Copper-catalyzed methylative difunctionalization of alkenes

Xu Bao1, Takayuki Yokoe1, Tu M. Ha1, Qian Wang1 & Jieping Zhu1

Trifluoromethylative difunctionalization and hydrofunctionalization of unactivated alkenes have been developed into powerful synthetic methodologies. On the other hand, methylative difunctionalization of olefins remains an unexplored research field. We report in this paper the Cu-catalyzed alkoxy methylation, azido methylation of alkenes using dicumyl peroxide (DCP), and di-tert-butyl peroxide (DTBP) as methyl sources. Using functionalized alkenes bearing a tethered nucleophile (alcohol, carboxylic acid, and sulfonamide), methylative cycloetherification, lactonization, and cycloamination processes are subsequently developed for the construction of important heterocycles such as 2,2-disubstituted tetrahydrofurans, tetrahydropyranos, γ-lactones, and pyrroliodines with concurrent generation of a quaternary carbon center. The results of control experiments suggest that the 1,2-alkoxy methylation of alkenes goes through a radical-cation crossover mechanism, whereas the 1,2-azido methylation proceeds via a radical addition and Cu-mediated azide transfer process.
he so-called magic methyl effect has long been known in medicinal chemistry and has been frequently used to optimize the biological and pharmacological properties of a drug candidate. In addition to traditional nucleophilic substitution reaction, transition metal-catalyzed cross-coupling reaction has recently been developed into a powerful tool for the methylation of (hetero)arenes, amides/carboxylic acids, and isocyanides have been exploited. In addition, methylation of electron-deficient olefins such as N-arylacylamides have also been developed. In the latter case, the resulting electrophilic radical adduct underwent rapid intramolecular HAS with the tethered aromatic ring to afford 2,2-disubstituted oxindoles. On the other hand, methylative difunctionalization of unactivated double bonds using peroxide as methyl source has, to the best of our knowledge, not been reported. This was probably due to the perception that methyl radical is nucleophilic, therefore, its addition to electron-rich alkenes would be polarity mismatched process. We report herein the realization of this endeavor by developing three-component 1,2-alkoxy methylation, 1,2-azido methylation, and methylative cycloetherification, lactonization, cycloamination of unactivated alkenes. The results of control experiments suggested that the 1,2-alkoxy methylation of alkenes went through a radical-cation crossover mechanism, whereas the azido methylation proceeded via a radical addition and Cu-mediated redox azide transfer process.

Results

Three-component 1,2-alkoxy methylation of alkenes. Examples of alkyloxy alkylation of alkenes are rare. Wang and co-workers reported a rhenium-catalyzed 1,2-acetoxy methylation of styrene derivatives using phenylidene diacetate (PIDA) as both the methyl and the acetoxy sources, while Glorius and Bao reported the alkyloxy alkylation of alkenes via decarboxylative generation of alkyl radicals.

We began our studies by examining the 1,2-alkoxy methylation of α-methylstyrene (1a). After extensive survey of the reaction parameters varying the Cu sources, the ligands, the Cu/ligand ratio, the peroxides, the bases, the solvents, the concentration, and the reaction temperature, the optimum conditions found consisted of heating a MeOH solution of 1a (0.1 M) in a sealed tube in the presence of a catalytic amount of Cu(BF4)2-6H2O (0.2 equiv), 4,4-dimethoxy-2,2′-bipyridine (L1, 0.3 equiv) and Na3HPO4 (0.2 equiv) at 120 °C for 4 h. Under these conditions, 2a was isolated in 96% yield. We note that reaction using

![Fig. 1](image-url)
Three-component 1,2-azido methylation of alkenes. There were only few examples on the three-component carboazidation of alkenes with the concurrent formation of a C(sp3)-N bond. Renaud and co-workers developed a carboazidation of alkenes with the concurrent formation of a C(sp3)-C(sp3) and a C(sp3)-N bond. The alkylation-induced heterocyclization is, on the other hand, poorly documented. For instance, only few examples of alkylative cycloetherification have been reported in the literature.

We investigated the methylative cycloetherification of alkenes using 4-phenylpent-4-en-1-ol (4a) as a test substrate. Gratefully, treatment of a BuOH solution of 4a under conditions established for the 1,2-alkoxy methylation of alkenes afforded the tetrahydrofuran 5a in 58% yield. Replacing DCP with DTBP gave a similar yield of 5a (57%). Therefore, DTBP was used as a methyl source for further condition optimization as it provided a cleaner reaction mixture. Performing the reaction in 2-hydroperoxy-2-methylbutane as ethyl donor under otherwise standard conditions provided a complex reaction mixture.

Fig. 2 1,2-Alkoxy methylation of unactivated alkenes. Unless specified, MeOH was used as solvent. (i) 140 °C; (ii) DTBP (4.0 equiv) was used instead of DCP; (iii) EtOH (2.0 mL, c 0.1 M); (iv) iPrOH (2.0 mL, c 0.1 M). Abbreviations: DTBP di-tert-butyl peroxide; DCP dicumyl peroxide.
Methylation of 4-aryl alkenes was next investigated. The reaction tolerated the presence of both electron-donating (Me, OMe, Ph, and iPr) and electron-withdrawing groups (F, Cl, Br, and CN) at different positions of the aryl ring. The 5-phenylhex-5-en-ol underwent similar methylative cycloetherification to afford 2-ethyl-2-phenyltetrahydrofuran (5a) in 82% yield.

Under the above-optimized conditions, a diverse set of 4-aryl substituted pent-4-en-1-ols 4 underwent methylative cycloetherification to afford the 2,2-disubstituted tetrahydrofurans (5b–5m) in good yields (Fig. 4a). The reaction tolerated the presence of both electron-donating (Me, OMe, Ph, and iPr) and electron-withdrawing groups (F, Cl, Br, and CN) at different positions of the aryl ring. The 5-phenylhex-5-en-ol underwent similar methylative cycloetherification to afford 2-ethyl-2-phenyltetrahydro-2H-pyran (5n) in 76% yield.

**Methylative cycloamination.** While trifluoromethylative cycloamination of alkenes have been reported recently, the methylative counterpart is to the best of our knowledge unknown. We therefore set out to examine this reaction using sulfonamide as internal nucleophile. Optimum conditions found for the methylative cycloamination of 8a with DTBP (4.0 equiv) consisted of heating a solution of 8a in tBuOH (0.1 M) in the presence of Cu(OAc)₂ (0.2 equiv), 1,10-Phen (1.2 equiv) and Na₃PO₄ (0.2 equiv) at 120 °C. Under these conditions, the pyrrolidine 9a was isolated in 71% yield. As it is shown in Fig. 4c, electron-donating (Me, OMe, Ph, and iPr) and electron-withdrawing groups (F, Br, Cl, and CN) on the phenyl ring of the α-methyl styrene derivatives were well tolerated leading to 2,2-disubstituted pyrrolidines (9a–9k) in good yields.

**Mechanistic studies.** Possible reaction pathways for the 1,2-methylation and 1,2-azido methylation of alkenes are depicted in Fig. 5a. Reduction of peroxide (DCP or DTBP) by the in situ generated Cu(I)X salt would generate two molecules of alkoxy radical and Cu(II) salt. Alternatively, thermal decomposition of peroxide would generate two molecules of alkoxy radical B. β-Scission of B would generate ketone D and methyl radical E. Addition of E to the alkenyl would produce the benzyl radical F which would be oxidized by Cu(II) salt to the carbenium G with the concurrent regeneration of the Cu(I)X salt. Trapping of the carbenium G by nucleophile would then afford the observed products (route a). Alternatively, radical F could be directly converted to the adduct via a Cu-centered redox transfer process (route b) or via radical rebound of F with C followed by reductive elimination of the resulting Cu(III) species H (route c).

Several experimental observations and the results of control experiments were in line with the proposed reaction pathway. First, 1,2-methoxy methylation of 1a was completely inhibited in the presence of 2,2,6,6-tetramethyl-1-piperidinoxyloxy (TEMPO, 10). 1-(Methoxy)-2,2,6,6-tetramethylpiperidine (11) was instead isolated in 29% yield (Fig. 5b). Second, submitting 1-(cyclopropylvinyl)benzene (12) to the standard 1,2-methoxy methylation conditions afforded dihydronaphthalene 13 in 43% yield (Fig. 5c). These two experiments clearly indicated the existence of both the...
methyl radical (Me•) and the adduct radical 14 in this three-component process. To gain further insight on the reaction mechanism, the 2-tert-butoxy-3-(1-phenylvinyl)cyclopropyl)benzene (15), developed by Newcomb as a supersensitive radical probe, was synthesized. It has been demonstrated that the cyclopropane will be opened at the phenyl-bearing carbon in a radical mechanism and at the oxygen-bearing carbon in a cationic mechanism. Eventually, treatment of 15 under our methoxy methylation conditions afforded a quite complex reaction mixture from which 1,4-disubstituted naphthalene 16 was isolated in 17% yield. On the other hand, compound 15 was converted, under 1,2-azido methylation conditions, cleanly to 16 in 56% yield (Fig. 5d).

Fig. 4 Methylative heterocyclization of alkenes. a) Methylative cycloetherification: 4 (0.2 mmol), Cu(OTf)₂ (0.2 equiv), L₁ (0.3 equiv), Na₃PO₄ (0.2 equiv), DTBP (4.0 equiv), CF₃CH₂OH (c 0.1 M), 120 °C. Yields refer to isolated products. b) Methylative lactonization: 6 (0.2 mmol), CuSO₄ (0.2 equiv), L₂ (0.3 equiv), Na₃PO₄ (0.3 equiv), DTBP (4.0 equiv), tBuOH (c 0.1 M), 120 °C. c) Methylative cycloamination: 8, Cu(OAc)₂ (0.2 equiv), L₂ (0.3 equiv), Na₃PO₄ (0.2 equiv), DTBP (4.0 equiv), tBuOH (c 0.1 M), 120 °C.

Formation of benzyl radical 17 followed by regioselective ring opening to 18 and intramolecular HAS reaction would provide dihydronaphthalene 20 which, upon elimination of tBuOH, would afford naphthalene 16. The observed regioselective ring opening of cyclopropane supported the involvement of the benzylic radical 17 as a possible reactive intermediate.

The significant difference in the yield of 16 from radical clock probe 15 under the methoxy methylation and azido methylation conditions was intriguing. We tentatively attributed to the different oxidation power of the copper salts. CuSO₄ is known to be a weaker oxidant than Cu(BF₄)₂·6H₂O, the benzylic radical generated under the azido methylation conditions (CuSO₄-
catalyzed) would, therefore, have a longer half-life than that generated under methoxy methylation conditions [Cu (BF₄)₂•6H₂O-catalyzed], hence the clean formation of product 16. This led us to hypothesize that the C–O bond formation in the present alkoxy methylation went through cationic intermediate (route a, Fig. 5a), whereas the C–N bond formation in the azido methylation proceeded via the Cu-mediated azide transfer process (route b or c, Fig. 5a).

In accordance with the aforementioned reaction manifolds, 1,2-methoxy methylation of 1-methyl-1-(4-nitrophenyl)ethylene (21) under standard conditions afforded a significant amount of dimer 22 and only a trace amount of the desired methoxy methylation product (Fig. 6a). The presence of the strong electron-withdrawing nitro group on the phenyl ring might significantly reduce the rate of the oxidation of benzyl radical 23 to carbenium, blocking therefore the methoxylolation process. It underwent instead the dimerization to afford 22. On the other hand, treatment of 21 under standard azido methylation conditions afforded the three-component adduct 3f in 78% yield together with a small amount of dimer 22 (Fig. 6b). The result supported the notion that oxidation of radical to cation is not involved in the azidation step and the azido group was transferred directly to the radical 23 via presumably a Cu-mediated redox transfer process. The azide transfer reaction was apparently faster than the dimerization process under our optimized azido methylation conditions. It is also worth noting that dimer was rarely observed under the optimized methoxy methylation of alkenes due presumably to the rapid oxidation of benzyl radical to benzyl cation (except for 21), while it was very often observed as a side product in the azido methylation process due to the relatively long-lived benzyl radical species. Finally, performing the azidomethylation of α-methylstyrene (1a) in MeOH and tBuOH/MeOH (v/v = 4:1) under otherwise standard conditions afforded the desired product 23a in yields of 46 and 62%, respectively. The potential competitive reaction leading to the 1,2-methoxy methylated product 2a was not observed. This result reinforced the hypothesis that benzyl cation might not be involved in the azidomethylation of alkenes.

At the outset of this research, we were concerned about the hydrogen abstraction of MeOH by tert-alkoxy radical B to generate the hydroxymethyl radical I (route d, Fig. 5a). This process has indeed been exploited in the disfunctionalization of activated alkenes. Two pathways, namely, thermal decomposition and reduction by Cu(I) salt, may contribute to the generation of the radical B from the peroxide. The formal process generates two molecules of alkoxide radical B, while the latter produces one molecule of B and one molecule of copper tert-butoxide C. Therefore, it was difficult to quantify the ratio of β-scission of B (generating Me•) vs H-abstraction of MeOH by B (leading to •CH₂OH) based on the ratio of acetophenone (D) vs 2-phenylpropan-2-ol (J). Nevertheless, the high J/D ratio (3/1) we obtained for the methylative methoxylolation of α-methylstyrene (1a) indicated that route d, a thermodynamically favorable process (BDE of H–CH₂OH: 96.06 ± 0.15 kcal/mol; tBuO–H: 106.3 ± 0.7 kcal/mol), was indeed occurring in parallel. However, the so-generated hydroxymethyl radical I did not interfere with the methylation process probably due to the pronounced nucleophilic nature of this radical or its rapid oxidation to formaldehyde.

In summary, we reported the Cu-catalyzed carboalkoxylation, carboazidation, carbocycloetherification, carbolactonization, and carbocyloamination of alkenes using dicumyl peroxide (DCP) or di-tert-butyl peroxide (DTBP) as methyl sources. A diverse set of...
stereoregularly prepared were converted to the methylated ethers, azides, tetrahydrofurans, tetrahydropyrans, γ-lactones, and pyrrolidines with concurrent generation of a quaternary carbon in good to excellent yields. The results of control experiments suggested that the 1,2-alkoxy methylation of alkenes went through a radical-cation crossover mechanism, whereas the azido methylation proceeded via a radical addition and Cu-mediated redox azide transfer process. This mechanistic insight would serve as a guideline in our searching for new alkene difunctionalization protocols.

Methods

Three-component 1,2-alkoxy methylation of alkenes. A screw cap tube was charged with CuBr(OTf)2 (13.8 mg, 0.0400 mmol), Na3PO4 (13.0 mg, 0.0601 mmol), Na2HPO4 (5.7 mg, 0.0402 mmol) and ROH (2.0 mL). The mixture was stirred at room temperature for 30 min, then substrate L1 (0.2 mmol, 1.0 equiv) and DCB (216.2 mg, 0.680 mmol) were added to the above mixture. After being stirred for 4 h at 120 °C under N2 atmosphere, the reaction mixture was quenched with water and the aqueous phase was extracted with EtOAc. The organic extracts were washed with brine, dried over Na2SO4. The solvent was removed under reduced pressure. The residue was purified by flash chromatography to give 3.

Methylation cycloalkenylation. A screw cap tube was charged with CuOAc2 (3.3 mg, 0.0068 mmol, 0.2 equiv), 1,10-phenanthroline L2 (10.8 mg, 0.06 mmol, 0.03 equiv) and CF3CH2OH (2.0 mL). The mixture was stirred at room temperature for 30 min. Substrate 6 (0.2 mmol, 1.0 equiv), Na2PO4 (6.5 mg, 0.04 mmol, 0.2 equiv) and DBTB (0.15 mL, 4.0 equiv) were added to the above mixture, and the reaction mixture was stirred at 120 °C for 6 h under N2 atmosphere. The reaction was quenched with water and the aqueous phase was extracted with EtOAc. The organic extracts were washed with brine, dried over Na2SO4. The solvent was removed under reduced pressure. The residue was purified by flash chromatography to give 5.

Methylative lactonization. A screw cap tube was charged with CuOAc2 (7.3 mg, 0.04 mmol, 0.2 equiv), 1,10-phenanthroline L2 (10.8 mg, 0.06 mmol, 0.03 equiv) and CF3CH2OH (2.0 mL). The mixture was stirred at room temperature for 30 min. Substrate 8 (0.2 mmol, 1.0 equiv), Na2PO4 (6.5 mg, 0.04 mmol, 0.2 equiv) and DFBT (0.15 mL, 4.0 equiv) were added to the above mixture, and the reaction mixture was stirred at 120 °C for 6 h under N2 atmosphere. The reaction was quenched with water and the mixture was extracted with EtOAc. The organic extracts were washed with brine, dried over Na2SO4. The solvent was removed under reduced pressure. The residue was purified by flash chromatography to give 7.

Data availability

The authors declare that the data supporting the findings of this study are available within the paper and Supplementary Information, as well as from the authors upon request.

Received: 13 June 2018 Accepted: 21 August 2018
Published online: 13 September 2018

References

1. Schönherr, H. & Cernak, T. Profound methyl effects in drug discovery and a call for new C–H methylation reactions. Angew. Chem., Int. Ed. 52, 12256–12267 (2013).
2. Yan, G., Borah, A. J., Wang, L. & Yang, M. Recent advances in transition-metal-catalyzed methylation reactions. Adv. Synth. Catal. 357, 1333–1350 (2015).
3. Hu, L., Liu, Y. A. & Liao, X. Recent progress in methylation of heteroarenes by cross-coupling or C–H activation. Synlett 29, 375–382 (2018).
4. Studer, A. A. “Renaissance” in radical trifluoromethylation. Angew. Chem., Int. Ed. 51, 8950–8958 (2012).
5. Merino, E. & Nevado, C. Addition of CF3 across unsaturated moieties: a powerful functionalization tool. Chem. Soc. Rev. 43, 6398–6408 (2014).
6. McGrath, N. A., Brice, A. M. & Njardarson, J. T. A. A graphical journey of innovative organic architectures that have improved our lives. J. Chem. Educ. 87, 1348–1349 (2010).
7. Charpentier, J., Früh, N. & Togni, A. Electrophilic trifluoromethylation by use of hypervalent iodine reagents. Chem. Rev. 115, 650–682 (2015).
8. Mukaiyama, T., et al. Oxidation-reduction hydration of olefins with molecular oxygen and 2-propanol catalyzed by bis(acetylacetonato)cobalt(II). Chem. Lett. 18, 449–452 (1989).
9. Waser, J., Gaspar, B., Nambu, H. & Carreira, E. M. Hydrazines and azides via the metal-catalyzed hydroarylation and hydroazidation of olefins. J. Am. Chem. Soc. 128, 11693–11712 (2006).
10. Barth, T. J. & Borer, D. L. Fe(II)/N3-mediated free radical hydrofunctionalization of unactivated alkenes. J. Am. Chem. Soc. 134, 13588–13591 (2012).
11. Shigeisha, H., et al. Catalytic synthesis of saturated oxygen heterocycles by hydrofunctionalization of unactivated olefins: unprotected and protected strategies. J. Am. Chem. Soc. 138, 10597–10604 (2016).
12. Girijavallabhan, V., Alvarez, C. & Njoroge, F. G. Regioselective cobalt-catalyzed addition of sulfides to unactivated alkenes. J. Org. Chem. 76, 6442–6446 (2011).
13. Green, S. A., Matos, J. L. M., Yagi, A. & Shenvi, R. A. Branch-selective hydroarylation: iodoarene–olefin cross-coupling. J. Am. Chem. Soc. 138, 12779–12782 (2016).
14. King, S. M., Ma, X. & Herzon, S. B. A method for the selective hydrogenation of alkyl halides to alkyl alcohols. J. Am. Chem. Soc. 136, 6884–6887 (2014).
15.Dao, H. T., Li, C., Michaudel, Q., Maxwell, B. D. & Baran, P. S. Hydromethylation of unactivated olefins. J. Am. Chem. Soc. 138, 8046–8049 (2015).
16. Crossley, S. W. M., Obrazd, C., Martinez, R. M. & Shenvi, R. A. Mn–Fe–Co-catalyzed radical hydrofunctionalizations of olefins. Chem. Rev. 116, 8912–9000 (2016).
17. Maimone, T. J., Shi, J., Ashida, S. & Baran, P. S. Total synthesis of vinigrol. J. Am. Chem. Soc. 131, 17066–17067 (2009).
18. Poulin, J., Grisé-Bard, C. M. & Barrauitt, L. A formal synthesis of vinigrol. Angew. Chem., Int. Ed. 51, 2111–2114 (2012).
19. Gray, P. & Williams, A. The thermochemistry and reactivity of alkoxyl radicals. Chem. Rev. 59, 239–328 (1959).
20. Maeda, M., Nushi, K. & Kawazoe, Y. Studies on chemical alterations of核酸 acids and their components-VII: C-alkylation of purine bases through free radical process catalyzed by ferrous ion. Tetrahedron 30, 2677–2682 (1974).
21. Zady, M. F. & Wong, J. L. Kinetics and mechanism of carbon–8 methylation of purine bases and nucleosides by methyl radical. J. Am. Chem. Soc. 99, 5096–5101 (1977).
22. Minisci, F., Vismara, E. & Fontana, F. Recent developments of free-radical substitutions of heteroaromatic bases. Heterocycles 28, 489–519 (1989).
23. Zhang, Y., Feng, J. & Li, C. Palladium-catalyzed methylation of aryl C−H bond by using peroxides. J. Am. Chem. Soc. 130, 2900–2901 (2008).
24. Kubo, T. & Chatani, N. Dicumyl peroxide as a methylation reagent in the Nicatalyzed methylation of ortho C–H bonds in aromatic amides. Org. Lett. 18, 1697–1701 (2016).
25. Zhang, P.-Z., et al. Metal-free radical C–H methylation of pyrimidinones and pyrimidinones with dicumyl peroxide. Green. Chem. 19, 919–923 (2017).
26. Li, Q., et al. Cobalt-catalyzed CrpH2− methylation by using Dicumyl peroxide as both the methylation reagent and hydrogen acceptor. Chem. Eur. J. 22, 12286–12289 (2016).
27. Xia, Q., Liu, X., Zhang, T., Chen, C. & Chen, W. Copper-catalyzed Nmethylation of amides and O-methylation of carboxylic acids by using peroxides as the methylation reagents. Org. Lett. 15, 3326–3329 (2013).
28. Zhu, Y., et al. Copper-catalyzed methyl esterification reactions via C–C bond cleavage. J. Org. Chem. 78, 9988–9995 (2013).
29. Teng, F., Cheng, J. & Yu, J.-T. Copper-catalyzed N-methylation/ethylation of sulfoximines. Org. Biomol. Chem. 13, 9593–9597 (2015).
30. Bao, Y., et al. Copper-catalyzed radical methylation/C–H amination/oxidation cascade for the synthesis of quinazolinones. J. Org. Chem. 80, 4736–4742 (2015).
31. Xu, Z., Yan, C. & Liu, Z.-Q. A free-radical cascade methylation/cyclization of N-arylacylamides and isocyanides with dimethyl peroxide. Org. Lett. 16, 5679–5682 (2014).
32. Dai, Q., et al. Di-tert butyl peroxide-promoted sequential methylation and intramolecular aromatization of isonitriles. Adv. Synth. Catal. 356, 3341–3346 (2014).
33. Xu, Z., Hang, Z. & Liu, Z.-Q. Free-radical triggered ordered domino reaction: an approach to C=C bond formation via selective functionalization of a hydroxyl-(sp)C H fluorinated alcohols. Org. Lett. 18, 4470–4473 (2016).
34. Zhang, X., et al. Selective oxidative coupling reaction of isocyanides using peroxide as switchable alkyllating and alkoxylating reagent. Adv. Synth. Catal. 360, 272–277 (2018).
35. Fan, J.-H., et al. Iron-catalyzed oxidative aminomethylation of activated alkenes using a peroxoacid as the methyl source. Synlett 25, 657–660 (2016).
36. Dai, Q., et al. The carbomethylation of arylacrylamides leading to 3-ethyl-3-substituted indolin-2-one by cascade radical addition/cyclization. Chem. Commun. 50, 3865–3867 (2014).
37. Tan, F.-L., Song, R.-J., Hu, M. & Li, J.-H. Metal-free oxidative 1,2-arylmethylation cascades of N-(aryl)sulfonyl)arylamides using peroxides as the methyl resource. Org. Lett. 18, 3198–3201 (2016).
38. Tan, F.-L., Hu, M., Song, R.-J. & Li, J.-H. Metal-free annulation cascades of 1,7-enynes using di-tert-butyl peroxide as the methyl source towards the synthesis of polyheterocyclic scaffolds. Adv. Synth. Catal. 359, 3602–3610 (2017).
39. Dai, Q., Jiang, Y., Yu, J.-T. & Cheng, J. Peroxide: A novel methylation reagent. Synthesis 48, 329–339 (2016).
40. Herk, L., Stefani, A. & Szwarc, M. Methyl affinities of some compounds related to acrylates and acrylonitriles. reactivities of conjugated systems involving atoms other than carbon. J. Am. Chem. Soc. 83, 3008–3011 (1961).
41. Minisci, F., Mondelli, R., Gardini, G. P. & Porta, O. Nucleophilic character of allyl radicals—VI. Substituent effects on the homolytic alkylation of protonated heteroaromatic bases with methyl, primary, secondary and tertiary alkyl radicals. Tetrahedron 28, 2403–2413 (1972).
42. Zytowski, T. & Fischer, H. Absolute rate constants for the addition of methyl radicals to alkenes in solution: new evidence for polar interactions. J. Am. Chem. Soc. 118, 437–439 (1996).
43. Zhu, N., Zhao, J. & Bao, H. Iron-catalyzed methylation and ethylation of vinyl amines. Chem. Sci. 8, 2081–2085 (2017).
44. Wang, Y., et al. Alkene oxaalkylation enabled by merging rhenium catalysis with hypervalent iodine(III) reagents via decarboxylation. J. Am. Chem. Soc. 135, 18048–18051 (2013).
45. Thalheux-Aca, A., Garza-Sanchez, R. A. & Glorius, F. Multicomponent oxaalkylation of styrenes enabled by hydroboronic acid–mediated copper-catalyzed alkylation. Org. Lett. 18, 3341–3344 (2016).
46. Li, Y., et al. Copper-catalyzed regioselective 1,2-alkylketonization of dienes to allylic esters. Org. Lett. 18, 392–395 (2016).
47. Wu, K., Liang, Y. & Jiao, N. Azidation in the difunctionalization of olefins. Molecules 21, 352 (2016).
48. Renaud, P., Ollivier, C. & Panchaud, P. Radical carboazidation of alkenes: an efficient tool for the preparation of pyrroldione derivatives. Angew. Chem., Int. Ed. 41, 3460–3462 (2002).
49. Weidner, K., Giroult, A., Panchaud, P. & Renaud, P. Efficient carboazidation of alkenes using a radical desulfonylative azide transfer process. J. Am. Chem. Soc. 132, 17515–17516 (2010).
50. Bunescu, A., Ha, T. M., Wang, Q. & Zhu, J. Copper-catalyzed three-component carboazidation of alkenes with acetonitrile and nitriles. Angew. Chem., Int. Ed. 56, 10555–10558 (2017).
51. Qian, B., Chen, S., Wang, T., Zhang, X. & Bao, H. Iron-catalyzed carboamination of olefins: synthesis of amines and disubstituted β-amino acids. J. Am. Chem. Soc. 139, 13076–13082 (2017).
52. Liu, Y.-Y., Yang, X.-H., Song, R.-J., Luo, S. & Li, J.-H. Oxidative 1,2-carboamination of alkenes with alkyl nitrites and amines toward γ- amino alcohols. Nat. Commun. 8, 14720–14725 (2017).
53. Wolfe, J. P. Palladium-catalyzed carbotherfication and carboxamidation reactions of γ-hydroxy- and γ-aminoalkanes for the synthesis of tetrahydrofurans and pyrrolidines. Eur. J. Org. Chem. 571–587 (2002).
54. Chemler, S. R. & Fuller, P. H. Heterocycle synthesis by copper facilitated addition of amines to ketones. J. Org. Chem. 72, 11531–11536 (2007).
55. Ha, T. M., Wang, Q. & Zhu, J. Copper-catalysed cyanocycloaddition of ketones to 1,3-dihydropyrazolofurans: development and application to the synthesis of citralopram. Chem. Commun. 52, 11100–11103 (2016).
56. Connolly, J. D. & Hill, R. A. Dictionary of terpenoids. Vol. 1, 476–545 (Chapman and Hall, London, 1991).