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Enantioselective Cyanation of Benzylic C–H Bonds via Copper-Catalyzed Radical Relay

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Abstract

Direct methods for stereoselective functionalization of C(sp^3)–H bonds in complex organic molecules could facilitate much more efficient preparation of therapeutics and agrochemicals. Here, we report a copper-catalyzed radical relay pathway for enantioselective conversion of benzylic C–H bonds into benzylic nitriles. Hydrogen-atom abstraction affords an achiral benzylic radical that undergoes asymmetric C(sp^3)–CN bond upon reaction with a chiral copper catalyst. The reactions proceed efficiently at room temperature with the benzylic substrate as limiting reagent, exhibit broad substrate scope with high enantioselectivity (typically 90-99% enantiomeric excess), and afford products that are key precursors to important bioactive molecules. Mechanistic studies provide evidence for diffusible organic radicals and highlight the difference between these reactions and C–H oxidations mediated by enzymes and other catalysts that operate via radical rebound pathways.

The clinical success of potential drug candidates has been shown to correlate with the fraction of sp^3-hybridized carbon atoms and number of stereogenic centers in the molecule (1). Consequently, synthetic methods that enable stereoselective functionalization of C(sp^3)–H bonds could have a major impact on the discovery and development of new pharmaceuticals. Enzymatic oxygenases and halogenases, such as cytochrome P450 and non-heme iron enzymes (2,3,4), have inspired the discovery of synthetic methods for selective oxidation of C–H bonds (see, for example, 5,6,7,8). These enzymes and related small-molecule catalysts function via generation of a reactive metal-oxo species that abstracts an H atom from a C(sp^3)–H bond, followed by radical rebound (9) to the metal-bound hydroxide or halide group (Fig. 1A). Here, we report a different, but complementary, enantioselective radical relay strategy for C(sp^3)–H oxidation whereby a reactive radical (**X·**) abstracts a hydrogen atom from an sp^3-hybridized carbon atom to produce a diffusible

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radical, which is then trapped by a second species that generates the functionalized sp^3 center (Fig. 1B). This concept is demonstrated in copper-catalyzed enantioselective cyanation of benzylic C–H bonds (Fig. 1C), Optically pure alkyl nitriles are featured in many bioactive natural products, pharmaceuticals and agricultural chemicals (10). Moreover, benzylic nitriles are direct precursors to phenethylamine derivatives, which represent a broad class of hormones, neurotransmitters and psychoactive drugs (11), as well as arylacetic acid derivatives, which are among the most widely used non-steroidal anti-inflammatory drugs (NSAIDs) (12). Stereoselectivity is proposed to arise from reaction of an achiral carbon radical with a chiral copper(II) species (L^*Cu^{II}–CN) (13), a pathway that contrasts with most enantioselective C–H functionalization reactions that involve selective, stereospecific activation of a prochiral C–H bond within an organic molecule (14,15).

In recent years, we have been investigating Cu-catalyzed methods for oxidation of styrenes and other alkenes (for example, 16,17), as well as C–H bonds (18). The former reactions are proposed to proceed via reaction of a benzylic radical intermediate with copper(II), generating an organocopper(III) species that undergoes reductive elimination to afford a new C–C or C– heteroatom bond. This pathway, which resembles a number of recently reported nickel- and copper-catalyzed cross-coupling methods that involve the reaction of a carbon-centered radical with a transition-metal center (e.g., 13,19-23), prompted us to consider how analogous concepts could be applied to C–H oxidation. Kharasch-Sosnovsky allylic oxidations and related reactions provide relevant precedent for this idea (24,25); however, these reactions face constraints that have greatly limited their synthetic utility over the nearly 60-year history of the reaction. For example, the alkene substrate is almost always used in large excess relative to the peroxide-based oxidant, a feature that severely restricts the net product yield and, in turn, the scope of suitable substrates. The majority of examples feature only simple cyclic alkene substrates, such as cyclopentene and cyclohexene. Reports of enantioselective reactivity retain this limited substrate scope and are characterized by poor catalytic efficiency that can result in multi-day reaction times (26,27). A synthetically useful radical-relay C–H oxidation method would need to overcome these limitations.

The pharmaceutical interest in benzylic nitriles and products derived therefrom, together with the formation of benzylic nitriles in certain alkene difunctionalization reactions (17,28; for broader context, see 29), prompted us to target a method for enanatioselective cyanation of benzylic C–H bonds. Initial efforts focused on generation of benzylic radicals via hydrogen-atom abstraction in the presence of copper(II) and a cyanide source. We posited that reductive activation of peroxides and other diheteroatom-bonded oxidants (cf. X–Z, Fig. 1C) with a copper(I) source should afford a reactive radical species and copper(II). A series of oxidants, including ^{t}BuO$_2$H, (^{t}BuO)$_2$, PhCO$_3{}^t$Bu, (PhCO$_2$)$_2$, oxone, *N*-fluorobenzenesulfonylimide (NFSI), and SelectFluor-BF$_4$, were tested in the cyanation of 1-ethylnaphthylene, **1a**, with trimethylsilyl cyanide (TMSCN) as cyanide source and [Cu(MeCN)$_4$]PF$_6$ as the copper(I) catalyst. An achiral bis(oxazoline) ligand (**L1**) was included in the reactions, but virtually all of the reactions failed to give the desired cyanation product. NFSI was the only oxidant that afforded any amount of the benzylic nitrile (**2a**, Fig. 2A, entry 1). The yield increased upon changing the solvent from acetonitrile to chlorobenzene (10% **2a**, entry 2) and using CuOAc as the copper source (25% **2a**, entry 3).

Replacing the ligand **L1** with an enantiomerically pure, benzyl-substituted bisoxazoline (BOX) derivative **L2** and performing the reaction in benzene led to a significant improvement in the yield (up to 91%, entry 5), and also afforded product **2a** in excellent enantiomeric excess (91% ee, entry 5). In each of the reactions in Fig. 2A, small quantities (trace – 12%) of benzylimide product derived from coupling with the bis(sulfonyl)imide of NFSI (30) were detected by ^{1}H NMR.

Assessment of various ligands showed that BOX ligands were the most effective ligand class (see Supplementary Material for screening data), and testing of other BOX-ligand variants led to further insights and improvements (Fig. 2B). Replacement of the *gem*-dimethyl substituents with a spirocyclic cyclopentyl group (**L3**) improved the enantioselectivity to 95% ee, whereas use of *tert*-butyl substituents on the oxazolines (**L4**), rather than benzyl groups, led to a significant dropoff in yield and enantioselectivity. Only trace product was observed with a ligand having an unsubstituted methylene linker between the two oxazolines (**L5**). Some of the best enantioselectivities were obtained with indane-derived BOX ligands, in particular, **L6** and **L8**.

In an effort to explore the scope of the benzylic cyanation reaction, three conditions identified in Fig. 2 were tested with a wide range of alkylarene substrates (Fig. 3). Simple 1-alkyl-substituted naphthylenes proved to be good substrates, providing the desired products **2a**-**2c** with excellent enantioselectivities (96-97% ee) in yields of 72-91%. Product **2d**, with a free primary alcohol, was obtained in excellent enantioselectivity (95% ee), but the reaction proceeded with only moderate conversion, resulting in a 42% product yield with 52% unreacted starting material. The analogous homobenzylic acetate derivative, however, exhibited very good reactivity (87% yield of **2e**), while retaining excellent enantioselectivity (99% ee). Versatile functional groups appended to the aliphatic chain, such as chloride, azide, phthalimide (Nphth), and carboxylic ester, were very well tolerated (**2f-2j**). A trifluoromethane sulfonate (OTf) group on the aromatic ring did not interfere with the reaction (products **2k** and **2m**) and provides a basis for subsequent derivatization of the product into more-complex molecules. The compatibility of these potentially sensitive functional groups included a primary alkyl bromide precursor to a CCR1 receptor antagonist of interest for treatment of chronic inflammation (31), highlighting the mildness of reactions conditions (Fig. 3B-i). 2-Alkyl naphthylenes also proved to be good substrates for the enantioselective cyanation, affording products **2l** and **2m** in good yield and enantioselectivity. Desymmetrization of acenaphthene (**2n**) was achieved with good enantioselectivity (79% ee).

Ethyl- and related alkylbenzene derivatives were similarly effective for this transformation (products **2o**-**2z** and **3a**-**3b**). The cases with reduced yields (e.g., 40-60%) typically reflect poor conversion, which would allow for recovery of valuable unreacted starting material, if desired. The enantioselectivity typically remained excellent (>90%). In substrates featuring more than one benzylic C–H site (e.g., **2n, 2r–2t, 2y, 3a**), selectivity for the monocyanation product was observed, with consistently high ee. Good results were observed in the reaction of 4-isobutyl biphenyl (**2z**), demonstrating tolerance of branching in the homobenzylic position (see below for further discussion). Tertiary benzylic C–H bonds and substrates with larger substituents in the homobenzylic position were found to be unreactive with these

catalyst systems (not shown), presumably because they present too much steric hindrance for effective hydrogen-atom abstraction. Numerous substrates containing pharmaceutically relevant heterocycles were tested, including those with a pyrazole, carbazole, benzothiazole, benzoxazole, thiophene and pyridine (**3c-3i**). Yields ranged from moderate to excellent (up to 89%), while enantioselectivities were consistently good-to-excellent (up to 98% ee). Alkyl phenol and anilide substrates were found to be unreactive (not shown). In these cases, the presence of weak O–H and N–H bonds could serve as radical traps. Benzene was typically used as the solvent in these reactions, on the basis of the initial optimization results, but a number of substrates were also tested in chlorobenzene as an alternate less toxic solvent, and excellent results were obtained (cf. **2a, 2c, 2e, 2f, 2h, 2p, 2r, 2v, 3c, 3h**). In addition, four substrates were demonstrated on 1 to 5 g scale to establish practical lab-scale utility (**2c**, **2h**, **3d**, **3h**).

The results in Fig. 3 represent the most streamlined method to date for the preparation of enantiomerically enriched benzylic nitriles from readily available starting materials. Asymmetric hydrocyanation of vinylarenes is perhaps the most compelling alternative. Such methods have been known for some time (32) and are the subject of ongoing development (33), but the present methods exhibit advantages with respect substrate accessibility (i.e., access to alkyl- versus vinyl-substituted arenes), functional-group compatibility and substrate scope, and enantioselectivity relative to asymmetric hydrocyanation of alkenes.

The enantiomerically enriched nitriles derived from these reactions are excellent precursors to phenethylamine and arylacetic acid derivatives. For example, benzylic nitriles **2d** and **2h** were subjected to hydrogenation over a Raney nickel catalyst and the resulting primary amines were converted to a Boc (Boc = *tert*-butyloxycarbonyl) derivative prior to isolation. This sequence afforded the desired products in good yield with no loss in ee relative to the starting material (Fig. 3B, ii). Traditional methods for nitrile hydrolysis (e.g., in the presence of aqueous acid) erode the enantiomeric excess, but a number of biocatalytic processes are emerging for nitrile hydrolysis that proceed under very mild conditions (34). Although these enzymatic methods weren't explored in the present study, they provide an excellent strategy for conversion of nitriles to arylacetic acids and could even provide a means to upgrade the enantioselectivity (Fig. 3B, iii).

Several observations suggest that site selectivity in these reactions is influenced by both steric and electronic effects (Fig. 4A). Subjection of 2-ethylfluorene **4b** to the Cu-catalyzed cyanation conditions results in selective cyanation of the benzylic site of the 2-ethyl group; no cyanation of the highly activated, doubly benzylic methylene group of the fluorene is observed. We attribute this outcome to steric effects. The contribution of electronic effects is evident in the reactivity of the substituted phenethylnapthalene derivatives **4c**–**4f**. The site selectivity with these substrates is quite high, always favoring the benzylic position adjacent to the naphthalene, but the preference increases from 12:1 to 29:1 as the substituent at the *para* position changes from an electron-donating *tert*-butyl group to an electron-deficient –CF_3 group. Excellent enantioselectivity (97–98% ee) is observed in each case. The site-selectivity is further evident from reaction of the homobenzylic methyl ether substrate **4g**, which affords only the benzylic C– H cyanation product in good yield and excellent ee. Similarly, benzylic over tertiary C–H activation is observed in the formation of **2z** and

suggests that the reactive imidyl radical shows exquisite selectivity in the hydrogen-atom-transfer (HAT) reaction. This observation contrasts with more-potent HAT reagents, such as photoexcited benzophenone, which exhibit only modest selectivity toward different C–H bonds (35).

Stereoselectivity issues were probed in the reaction of enantiomerically pure homobenzylic acetate (*R*)-**4h**. Catalysts with the each of the enantiomers of ligand **L3** were tested, and both led to products with excellent diastereoselectivity, reflecting high levels of catalyst- rather than substrate-controlled stereoselectivity. The differences in diastereomeric ratio and yield of the two products probably reflect a matched-mismatched effect between the ligand and substrate chirality.

A competition deuterium kinetic isotope effect (KIE) study, employing a mixture of **1a** and **1a-*d*$_2$**, revealed a KIE of 3.5 (Fig. 4B). On the other hand, independent measurement of the reaction rate of these two substrates revealed only a modest difference in rate (KIE = 1.6 ± 0.2). These values suggest that C–H cleavage is only partially turnover-limiting, and that another mechanistic step also contributes to the catalytic turnover rate (e.g., generation of the reactive radical via activation of NFSI by Cu^{I}). Additional mechanistic studies are ongoing to secure further insights, but several observations provide clear evidence for formation of a diffusible carbon-centered radical in the reaction (Fig. 4C). Subjection of the cyclopropane-containing substrate **4i** to the reaction conditions results in a mixture of the benzylic cyanation product **5i** and a ring-opened product (**7**) in 7% and 32% yield, respectively, together with a mixture of other unidentified byproducts. Additional evidence for a radical intermediate was obtained by performing the catalytic reactions of 1-ethylnaphthalene (**1a**) in the presence of O_2 or $BrCCl_3$. Under ambient air as a source of O_2, the reaction generated the racemic benzylic alcohol and ketone in 24% and 55% yields, respectively. This product mixture is consistent with trapping of the organic radical by O_2 and subsequent conversion of the organic peroxyl radical into the alcohol/ketone mixture. No cyanation product (**2a**) was observed under the aerobic conditions. When the reaction was performed in the presence of $BrCCl_3$ (2 equivalents), a mixture of the benzylic nitrile and bromide products was obtained (44% and 24% yields, respectively). This product ratio, together with precedent for efficient trapping of organic radicals by $BrCCl_3$ (36), implicates very rapid trapping of organic radicals by a chiral L*Cu^{II}(CN) species under the reaction conditions.

The reaction of organic radicals with the L*Cu^{II}(CN) species is the subject of ongoing investigation, but the high enantioselectivity observed in the reactions suggests the benzylic position is in close proximity to the chiral Cu center in the enantioselectivity-determining step. A plausible pathway involves reaction of the intermediate organic radical with Cu^{II}, an open-shell, d^9 metal center, to afford a benzyl–Cu^{III} species, and preliminary density functional theory (DFT) calculations support the viability of this pathway (Fig. 4D). An ethylbenzene-derived radical reacts at Cu^{II} in an (**L2**)$Cu^{II}(CN)_2$ species with a low barrier to afford a benzyl-Cu^{III} species. Subsequent C(sp^3)–CN reductive elimination generates the benzylic nitrile product. The calculations suggest the transition state for the addition of the benzylic radical to Cu^{II} is lower in energy than reductive elimination, indicating that formation of the alkyl-Cu^{III} species is reversible and that enantioselectivity is determined by

the reductive elimination step. An analogous conclusion was reached in a recent DFT study of Ni-catalyzed cross-coupling reactions, wherein reversible addition of an alkyl radical to a Ni^{II} catalyst precedes enantiodetermining reductive elimination (37). For the present system, the difference in the computed activation free energy for reductive elimination of the two enantiomeric benzylic nitriles ($\Delta\Delta G^{\ddagger}$ = 1.6 kcal/mol) is very similar to the $\Delta\Delta G^{\ddagger}$ associated with the experimentally observed enantioselectivity (e.g., $\Delta\Delta G^{\ddagger}$ = 1.5 kcal/mol for **2q**, cf. Fig. 3). Moreover, the reductive elimination transition states for this pathway are calculated to be slightly lower than the calculated barrier for bromine transfer from $BrCCl_3$ to an ethylbenzene-derived radical ($\Delta G^{\ddagger}$ = 12.2 kcal/mol; Fig. 4D), matching the slight preference for cyanation over bromination noted in Fig. 4C. While the agreement between the computed pathways and several key experimental observations is quantitatively closer than can be justified by the uncertainties in the computational methods, the qualitative agreement is consistent with the proposed radical coupling pathway with $L^*Cu^{II}(CN)_2$.

The copper-catalyzed method for enantioselective cyanation of $C(sp^3)$–H bonds described herein represent a unique demonstration of radical relay catalysis. The ability to use the $C(sp^3)$– H substrate as the limiting reagent, together with the mild reaction conditions, excellent enantioselectivity, and broad substrate scope, provide key foundations for the pursuit of other chemo-, regio-, and stereoselective C–H oxidation reactions.

Supplementary Material

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Acknowledgments

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References

1. Lovering F, Bikker J, Humblet C. Escape from flatland: increasing saturation as an approach to improving clinical success. J Med Chem. 2009; 52:6752–6756. [PubMed: 19827778]
2. de Montellano PRO. Hydrocarbon hydroxylation by cytochrome P450 enzymes. Chem Rev. 2010; 110:932–948. [PubMed: 19769330]
3. Meunier B, de Visser SP, Shaik S. Mechanism of oxidation reactions catalyzed by cytochrome P450 enzymes. Chem Rev. 2004; 104:3947–3980. [PubMed: 15352783]
4. Butler A, Sandy M. Mechanistic considerations of halogenating enzymes. Nature. 2009; 460:848–854. [PubMed: 19675645]
5. Chen MS, White MC. A predictably selective aliphatic C–H oxidation reaction for complex molecule synthesis. Science. 2007; 318:783–787. [PubMed: 17975062]
6. Liu W, Groves JT. Manganese catalyzed C–H halogenation. Acc Chem Res. 2015; 48:1727–1735. [PubMed: 26042637]
7. Sharma A, Hartwig JF. Metal-catalysed azidation of tertiary C–H bonds suitable for late-stage functionalization. Nature. 2015; 517:600–604. [PubMed: 25631448]
8. Lewis JC, Coelho PS, Arnold FH. Enzymatic functionalization of carbon–hydrogen bonds. Chem Soc Rev. 2011; 40:2003–2021. [PubMed: 21079862]

9. Groves JT. Key elements of the chemistry of cytochrome P-450. The oxygen rebound mechanism. J Chem Ed. 1985; 62:928–931.
10. Fleming FF, Yao LH, Ravikumar PC, Funk L, Shook BC. Nitrile-containing pharmaceuticals: efficacious roles of the nitrile pharmacophore. J Med Chem. 2010; 53:7902–7917. [PubMed: 20804202]
11. Bentley KW. β-Phenylethylamines and the isoquinoline alkaloids. Nat Prod Rep. 2001; 17:148–170.
12. Harrington PJ, Lodewijk E. Twenty years of Naproxen technology. Org Process Res Dev. 1997; 1:72–76.
13. Kainz QM, Matier CD, Bartoszewicz A, Zultanski SL, Peters JC, Fu GC. Asymmetric copper-catalyzed C-N cross-couplings induced by visible light. Science. 2016; 351:681–684. [PubMed: 26912852]
14. Zhang FL, Hong K, Li TJ, Park H, Yu JQ. Functionalization of C(sp^3)-H bonds using a transient directing group. Science. 2016; 351:252–256. [PubMed: 26816374]
15. Davies HML, Manning JR. Catalytic C–H functionalization by metal carbenoid and nitrenoid insertion. Nature. 2008; 451:417–424. [PubMed: 18216847]
16. Wang F, Wang D, Mu X, Chen P, Liu G. Copper-catalyzed intermolecular trifluoromethylarylation of alkenes: mutual activation of arylboronic acid and CF_3^+ reagent. J Am Chem Soc. 2014; 136:10202–10205. [PubMed: 24983408]
17. Liang Z, Liu G. Copper-catalyzed intermolecular three components coupling for the convenient synthesis of CF_3-containing alkyl nitriles. J Fluorine Chem. 2014; 167:55–60.
18. Wendlandt AE, Suess AM, Stahl SS. Copper-catalyzed aerobic oxidative C–H functionalizations: trends and mechanistic insights. Angew Chem Int Ed. 2011; 50:11062–11087.
19. Tellis JC, Primer DN, Molander GA. Single-electron transmetalation in organoboron cross-coupling by photoredox/nickel dual catalysis. Science. 2015; 345:433–436.
20. Zuo Z, Ahneman DT, Chu L, Terrett JA, Doyle AG, MacMillan DWC. Merging photoredox with nickel catalysis: coupling of α-carboxyl sp^3-carbons with aryl halides. Science. 2014; 345:437–440. [PubMed: 24903563]
21. Weix DJ. Methods and mechanisms for cross-electrophile coupling of Csp^2 halides with alkyl electrophiles. Acc Chem Res. 2015; 48:1767–1775. [PubMed: 26011466]
22. Schley ND, Fu GC. Nickel-catalyzed Negishi arylations of propargylic bromides: a mechanistic investigation. J Am Chem Soc. 2014; 136:16588–16593. [PubMed: 25402209]
23. Ratani TS, Bachman S, Fu GC, Peters JC. Photoinduced copper-catalyzed carbon-carbon bond formation with alkyl electrophiles: cyanation of unactivated secondary alkyl chlorides at room temperature. J Am Chem Soc. 2015; 137:13902–13907. [PubMed: 26491957]
24. Kharasch MS, Sosnovsky G. The reactions of *t*-butyl perbenzoate and olefins–a stereospecific reaction. J Am Chem Soc. 1958; 80:756.
25. Gephart RT III, McMullin CL, Sapiezynski NG, Jang ES, Aguila MJB, Cundari TR, Warren TH. Reaction of Cu^I with dialkyl peroxides: Cu^{II}-alkoxides, alkoxy radicals, and catalytic C–H etherification. J Am Chem Soc. 2012; 134:17350. [PubMed: 23009158]
26. Andrus MB, Zhou Z. Highly enantioselective copper-bisoxazoline-catalyzed allylic oxidation of cyclic olefins with *tert*-butyl *p*-nitroperbenzoate. J Am Chem Soc. 2002; 124:8806–8807. [PubMed: 12137528]
27. Eames J, Watkinson M. Catalytic allylic oxidation of alkenes using an asymmetric Kharasch-Sosnovsky reaction. Angew Chem Int Ed. 2001; 40:3567–3571.
28. Zhang H, Pu W, Xiong T, Li Y, Zhou X, Sun K, Liu Q, Zhang Q. Copper-catalyzed intermolecular aminocyanation and diamination of alkenes. Angew Chem Int Ed. 2013; 52:2529–2533.
29. Gaspar B, Carreira EM. Mild cobalt-catalyzed hydrocyanation of olefins with tosyl cyanide. Angew Chem Int Ed. 2007; 46:4519–4522.
30. Ni Z, Zhang Q, Xiong T, Zheng Y, Li Y, Zhang H, Zhang J, Liu Q. Highly regioselective copper-catalyzed benzylic C–H amination by N-fluorobenzenesulfonimide. Angew Chem Int Ed. 2012; 51:1244–1247.

31. Ng HP, May K, Bauman JG, Ghannam A, Islam I, Liang M, Horuk R, Hesselgesser J, Snider RM, Perez HD, Morrissey MM. Discovery of novel non-peptide CCR1 receptor antagonists. J Med Chem. 1999; 42:4680–4694. [PubMed: 10579830]
32. Rajan Babu TV, Casalnuovo AL. Role of electronic asymmetry in the design of new ligands: the asymmetric hydrocyanation reaction. J Am Chem Soc. 1996; 118:6325–6326.
33. Falk A, Cavalieri A, Nichol GS, Vogt D, Schmalz HG. Enantioselective nickel-catalyzed hydrocyanation using chiral phosphine-phosphite ligands: recent improvements and insights. Adv Synth Catal. 2015; 357:3317–3320.
34. Kourist R, Domínguez de María P, Miyamoto K. Biocatalytic strategies for the asymmetric synthesis of profens – recent trends and developments. Green Chem. 2011; 13:2607–2618.
35. Hoshikawa T, Yoshioka S, Kamijo S, Inoue M. Photoinduced direct cyanation of C(sp^3)–H bonds. Synthesis. 2013; 45:874–887.
36. Mathew L, Warkentin J. Rate constants for abstraction of bromine from bromotrichloromethane by butyl, cyclopropylmethyl, and phenyl radicals in solution. Can J Chem. 1988; 66:11–16.
37. Gutierrez O, Tellis JC, Primer DN, Molander GA, Kozlowski MC. Nickel-catalyzed cross-coupling of photoredox-generated radicals: uncovering a general manifold for stereoconvergence in nickel-catalyzed cross-couplings. J Am Chem Soc. 2015; 137:4896–4899. [PubMed: 25836634]
38. Natte K, Dumrath A, Neumann H, Beller M. Palladium-catalyzed carbonylations of aryl bromides using paraformaldehyde: synthesis of aldehydes and esters. Angew Chem Int Ed. 2014; 53:10090–10094.
39. Smith CR, Rajan Babu TV. Low pressure vinylation of aryl and vinyl halides via Heck–Mizoroki reactions using ethylene. Tetrahedron. 2010; 66:1102–1110. [PubMed: 20676383]
40. Lv X, Bao W. A β-keto ester as a novel, efficient, and versatile ligand for copper(I)-catalyzed C–N, C–O, and C–S coupling reactions. J Org Chem. 2007; 72:3863–3867. [PubMed: 17432916]
41. Cho SH, Yoon J, Chang S. Intramolecular oxidative C–N bond Formation for the synthesis of carbazoles: comparison of reactivity between the copper-catalyzed and metal-free conditions. J Am Chem Soc. 2011; 133:5996–6005. [PubMed: 21446710]
42. Wang H, Wang L, Shang J, Li X, Wang H, Gui J, Lei A. Fe-catalysed oxidative C-H functionalization/C-S bond formation. Chem Commun. 2012; 48:76–78.
43. Ueda S, Nagasawa H. Synthesis of 2-arylbenzoxazoles by copper-catalyzed intramolecular oxidative C–O coupling of benzanilides. Angew Chem Int Ed. 2008; 47:6411–6413.
44. Whelligan DK, Solanki S, Taylor D, Thomson DW, Cheung KMJ, Boxall K, Mas-Droux Corine, Barillari C, Burns S, Grummitt CG, Collins I, van Montfort Rob LM, Aherne GW, Bayliss R, Hoelder S. Aminopyrazine inhibitors binding to an unusual inactive conformation of the mitotic kinase Nek2: SAR and structural characterization. J Med Chem. 2010; 53:7682–7698. [PubMed: 20936789]
45. Kawakami T, Murakami K, Itami K. Catalytic C–H imidation of aromatic cores of functional molecules: ligand-accelerated Cu catalysis and application to materials- and niology-oriented aromatics. J Am Chem Soc. 2015; 137:2460–2463. [PubMed: 25669319]
46. Ofosu-Asante K, Stock LM. Selective deuteriation of arylalkanes with mixed metal reagents. J Org Chem. 1990; 55:3409–3410.
47. Patra T, Agasti S, Akanksha, Maiti D. Nickel-catalyzed decyanation of inert carbon-cyano bonds. Chem Commun. 2013; 49:69–71.
48. Mermerian AH, Fu GC. Nucleophile-catalyzed asymmetric acylations of silyl ketene imines: application to the enantioselective synthesis of verapamil. Angew Chem Int Ed. 2005; 44:949–952.
49. Yang Y, Tang S, Liu C, Zhang H, Sun Z, Lei A. Novel α-arylnitriles synthesis via Ni-catalyzed cross-coupling of a-bromonitriles with arylboronic acids under mild conditions. Org Biomol Chem. 2011; 9:5343–5345. [PubMed: 21677998]
50. Shang R, Ji DS, Chu L, Fu Y, Liu L. Synthesis of α-aryl nitriles through palladium-catalyzed decarboxylative coupling of cyanoacetate salts with aryl halides and triflates. Angew Chem Int Ed. 2011; 50:4470–4474.
51. Raffaelli A, Rosini C, Dini M, Salvadori P. A simple route to racemic acenaphthene-1-carboxylic acid via hydroformylation of acenaphthylene. Synthesis. 1988; 1988:893–894.

52. Kitano Y, Manoda T, Miura T, Chiba K, Tada M. A convenient method for the preparation of benzyl isocyanides. Synthesis. 2006; 2006:405–410.

53. Turnbull BWH, Evans PA. Enantioselective rhodium-catalyzed allylic substitution with a nitrile anion: construction of acyclic quaternary carbon stereogenic centers. J Am Chem Soc. 2015; 137:6156–6159. [PubMed: 25941763]

54. de Greef M, Breit B. Self-assembled bidentate ligands for the nickel-catalyzed hydrocyanation of alkenes. Angew Chem Int Ed. 2009; 48:551–554.

55. Li F, Zou X, Wang N. Direct coupling of arylacetonitriles and primary alcohols to α-alkylated arylacetamides with complete atom economy catalyzed by a rhodium complex–triphenylphosphine–potassium hydroxide system. Adv Synth Catal. 2015; 357:1405–1415.

56. Anxionnat B, Gomez Pardo D, Ricci G, Cossy J. First intramolecular alkylation of nitriles with primary and secondary alcohols catalyzed by iridium complexes. Eur J Org Chem. 2012; 2012:4453–4456.

57. Fan X, Guo K, Guan YH, Fu LA, Cui XM, Lv H, Zhu HB. Efficient assembly of α-aryl and α-vinyl nitriles via iron-catalyzed ether bond activation. Tetrahedron Lett. 2014; 55:1068–1071.

58. Frisch, MJ., Trucks, GW., Schlegel, HB., Scuseria, GE., Robb, MA., Cheeseman, JR., Scalmani, G., Barone, V., Mennucci, B., Petersson, GA., Nakatsuji, H., Caricato, M., Li, X., Hratchian, HP., Izmaylov, AF., Bloino, J., Zheng, G., Sonnenberg, JL., Hada, M., Ehara, M., Toyota, K., Fukuda, R., Hasegawa, J., Ishida, M., Nakajima, T., Honda, Y., Kitao, O., Nakai, H., Vreven, T., Montgomery, JA., Jr, Peralta, JE., Ogliaro, F., Bearpark, M., Heyd, JJ., Brothers, E., Kudin, KN., Staroverov, VN., Kobayashi, R., Normand, J., Raghavachari, K., Rendell, A., Burant, JC., Iyengar, SS., Tomasi, J., Cossi, M., Rega, N., Millam, JM., Klene, M., Knox, JE., Cross, JB., Bakken, V., Adamo, C., Jaramillo, J., Gomperts, R., Stratmann, RE., Yazyev, O., Austin, AJ., Cammi, R., Pomelli, C., Ochterski, JW., Martin, RL., Morokuma, K., Zakrzewski, VG., Voth, GA., Salvador, P., Dannenberg, JJ., Dapprich, S., Daniels, AD., Farkas, Ö., Foresman, JB., Ortiz, JV., Cioslowski, J., Fox, DJ. Gaussian 09, Revision D.01. Gaussian, Inc; Wallingford CT: 2009.

59. Cramer, CJ. Essentials of Computational Chemistry: Theories and Models. 2. Wiley; 2004.

60. Marenich AV, Cramer CJ, Truhlar DG. Universal solvation model based on solute electron density and on a continuum model of the solvent defined by the bulk dielectric constant and atomic surface tensions. J Phys Chem B. 2009; 113:6378–6396. [PubMed: 19366259]

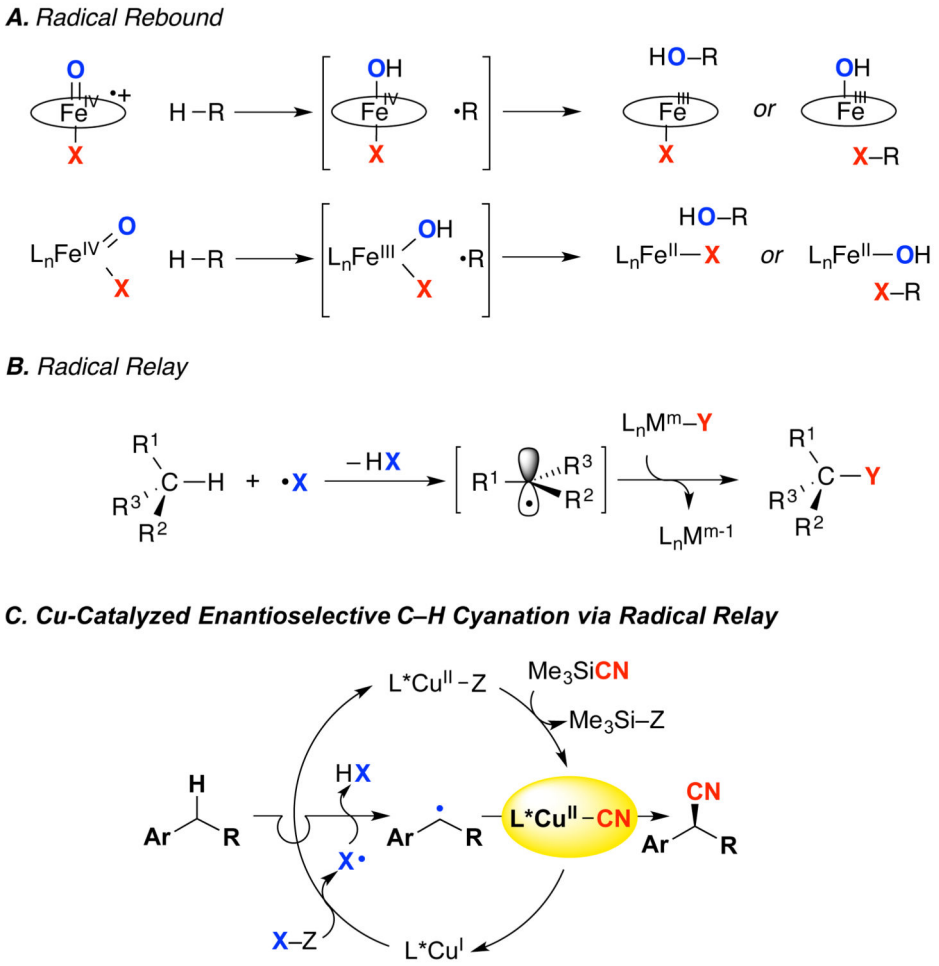

Fig. 1. Strategies for hydrogen-atom-transfer-mediated C–H oxidation

(A) Radical rebound mechanism for enzymatic and biomimetic C–H hydroxylation and halogenation (X = halide). (B) Radical relay pathway for C–H oxidation involving formation of a free radical that is trapped by a reactive metal center. (C) Proposed mechanism for Cu-catalyzed enantioselective cyanation of benzylic C–H bonds via radical relay.

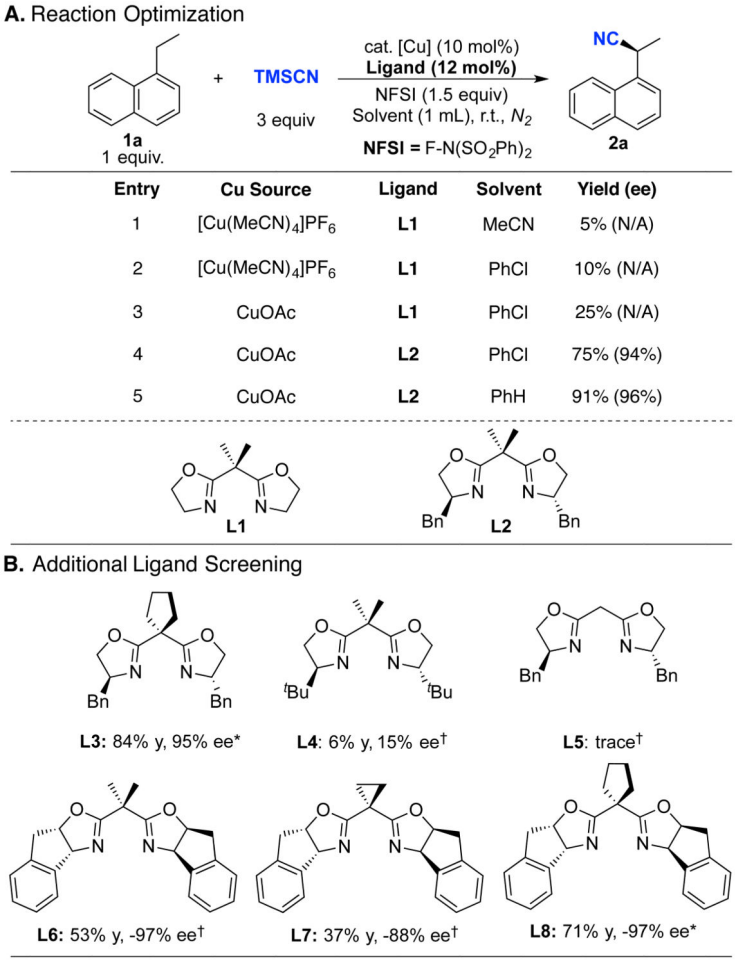

Figure 2. Reaction optimization and representative ligand screening data

General reaction conditions: **1a** (0.2 mmol), TMSCN (0.6 mmol), NFSI (0.3 mmol), CuOAc (0.02 mmol), ligand (0.024 mmol) in 1.0 mL of solvent at r.t. for 10 h. Yield determined by ^{1}H NMR, CF_3CONMe_2 as internal standard. The ee (enantiomertic excess) value was determined by HPLC with a chiral stationary phase. * Reaction conducted in PhH; † Reaction conducted in PhCl.

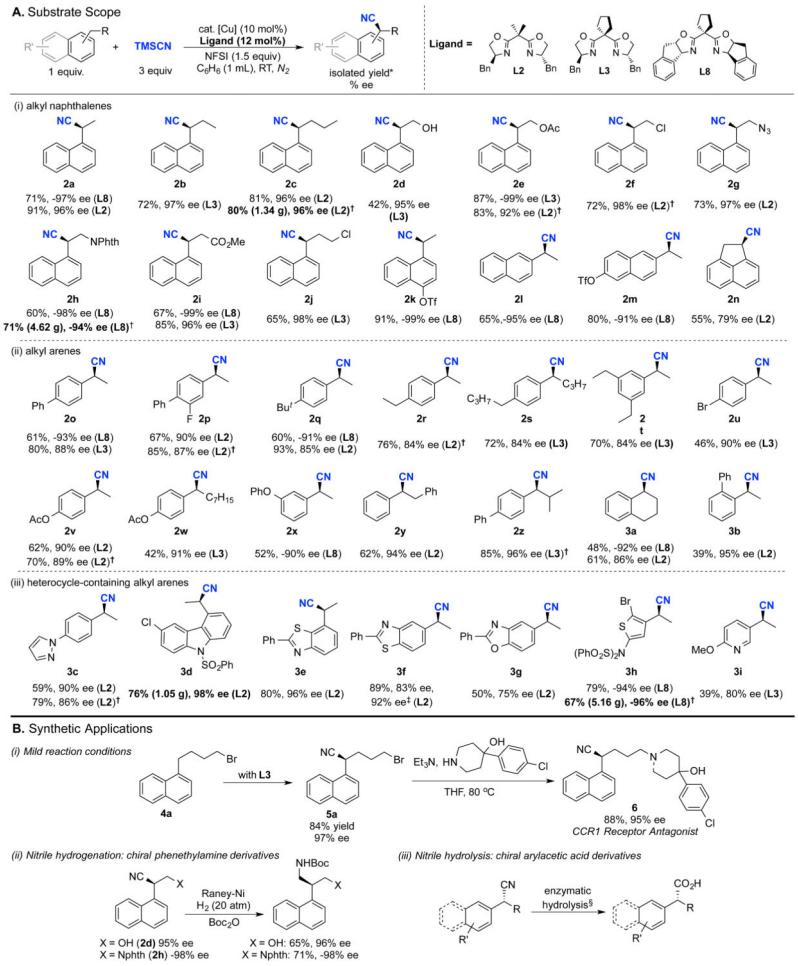

Figure 3. Substrate scope and synthetic applications of Cu-catalyzed cyanation of benzylic C–H bonds

* All the reactions were conducted with alkylarenes as the limiting reagent in 0.2-1 mmol scale; isolated yields reported. † Chlorobenzene used as the solvent. ‡ *ee* value of product after recrystallization. § See ref. 34.

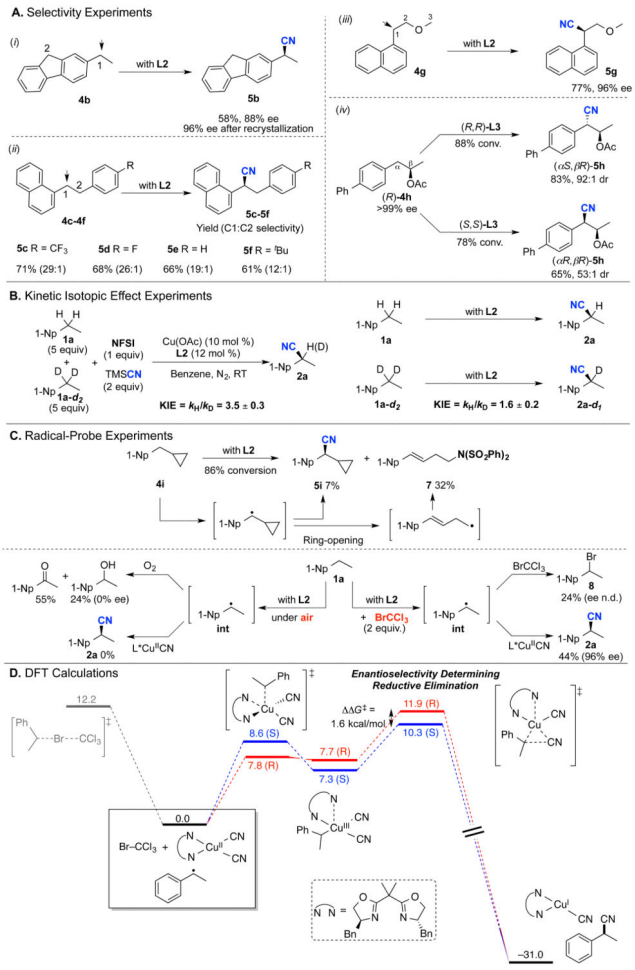

Figure 4. Experimental and computational studies providing insight into the mechanism of the copper-catalyzed cyanation reaction

These include (A) reaction selectivity studies, (B) kinetic isotope effects, (C) radical trapping experiments, and (D) DFT computational studies.