[20] the generated cyclopopoxy radical **int-III** undergoes rapid ring-opening to generate a distal benzylic radical **int-IV**. Meanwhile, the active radical species BzO•, generated from initial SET process,[21] is

trapped by (**L***)$Cu^{I}$(CN) to form another copper(II) complex **A**,[22] which reacts with TMSCN to give (**L***)$Cu^{II}(CN)_2$ (**B**). Finally, the benzylic radical **int-IV** is stereoselectively captured by **B** to yield the desired product **2** with a high level of enantioselective control. [10a, 11] Under this mechanistic scenario, owing to the strong binding of cyanide, copper complex **A** can be converted to **B** quickly in the presence of exogenous cyanide, but also exhibits slower coordination and deprotonation to give the key intermediate **int-I**, resulting in a decrease in overall reaction rate (Figure 2a).




***Scheme 4***. Proposed mechanism.

Alternatively, complex **int-V** could undergo direct hydrogen atom abstraction of **int-V** by BzO• to give the key cyclopropoxy radical **int-III** (Scheme 4b). To differentiate these two possible pathways (a versus b in Scheme 4), several substituted aryl acylperoxides were employed to test the electronic effect of the oxidants, and a small negative ρ-value (-0.26) was observed from the Hammett plot, suggesting that complex **int-V** with an electron-rich $ArCO_2$ group reacts more rapidly than that with an electron-poor $ArCO_2$ group. We prefer the pathway in Scheme 4a because the intramolecular deprotonation of **int-V** O-H moiety by the inner base $ArCO_2$ (Scheme 4a) should be entropic more favorable. It is also more consistent with the observed small Hammett ρ-value and relatively small KIE value (1.6).[23]

In conclusion, we have demonstrated that a copper-catalyzed radical relay strategy can be successfully applied to enantioselective ring-opening of cyclopropanols and cyclopropanone acetals. This has led to a practical and streamlined approach to chiral β-carbonyl nitriles that are key synthons in organic synthesis. The mechanistic details and further applications based on this new process are ongoing efforts in our laboratories.

## Acknowledgements

We are grateful for financial support from the National Nature Science Foundation of China (Nos. 21532009, 21472217, 21790330 and 21728201), the Science and Technology Commission of Shanghai Municipality (Nos. 17QA1405200 and 17JC1401200), and the strategic Priority Research Program (No. XDB20000000) and the Key Research Program of Frontier Science (QYZDJSSW-SLH055) of the Chinese Academy of Sciences.

**Keywords:** asymmetric radical reaction • radical ring-opening • cyclopropanol • copper-catalyzed radical relay • β-carbonyl nitriles

[1] For leading references, see: a) F. F. Fleming, *Nat. Prod. Rep.* **1999**, *16*, 597. b) F. F. Fleming, L. Yao, P. C. Ravikumar, L. Funk, B. C. Shook, *J. Med. Chem.* **2010**, *53*, 7902.
[2] For leading references, see: Science of Synthesis; Murahashi, S.-I., Ed.; Georg Thieme Verlag: Stuttgart, Germany, **2004**; Vol. *19*.
[3] For leading references, see: a) D. Enders, O. Niemeier, *Heterocycles*. **2005**, *66*, 385. b) A. Fryszkowska, K. Fisher, J. M. Gardiner, G. M. Stephens, *Org. Biomol. Chem.*, **2010**, *8*, 533.
[4] a) G. M. Sammis, E. N. Jacobsen, *J. Am. Chem. Soc.* **2003**, *125*, 4442. b) Y. Tanaka, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2008**, *130*, 6072. c) M. Hatano, K. Yamakawa, K. Ishihara, *ACS Catal.* **2017**, *7*, 6686.
[5] a) S. Debarge, P. McDaid, P. OÏNeill, J. Frahill, J. W. Wong, D. Carr, A. Burrell, S. Davies, M. Karmilowicz, J. Steflik, *Org. Process Res. Dev.* **2014**, *18*, 109. b) E. Brenna, M. Crotti, F. G. Gatti, D. Monti, F. Parmeggiani, R.W. Powell III, S. Santangelo, J. D. Stewart, *Adv. Synth. Catal.* **2015**, *357*, 1849.
[6] J. Choi, G.C. Fu, *J. Am. Chem. Soc.* **2012**, *134*, 9102.
[7] For selected examples, see: a) P. P. Das, K. Belmore, J. K. Cha, *Angew. Chem. Int. Ed.* **2012**, *51*, 9517. b) D. G. Kananovich, Y. A. Konik, D. M. Zubrytski, I. Järvinga, M. Lopp, *Chem. Commun.*, **2015**, *51*, 8349. c) T. Seiser, T. Saget, D. N. Tran, N. Cramer, *Angew. Chem. Int. Ed.* **2011**, *50*, 7740. d) T. Nishimura, S. Matsumura, Y. Maeda, S. Uemura, *J. Am. Chem. Soc.* **2003**, *125*, 8862. e) T. Seiser, N. Cramer, *J. Am. Chem. Soc.* **2010**, *132*, 5340. f) J. Yang, Q. Sun, N. Yoshikai, *ACS Catal.* **2019**, *9*, 1973. g) L. R. Mills, C. H. Zhou, E. Fung, S. A. L. Rousseaux, *Org. Lett.* **2019**, *21*, 8805.
[8] For metal-mediated ring-opening of cyclopropanols via a radical process, see: a) K. Meyer, J. Rocek, *J. Am. Chem. Soc.* **1972**, *94*, 1209; b) N. Iwasawa, S. Hayakawa, M. Funahashi, K. Isobe, K. Narasaka, *Bull. Chem. Soc. Jpn.* **1993**, *66*, 819. For recent catalytic examples, see: c) H. Zhao, X. Fan, J. Yu, C. Zhu, *J. Am. Chem. Soc.* **2015**, *137*, 3490; d) R. Ren, H. Zhao, L. Huan, C. Zhu, *Angew. Chem., Int. Ed.*, **2015**, *54*, 12692; e) R. Ren, Z. Wu, Y. Xu, C. Zhu, *Angew. Chem., Int. Ed.*, **2016**, *55*, 2866; f) X. Fan, H. Zhao, J. Yu, X. Bao, C. Zhu, *Org. Chem. Front.*, **2016**, *3*, 227; g) Y. Wang, S. Chiba, *J. Am. Chem. Soc.* **2009**, *131*, 12570; h) Y. Wang, K. K. Toh, E. P. J. Ng, S. Chiba, *J. Am. Chem. Soc.* **2011**, *133*, 6411; i) A. Ilangovan, S. Saravanakumar, S. Malayappasamy, *Org. Lett.* **2013**, *15*, 4968; j) F. Huang, J. Xie, J. Sun, Y. Wang, X. Dong, L. Qi, B. Zhang, *Org. Lett.* **2016**, *18*, 684; k) S. Ren, C. Feng, T.-P. Loh, *Org. Biomol. Chem.* **2015**, *13*, 5105; l) X.-P. He, Y.-J. Shu, J.-J. Dai, W.-M. Zhang, Y.-S. Feng, H.-J. Xu, *Org. Biomol. Chem.*, **2015**, *13*, 7159; m) Y.-S. Feng, Y.-J. Shu, P. C, T. Xu, H.-J. Xu, *Org. Biomol. Chem.*, **2017**, *15*, 3590.
[9] For selected reviews, see: a) F. Wang, P. Chen, G. Liu, *Acc. Chem. Res.* **2018**, *51*, 2036. b) G. C. Fu, *ACS Cent. Sci.*, **2017**, *3*, 692. c) U. Jahn, *Top. Curr. Chem.* **2011**, *320*, 323. d) Coupling Reactions between sp3 and sp2 carbon centers. In Comprehensive Organic Synthesis; G. Manolikakes, P. Knochel, G. A. Molander, Eds.; Elsevier: Amsterdam, **2014**; Vol. *3*, pp 392. e) Q.-S. Gu, Z.-L. Li, X.-Y. Liu, *Acc. Chem. Res.* **2020**, *53*, 170. For elegant examples, see: f) X.-Y. Dong, Y.-F. Zhang, C.-L. Ma, Q.-S. Gu, F.-L. Wang, Z.-L. Li, S.-P. Jiang, X.-Y. Liu, *Nat. Chem.* **2019**, *11*, 1158. g) Z. Wang, H. Yin, G. C. Fu, *Nature* **2018**, *563*, 379. h) N. D. Schley, G. C. Fu, *J. Am. Chem. Soc.* **2014**, *136*, 16588.
[10] For the asymmetric cyanation, see: a) F. Wang, D. Wang, X. Wan, L. Wu, P. Chen, G. Liu, *J. Am. Chem. Soc.* **2016**, *138*, 15547; b) D. Wang, F. Wang, P. Chen, Z. Lin, G. Liu, *Angew. Chem., Int. Ed.* **2017**, *56*, 2054. For the asymmetric arylation, see: c) L. Wu, F. Wang, X. Wan, D. Wang, P. Chen, G. Liu, *J. Am. Chem. Soc.* **2017**, *139*, 2904; d) D. Wang, L. Wu, F. Wang, X. Wan, P. Chen, Z. Lin, G. Liu, *J. Am. Chem. Soc.* **2017**, *139*, 6811; e) L. Wu, F. Wang, P. Chen, G. Liu, *J. Am. Chem. Soc.* **2019**, *141*, 1887. f) J. Li, Z. Zhang, L. Wu, W. Zhang, P. Chen, Z. Lin, G. Liu, *Nature* **2019**, *574*, 516. For the asymmetric alkynylation, see: g) L. Fu, S. Zhou, X. Wan, P. Chen, G. Liu, *J. Am. Chem. Soc.* **2018**, *140*, 10965. For enantioselective decarboxylative cyanation, see: h) D. Wang, N. Zhu, P. Chen, Z. Lin, G. Liu, *J. Am. Chem. Soc.* **2017**, *139*, 15632.
[11] W. Zhang, F. Wang, S. D. McCann, D. Wang, P. Chen, S. S. Stahl, G. Liu, *Science* **2016**, *353*, 1014.
[12] J. Li, Z. Zhang, L. Wu, W. Zhang, P. Chen, Z. Lin, G. Liu, *Nature* **2019**, *574*, 516.
[13] It should be highlighted that Wang and coworkers just reported an elegant enantioselective cyanation via radical-mediated C–C single bond cleavage of cyclopentanone (cyclobutanone) oxime ester, please see: T. Wang, Y.-N. Wang, R. Wang, B.-C. Zhang, C. Yang, Y.-L. Li, X.-S. Wang, *Nat. Commun.* **2019**, *10*, 5373.
[14] CCDC 1988457 [(*S*)-**4d**] contain the supplementary crystallographic data, which can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc. cam.ac.uk/services/structure_deposit/cif.
[15] a) K. M. Brown, K. K. Roy, G. H. Hockerman, R. J. Doerksen, D. A. Colby, *J. Med. Chem*, **2015**, *58*, 6336; b) G. Costantino, A. Macchiarulo, A. E. Guadix, R. Pellicciari, *J. Med. Chem.* **2001**, *44*, 1827; c) R. B. Silverman, R. Andruszkiewicz, S. M. Nanavati, C. P. Taylor, M. G. Vartaniant, *J. Med. Chem.*, **1991**, *34*, 2298.
[16] a) H. R. Olpe, H. Demiéville, V. Baltzer, W. L. Bencze, W. P. Koella, P. Wolf, H. L. Haas, *Eur. J. Pharmacol.* **1978**, *52*, 133; b) N. G. Bowery, *Trends Pharmacol. Sci.* **1982**, *3*, 400; c) D. I. B. Kerr, J. Ong, *Med. Res. Rev.* **1992**, *12*, 593; d) J. Ong, D. I. S. Kerr, D. J. Doo-lette, R. K. Duke, K. N. Mewett, R. D. Allen, G. A. R. Johnson, *Eur. J. Pharmacol.* **1993**, *233*, 169; e) C. Shao, H.-J. Yu, N.-Y. Wu, P. Tian, R. Wang, C.-G. Feng, G.-Q. Lin, *Org. Lett.* **2011**, *13*, 788; f) Q.-W. Lang, G.-X. Gu, Y.-T. Cheng, Q. Yin, X.-M. Zhang, *ACS Catal.* **2018**, *8*, 4824; g) F.-Y. Zhang, E. J. Corey, *Org. Lett.* **2000**, *2*, 4257.

10.1002/adsc.202000202



[17] a) Z. Ye, M. Dai, *Org. Lett.* **2015**, *17*, 2190; b) Y. Li, Z. Ye, T. M. Bellman, T. Chi, M. Dai, *Org. Lett.* **2015**, *17*, 2186; c) Z. Ye, K. E. Gettys, X. Shen, M. Dai, *Org. Lett.* **2015**, *17*, 6074.
[18] C. H. DePuy, H. L. Jones, W. M. Moore, *J. Am. Chem. Soc.* **1973**, *95*, 477.
[19] For intramolecular base assisted deprotonation, see: a) S. L. Gorelsky, D. Lapointe, K. Fagnou, *J. Am. Chem. Soc.* **2008**, *130*, 10848; b) A. D. Ryabov, *Chem. Rev.* **1990**, *90*, 403; c) L. Ackermann, R. Vicente, A. R. Kapdi, *Angew. Chem., Int. Ed.* **2009**, *48*, 9792.
[20] E. Hasegawa, M. Tateyama, R. Nagumo, E. Tayama, H. Iwamoto. *Beilstein J. Org. Chem.* **2013**, *9*, 1397.
[21] A small amount of benzene was detected by GC-MS, providing another pieces of evidence to support the involvement of benzoic radical, which could undergo decarboxylation to give phenyl radical followed by hydrogen atom abstraction from acetone to form benzene. For details, see SI.
[22] R. T. Gephart III, C. L. McMullin, N. G. Sapiezynski, E. S. Jang, M. J. B. Aguila, T. R. Cundari, T. H. Warren, *J. Am. Chem. Soc.* **2012**, *34*, 17350.
[23] Small kinetic isotope effects (KIEs) and Hammett ρ-values have been observed in other intramolecular base assisted deprotonation processes, see: a) D. L. Davies, S. M. A. Donald, S. A. Macgregor, *J. Am. Chem. Soc.* **2005**, *127*, 13754; b) A. D. Ryabov, I. K. Sakodinskaya, A. K. Yatsimirsky, *J. Chem. Soc., Dalton Trans.* **1985**, 2629.

10.1002/adsc.202000202

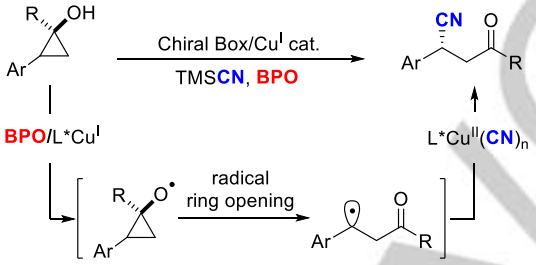
**Very Important Publication** **COMMUNICATION**

**Entry for the Table of Contents** (Please choose one layout)

Layout 1:

## COMMUNICATION

Novel enantioselective cyanation of cyclopropanols and their derivatives has been developed via copper-catalyzed radical relay processes. Various cyclopropanols and cyclopropanone acetals are employed to provide β-carbonyl nitriles with excellent enantioselectivity. Preliminary mechanistic studies suggest that the reaction involves radical ring-opening of cyclopropanols followed by copper-catalyzed enantioselective cyanation of benzylic radicals.




*L. Wu, L, Wang, P. Chen, Y.-L. Guo, H. Guan,* G. Liu**

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**Title**
Enantioselective Copper-Catalyzed Radical Ring-Opining Cyanation of Cyclopropanols and Cycloproanone Acetals