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Cu-catalyzed cyanomethylation of imines and α,β -alkenes with acetonitrile and its derivatives†

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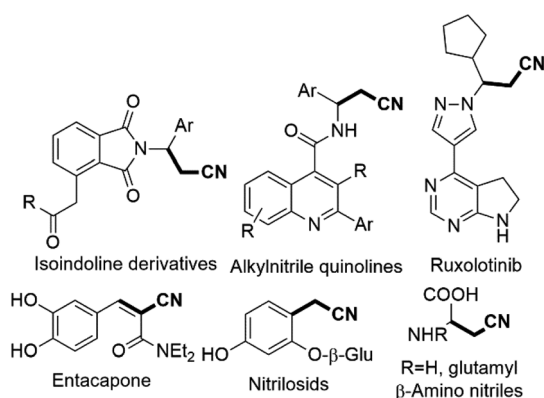
We describe copper-catalyzed cyanomethylation of imines and α,β -alkenes with a methyl nitrile source and provide an efficient route to synthesize acrylonitriles and β,γ -unsaturated nitriles. This method tolerates aliphatic and aromatic alkenes substituted with a variety of functional groups such as F, Cl, Br, Me, OMe, *tert*-Bu, NO₂, NH₂ and CO₂H with good to excellent yields (69–98%). These systems consist of inexpensive, simple copper catalyst and acetonitrile with its derivatives (α -bromo/ α -iodo-acetonitrile) and are highly applicable in the industrial production of acrylonitriles.

Introduction and importance

Acrylonitrile and cyanomethyl are versatile functional units found in many dyes, herbicides, agrochemicals, pharmaceuticals, and natural products.¹ For example, β,γ -unsaturated nitriles are found in natural products such as alkanenitriles, β -amino nitriles, nitrilosids (Scheme 1).² The biologically active ruxolitinib, alkyl nitrile and acrylonitrile containing entacapone are also shown in Scheme 1.² These β,γ -unsaturated nitriles and alkenyl nitriles are also key structural units as antifungal agents and vitamin D receptor.³ Besides, the cyano group serves as a valuable intermediate for transformation into aldehydes, amines, amides, tetrazoles, and carboxyl derivatives.² A lot of

approaches for the synthesis of β,γ -unsaturated nitriles have been progressed in recent decades.⁴ However, the cyanation of allyl substrates containing leaving groups such as carbonate, or ester alcohol, halide, acetate, phosphate, are frequently used in the transformation into β,γ -unsaturated nitriles.^{4a-f} Our many efforts have been paid attention in developing non-toxic and slow-releasing cyano-methyl reagents like alkyl nitriles, especially acetonitrile. However, due to its high pK_a value [pK_a (CH₃CN) = 31.3 in DMSO], relatively difficult to be used as a nucleophile. The catalytic C–H bond activation of acetonitrile by transition metals has rarely been explored in last decades.^{2b} A few strategies has been reported for cyano-methylation by using acetonitrile for various substrates such as phenazines, 2,2,6,6-tetramethylpiperidine, C₂-quaternary indolin-3-ones, cyclo-alkene, simple arenes, aryl-ketone, diarylethenes, azoles, aldehydes, aliphatic amides, allylic alcohols, diazonium salts, arylacrylamides, alkenes, 1,3-dicarbonyls, benzaldehyde and coumarins substrates.⁵

Consequently, the reactivity of imines have been rarely explored for chiral cyanomethyl product by transfer of hydrogen atom.⁶ However, synthesis of phenylacrylonitriles from imines not yet explored so far (Scheme 2).⁷ A number of pharmaceutical reagents contain α,β -unsaturated cyanide moiety such as entacapone and rilpivirine, which can be used as anti-Parkinson's and anti-HIV agents.²



Scheme 1 The natural with biologically active alkyl nitriles and acrylonitriles.

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This work



Scheme 2 Our Cu-catalyzed cyanomethylation of aromatic imines and styrenes.



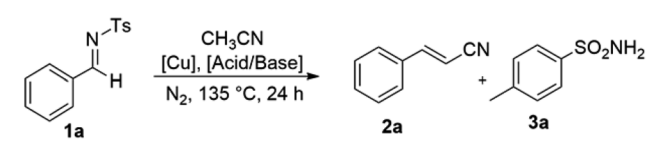
Results and discussion

For this copper-catalyzed cyanomethylation of aromatic imines with green MeCN solvent, we used (*E*)-*N*-benzylidene-4-methylbenzenesulfonamide (**1a**) as a model substrate (Table 1). The compound **1a** was treated with Cu(OAc)₂ (20 mol%) and HOAc (1.0 eq.) under N₂ atmosphere at 135 °C, which gave cyano-methylated product (**2a**) in 10% yield (Table 1, entry 1). Moreover, the amination occurs and 4-methylbenzenesulfonamide obtained as directing auxiliary (**3a**) with low yield (11%) and decomposition of remaining substrate into complex mixture (Table 1, entry 1). For further week acid screening such as HCO₂H and alcohols (*t*-BuOH, *i*-PrOH) were elaborated low to mild yields (10–39%) (Table 1, entries 2–4). However, strong acid (HCl) unable to produce desired product (Table 1, entry 5). To further explore the reaction parameters, a variety of boronated bases such as KO^tBu^t, NaO^tBu^t, LiO^tBu^t and Cs₂CO₃ were screened. However, these bases are not suitable for reaction and gave the product (**2a**) in lower to medium yields (25–51%) (Table 1, entries 6–9). Importantly, Cu(OAc)₂ evaluated 98% yield of phenylacrylonitrile (**2a**) with more than 99% of directing auxiliary (4-methylbenzenesulfonamide) in the absence of additive and base or acid (Table 1, entry 10). For further Cu catalyst optimization, a wide variety of Cu(II) catalysts such as Cu(OTf)₂, Cu(ClO₄)₂, Cu(C₂H₅O₂)₂, CuCl₂, and Cu(I)

catalysts (CuI, CuBr, CuCl) were screened (Table 1, entries 11–17).

To our delight, these Cu(II) catalysts have good reactivity, which gave the corresponding alkenyl cyanated product (**2a**) in 31% to 79% yield (Table 1, entries 11–14). Moreover, copper(I) halides (I, Br and Cl) catalytic system such as CuI, CuBr and CuCl elaborated cyanomethyl products in 63%, 58% and 46% (Table 1, entries 15–17) respectively. Gratifyingly, all these copper catalysts have worse reactivity than the commercially abundant Cu(OAc)₂ which produced good yield of phenylacrylonitrile (**2a**) product. In this context, a various quantities of Cu(OAc)₂ such as 5 mol%, 10 mol%, 15 mol%, 25 mol% and 30 mol% were examined to find best quantity of Cu(OAc)₂ as catalyst (Table 1, entries 18–22). Notably, the yields of desired product (**2a**) dramatically varied when using 5 mol%, 10 mol%, 15 mol%, 25 mol% and 30 mol% of Cu(OAc)₂ (Table 1, entries 18–22). For example, 62% to 98% yields were obtained by using wide range of quantities for the Cu(OAc)₂, instead of 20 mol% (Table 1, entries 18–22). After optimization, we elaborate the scope of substrate by varying the substituent on the *N*-benzylidene-4-methylbenzenesulfonamide (Scheme 3). A variety of *N*-benzylidene-4-methylbenzenesulfonamide (**1a–1d**) with electron-donating group such as Me, OMe, *tert*-butyl at para position of benzene ring afforded the corresponding desired products (**2a–2d**) in 75% to 98% yields (Scheme 3).

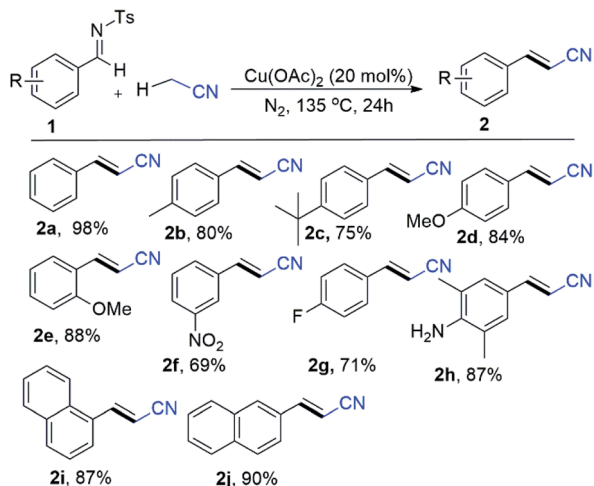
Table 1 Optimization of conditions for imine using CH₃CN.^{a,b}



| Entry | [Acid/base] | [Cu(X) _n] | [Cu quant.] | Yield 2a ^b (%) | Yield 3a ^b (%) |
|-------|---------------------------------|--|-------------|----------------------------------|----------------------------------|
| 1 | HOAc | Cu(OAc) ₂ | 20 mol% | 10 | 11 |
| 2 | HCO ₂ H | Cu(OAc) ₂ | 20 mol% | 10 | 36 |
| 3 | <i>t</i> -BuOH | Cu(OAc) ₂ | 20 mol% | 46 | 51 |
| 4 | <i>i</i> -PrOH | Cu(OAc) ₂ | 20 mol% | 39 | 55 |
| 5 | HCl | Cu(OAc) ₂ | 20 mol% | 0 | n.d |
| 6 | KO ^t Bu | Cu(OAc) ₂ | 20 mol% | 51 | 60 |
| 7 | NaO ^t Bu | Cu(OAc) ₂ | 20 mol% | 41 | 53 |
| 8 | LiO ^t Bu | Cu(OAc) ₂ | 20 mol% | 25 | 40 |
| 9 | Cs ₂ CO ₃ | Cu(OAc) ₂ | 20 mol% | 28 | 49 |
| 10 | None | Cu(OAc) ₂ | 20 mol% | 98 | >99 |
| 11 | None | Cu(OTf) ₂ | 20 mol% | 31 | 47 |
| 12 | None | Cu(ClO ₄) ₂ | 20 mol% | 59 | 71 |
| 13 | None | Cu(C ₂ H ₅ O ₂) ₂ | 20 mol% | 68 | 79 |
| 14 | None | CuCl ₂ | 20 mol% | 79 | 81 |
| 15 | None | CuI | 20 mol% | 63 | 88 |
| 16 | None | CuBr | 20 mol% | 58 | 80 |
| 17 | None | CuCl | 20 mol% | 46 | 59 |
| 18 | None | Cu(OAc) ₂ | 5 mol% | 62 | 74 |
| 19 | None | Cu(OAc) ₂ | 10 mol% | 75 | 83 |
| 20 | None | Cu(OAc) ₂ | 15 mol% | 88 | 91 |
| 21 | None | Cu(OAc) ₂ | 25 mol% | 97 | 99 |
| 22 | None | Cu(OAc) ₂ | 30 mol% | 98 | 99 |

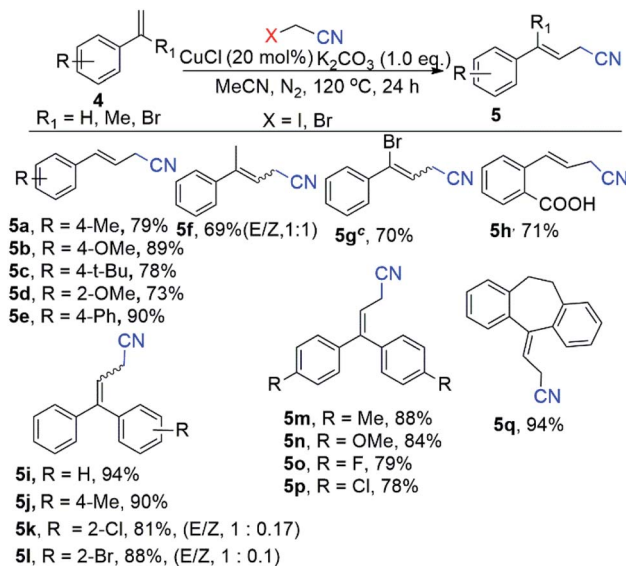
^a Conditions: **1a** (0.2 mmol), Cu(X)_n (Cu-catalysts), acid/base (1.0 eq.), N₂, 135 °C, CH₃CN (1.2 mL), 24 h. ^b Isolated yield. n.d; not determined.





Scheme 3 Substrate scope for imines using CH_3CN .^{a,b} ^aConditions: **1** (0.2 mmol), Cu(OAc)_2 (20 mol%), N_2 , 135°C , CH_3CN (1.2 mL), 24 h. ^bIsolated yield.

In this context, electron-rich methoxy substituent at ortho position of benzene ring such as (*E*)-*N*-(2-methoxybenzylidene)-4-methylbenzenesulfonamide (**1e**) efficiently evaluated the corresponding product (**2e**) in 88% yields (Scheme 3). Gratifyingly, scope of substrate extended to electron sensitive electron functional groups such as nitro (**1f**), fluoro (**1g**) and free amino (**1h**) groups were attached to the benzene of *N*-benzylidene-4-methylbenzenesulfonamide, which worked well and formed aryl-alkenyl cyanated products (**1f–1h**) in 69%, 71% and 87% yields (Scheme 3) respectively. Delightfully, we used the 4-methyl-*N*-(naphthalen-1-ylmethylene)benzenesulfonamide (**1i**) and 2-naphthalene 4-methyl-*N*-(naphthalen-2-ylmethylene) benzenesulfonamide (**1j**) for the Cu-catalyzed cyanomethylation and obtained excellent yields (87% for **1i** and 90% for **1j**) (Scheme 3). Additionally, our optimization shows that the reaction system was significantly improved with CuCl as a catalyst with K_2CO_3 as base at 120°C for styrene derivatives as a substrate with α -haloacetonitriles (α -bromo/ α -iodoacetonitrile) as cyanomethyl source (Scheme 4). In order to elaborate the scope of substrate, a variety of styrenes were examined to get the variety of β,γ -unsaturated nitriles products (Scheme 4). The electron donating substituted styrenes such as *p*-1-methyl-4-vinylbenzene (**4a**), 1-methoxy-4-vinylbenzene (**4b**), 1-(*tert*-butyl)-4-vinylbenzene (**4c**), 1-methoxy-2-vinylbenzene (**4d**) and 4-vinyl-1,1'-biphenyl (**4e**) were allowed 73% to 90% yields of β,γ -unsaturated cyanated products (**5a–5e**) (Scheme 4). Gratifyingly, prop-1-en-2-ylbenzene (**4f**) underwent into desired 4-phenylpent-3-enitrile (**5f**) products with 69% yields and (1 : 1) *E/Z* (Scheme 4). Moreover, by using α -iodo-acetonitrile as cross coupling partner of the (1-bromovinyl)benzene (**4g**) to form 4-bromo-4-phenylbut-3-enitrile (**5g**) in 70% yield (Scheme 4). To our surprise, 2-vinylbenzoic acid (**4h**) gave the corresponding product (*E*)-2-(3-cyanoprop-1-en-1-yl)benzoic acid (**5h**) product with high yield (71%) (Scheme 4). Remarkably, the reaction with 1,1-diphenylethylene (**4i**) worked well and afforded the target product (**5i**) with 94% yield (Scheme 4). Delightfully, when one



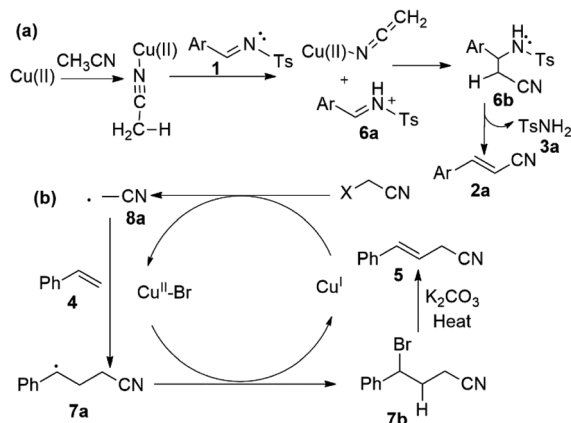
Scheme 4 Substrate scope for styrenes using CH_3CN derivatives.^{a,b} ^aConditions: **4** (0.2 mmol), CuCl (20 mol%), K_2CO_3 (1.0 eq.), bromoacetonitrile (2.0 eq.), N_2 , 135°C , CH_3CN (1.2 mL), 24 h. ^bIsolated yield. ^ciodoacetonitrile (2.0 eq.).

non-fused ring (ethene-1,1-diylidibenzene) was installed with electron donating substituent methyl (**4j**), and electron withdrawing substituents (bromo and chloro) for β,γ -unsaturated products (**5j**, **5k**, **5l**) in good to excellent yields (81–88%) with (1 : 0.17 and 1 : 0.1) *E/Z* respectively. Additionally, both non-fused rings of ethene-1,1-diylidibenzene installed with electron donating substituent methyl (**4m**), methoxy (**4n**), and electron withdrawing substituents bromo (**4o**) and chloro (**4p**) have low impact on the reaction efficiency, resulting β,γ -unsaturated products (**5m** to **5p**) with good to excellent yields (78–88%). Moreover, the product 3-(10,11-dihydro-5*H*-dibenzo[*a,d*][7]annulen-5-ylidene)propanenitrile (**5q**), mainly found in the biological active compounds, could synthesize in our reaction system by allowing cyanomethyl functionalization through a cross-coupling of 5-methylene-10,11-dihydro-5*H*-dibenzo[*a,d*][7]annulene (**4q**) and α -bromo-acetonitrile with 94% yield (Scheme 4).

On the basis of reported mechanistic studies^{8,9} we examined this reaction and propose a possible pathway of reaction as described in Scheme 5. Accordingly, the $\text{C(sp}^3\text{)}\text{–H}$ activation of acetonitrile was possibly promoted by copper species (Scheme 5a).¹⁰ Firstly, cyano of acetonitrile could coordinates with Cu species and speculate that the acetonitrile deprotonated *via* capture of proton by imine substrate (**1**) to generate nucleophile of acetonitrile (Scheme 5a). Further, it can coordinates with proposed **6a** and produces **6b** possible species (Scheme 5a). Moreover, **3a** (methylbenzenesulfonamide) and **2a** (phenylacrylonitrile) could be formed by dehydrogenation and recovered proton transferred to imine (Scheme 5a).

Similarly, bromo-acetonitrile activated by copper metal into radical species **8a** (Scheme 5b). Consequently, substrate (**4**) was converted into **7a** with Cu(I) species through single electron transfer (SET), was observed by adding 2 equivalent of TEMPO,





Scheme 5 Proposed mechanism for Cu-catalyzed cyanomethylation of imines and styrenes.

which abstract a radical hydrogen to form TEMPOH. In addition, TEMPOCH₂CN was isolated and confirmed by NMR and spectra was mentioned in ESI.†

Radical of acetonitrile (**8a**) coupled with substrate (**4**) and generated intermediate **7a** (Scheme 5b). Additionally, this **7a** could be converted into **7b** intermediate by bromide transfer from Cu(II)–Br species (Scheme 5b). This kind of intermediate **7b–1** confirmed by NMR spectroscopy though performing the reaction using 1-chloro-3-vinylbenzene (**4r**) as substrate under our standard conditions and isolated 4-bromo-4-(3-chlorophenyl) butanenitrile (**7b–1**) (ESI).† The Cu(I) completed catalytic cycle and intermediate **7b** or **7b–1** underwent elimination of proton and gave β,γ-unsaturated cyanomethylated product (**5**) in the presence of K₂CO₃ (Scheme 5b). Currently, further mechanistic study is ongoing in our laboratory.

Conclusion

We report copper catalyzed cyanomethylation of imines and α,β-alkenes with acetonitrile (MeCN) and its derivatives for the synthesis of arylacrylonitriles and β,γ-unsaturated nitriles. Moreover, considering the importance of acrylonitrile and β,γ-unsaturated nitriles, this protocol has potential in the industrial production. This method could tolerate a broad scope of substrate with substitution of variety of functional groups led good to excellent yields (69–98%). These aromatic acrylonitriles and β,γ-unsaturated nitriles have application in organic reactions and medicinal chemistry which founded in biologically active products.

Conflicts of interest

There are no conflicts to declare.

Notes and references

- (a) A. Kleemann, J. Engel, B. Kutscher and D. Reichert, *Pharmaceutical Substance: Synthesis, Patents, Applications*, Georg Thieme, Stuttgart, Germany, 4th edn, 2001; (b)

R. C. Larock, in *Comprehensive organic transformations: a guide to functional group preparations*, Wiley-VCH, Weinheim, Germany, 1989, pp. 819–995.

- (a) P. Anbarasan, T. Schareina and M. Beller, *Chem. Soc. Rev.*, 2011, **40**, 5049; (b) M. S. Ahmad, I. N. Pulidindi and C. Li, *New J. Chem.*, 2020, **44**, 17177.
- (a) M. Murakami, T. Kato and T. Mukaiyama, *Chem. Lett.*, 1987, 1167; (b) Y. Hayashi and T. Mukaiyama, *Chem. Lett.*, 1987, 1811; (c) S. Araki, K. Minami and Y. Butsugan, *Bull. Chem. Soc. Jpn.*, 1981, **54**, 629; (d) K. Otaka, D. Oohira and S. Okada, *PCT Int. Appl.*, 2002 WO 2002090320 A2, .
- (a) D. Munemori, H. Tsuji, K. Uchida, T. Suzuki, K. Isa, M. Minakawa and M. Kawatsura, *Synthesis*, 2014, **46**, 2747; (b) A. J. Grenning and J. A. Tunge, *J. Am. Chem. Soc.*, 2011, **133**, 14785; (c) M. N. Soltani Rad, A. Khalafi-Nezhad, S. Behrouz and M. A. Faghihi, *Tetrahedron Lett.*, 2007, **48**, 6779; (d) S. H. Yoneda and T. Kurihara, *J. Org. Chem.*, 1991, **56**, 1827; (e) Y. Tsuji, N. Yamada and S. Tanaka, *J. Org. Chem.*, 1993, **58**, 16; (f) N. W. M. Michel, A. D. M. Jeanneret, H. Kim and S. A. L. Rousseaux, *J. Org. Chem.*, 2018, **83**, 11860; (g) B. Gao, Y. Xie, L. Yang and H. Huang, *Org. Biomol. Chem.*, 2016, **14**, 2399; (h) G. Rong, J. Mao, Y. Zheng, R. Yao and X. Xu, *Chem. Commun.*, 2015, **51**, 13822; (i) F. M. Irudayanathan and S. Lee, *Org. Lett.*, 2017, **19**, 2318; (j) Y. Amako, S. Arai and A. Nishida, *Org. Biomol. Chem.*, 2017, **15**, 1612; (k) L. Bini, C. Müller, J. Wilting, S. A. L. von Chrzanowski and D. Vogt, *J. Am. Chem. Soc.*, 2007, **129**, 12622; (l) H. R. Hoveyda and M. Vézina, *Org. Lett.*, 2005, **7**, 2113; (m) J. M. Concellón, H. Rodríguez-Solla, C. Simal, D. Santos and N. R. Paz, *Org. Lett.*, 2008, **10**, 4549; (n) R. Oda, T. Kawabata and S. Tanimoto, *Tetrahedron Lett.*, 1964, **25**, 1653.
- (a) M. Masui, K. Yamagata, C. Ueda and H. Ohmori, *J. Chem. Soc., Chem. Commun.*, 1985, 272; (b) R. S. Hiriksan, S. Nanjundian and G. S. Virendra, *J. Chem. Soc., Chem. Commun.*, 1990, 1603; (c) T. Yamashita, M. Yasuda, M. Watanabe, R. Kojima, K. Tanabe and K. Shima, *J. Org. Chem.*, 1996, **61**, 6438; (d) T. Michida and Y. Yamaoka, *Chem. Pharm. Bull.*, 1998, **46**, 207; (e) P. Kisanga, M. Dale, D. S. Bosco and V. John, *J. Org. Chem.*, 1999, **64**, 3090; (f) G.-W. Wang, A.-X. Zhou, J.-J. Wang, R.-B. Hu and S.-D. Yang, *Org. Lett.*, 2013, **15**, 5270; (g) H. Yoshida, Y. Fujimura, H. Yuzawa, J. Kumagai and T. Yoshida, *Chem. Commun.*, 2013, **49**, 3793; (h) S. Chakraborty, Y. J. Patel, J. A. Krause and H. Guan, *Angew. Chem., Int. Ed.*, 2013, **52**, 7523; (i) J. Shen, D. Yang, Y. Liu, S. Qin, J. Zhang, J. Sun, C. Liu, C. Liu, X. Zhao, C. Chu and R. Liu, *Org. Lett.*, 2014, **16**, 350; (j) J. Li, Z. Wang, N. Wu, G. Gao and J. You, *Chem. Commun.*, 2014, **50**, 15049; (k) A. Bunesco, Q. Wang and J. Zhu, *Angew. Chem., Int. Ed.*, 2015, **54**, 1; (l) J. B. Smith and A. J. M. Miller, *Organometallics*, 2015, **34**, 4669; (m) C. Pan, H. Zhang and C. Zhu, *Org. Biomol. Chem.*, 2015, **13**, 361; (n) X.-Q. Chu, X.-P. Xu, H. Meng, Y. Zi and S.-J. Ji, *Org. Chem. Front.*, 2015, **2**, 216; (o) X.-Q. Chu, X.-P. Xu, H. Meng and S.-J. Ji, *RSC Adv.*, 2015, **5**, 67829; (p) J. Zhang, W. Wu, X. Ji and S. Cao, *RSC Adv.*, 2015, **5**, 20562; (q) Z. Qin, X. Huang, J. Wang and Y. Pan, *RSC Adv.*, 2015, **6**, 522; (r)



- C. Wang, Y. Li, M. Gong, Q. Wu, J. Zhang, J. K. Kim, M. Huang and Y. Wu, *Org. Lett.*, 2016, **18**, 4151; (s) Y. Yu, S. Zhuang, P. Liu and P. Sun, *J. Org. Chem.*, 2016, **81**, 11489; (t) W. Zhang, S. Yang and Z. Shen, *Adv. Synth. Catal.*, 2016, **358**, 2392; (u) Y. Liu, K. Yang and H. Ge, *Chem. Sci.*, 2016, **7**, 2804; (v) Z. Deng, X. Peng, P. Huang, L. Jiang, D. Ye and L. Liu, *Org. Biomol. Chem.*, 2017, **15**, 442; (w) H. Su, L. Wang, H. Rao and H. Xu, *Org. Lett.*, 2017, **19**, 2226; (x) E. Wada, T. Takeuchi, Y. Fujimura, A. Tyagi, T. Kato and H. Yoshida, *Catal. Sci. Technol.*, 2017, **7**, 2457; (y) W. Xuesong, R. Jan and Vy M. Dong, *Angew. Chem., Int. Ed.*, 2017, **56**, 11589; (z) A. Bunesco, T. M. Ha, Q. Wang and J. Zhu, *Angew. Chem., Int. Ed.*, 2017, **56**, 10555; (aa) D. A. Culkin and J. F. Hartwig, *Acc. Chem. Res.*, 2003, **36**, 234; (ab) J. You and J. G. Verkade, *Angew. Chem., Int. Ed.*, 2003, **42**, 5051; *Angew. Chem., Int. Ed.*, 2003, **115**, 5205; (ac) Y. Suto, N. Kumagai, S. Matsunaga, M. Kanai and M. Shibasaki, *Org. Lett.*, 2003, **5**, 3147; (ad) N. Kumagai, S. Matsunaga and M. Shibasaki, *J. Am. Chem. Soc.*, 2004, **126**, 13632; (ae) Y. Suto, R. Tsuji, M. Kanai and M. Shibasaki, *Org. Lett.*, 2005, **7**, 3757; (af) T. Wu, X. Mu and G. Liu, *Angew. Chem., Int. Ed.*, 2011, **50**, 12578; *Angew. Chem., Int. Ed.*, 2011, **123**, 12786; (ag) Y. Kawato, N. Kumagai and M. Shibasaki, *Chem. Commun.*, 2013, **49**, 11227; (ah) D. S. Kumar, V. Ganesh, N. Kumagai and M. Shibasaki, *Chem. –Eur. J.*, 2014, **20**, 15637; (ai) D. Sureshkumar, V. Ganesh, N. Kumagai and M. Shibasaki, *Chem. –Eur. J.*, 2014, **20**, 15723; (aj) A. Goto, K. Endo, Y. Ukai, S. Irle and S. Saito, *Chem. Commun.*, 2008, 2212; (ak) A. Goto, H. Naka, R. Noyori and S. Saito, *Chem. –Asian J.*, 2011, **6**, 1740.
- 6 (a) N. Abermil, G. Masson and J. Zhu, *J. Am. Chem. Soc.*, 2008, **130**, 12596; (b) N. Abermil, G. Masson and J. Zhu, *Org. Lett.*, 2009, **11**, 4648; (c) N. Abermil, G. Masson and J. Zhu, *Adv. Synth. Catal.*, 2010, **352**, 656; (d) S. Kawahara, A. Nakano, T. Esumi, Y. Iwabuchi and S. Hatakeyama, *Org. Lett.*, 2003, **5**, 3103; (e) K. Matsui, S. Takizawa and H. Sasai, *J. Am. Chem. Soc.*, 2005, **127**, 3680; (f) S. Takizawa, N. Inoue, S. Hirata and H. Sasai, *Angew. Chem., Int. Ed.*, 2010, **49**, 9725; *Angew. Chem.*, 2010, **122**, 9919; (g) I. T. Raheem and E. N. Jacobsen, *Adv. Synth. Catal.*, 2005, **347**, 1701; (h) M. S. Taylor and E. N. Jacobsen, *Angew. Chem., Int. Ed.*, 2006, **45**, 1520; *Angew. Chem.*, 2006, **118**, 1550; (i) K. Hyodo, S. Nakamura and N. Shibata, *Angew. Chem., Int. Ed.*, 2012, **51**, 10337; *Angew. Chem.*, 2012, **124**, 10483; (j) T. Yukawa, B. Seelig, Y. Xu, H. Morimoto, S. Matsunaga, A. Berkessel and M. Shibasaki, *J. Am. Chem. Soc.*, 2010, **132**, 11988; (k) Y. L. Shi and M. Shi, *Adv. Synth. Catal.*, 2007, **349**, 2129; (l) R. Gausepohl, P. Buskens, J. Kleinen, A. Bruckmann, C. W. Lehmann, J. Klankermayer and W. Leitner, *Angew. Chem., Int. Ed.*, 2006, **45**, 3555; *Angew. Chem.*, 2006, **118**, 3635; (m) S. Čhalov, P. Dziedzic, A. Čjrdova and J. Veselý, *Adv. Synth. Catal.*, 2011, **353**, 1906.
- 7 (a) -F. W. Xiao, V.-L. Chloé, L. B. Bray and D. Christophe, *Tetrahedron*, 2009, **65**, 7380; (b) D.-G. Maria and T. C. Brian, *Tetrahedron*, 2011, **67**, 7901; (c) Z. C. Jessica, Y. Wenzhi, T. H. Brian, K. L. Charles and W. Masayuki, *Angew. Chem., Int. Ed.*, 2016, **55**, 13877; (d) C. Hao, Z. Yu, Z. Dong, X. Jinyi and L. Hong, *Chem. Commun.*, 2014, **50**, 14771; (e) K. G. Manas, D. Subhomoy, D. Kalpataru and K. Amit, *Org. Biomol. Chem.*, 2015, **13**, 9042; (f) F. Mar, C. C. Ana, F. Alberto and A. Jos, *Chem.–Eur. J.*, 2018, **24**, 3117; (g) Z. Abdolkarim, R. M.-Z. Ahmad, H. Alireza, P. Abolfath, K.-N. Ali and H. B. Mohammad, *Synth. Commun.*, 2009, **39**, 3156.
- 8 For selected reviews on CDC reactions, see: (a) Z. Li, D. S. Bohle and C.-J. Li, *Proc. Natl. Acad. Sci. U. S. A.*, 2006, **103**, 8928; (b) C.-J. Li, *Acc. Chem. Res.*, 2009, **42**, 335; (c) S. A. Girard, T. Knauber and C.-J. Li, *Angew. Chem.*, 2014, **126**, 76; *Angew. Chem., Int. Ed.*, 2014, **53**, 74.
- 9 For mechanistic studies, see: (a) E. Boess, D. Sureshkumar, A. Sud, C. Wirtz, C. Fars and M. Klussmann, *J. Am. Chem. Soc.*, 2011, **133**, 8106; (b) E. Boess, C. Schmitz and M. Klussmann, *J. Am. Chem. Soc.*, 2012, **134**, 5317; (c) A. Gogoi, S. Guin, S. K. Rout and B. K. Patel, *Org. Lett.*, 2013, **15**, 1802; (d) A. Gogoi, A. Modi, S. Guin, S. K. Rout, D. Das and B. K. Patel, *Chem. Commun.*, 2014, **50**, 10445.
- 10 R. Lpez and C. Palomo, *Angew. Chem.*, 2015, **127**, 13366; *Angew. Chem., Int. Ed.*, 2015, **54**, 13170.

