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Copper-Catalyzed C(sp3)−H Methylation via Radical Relay

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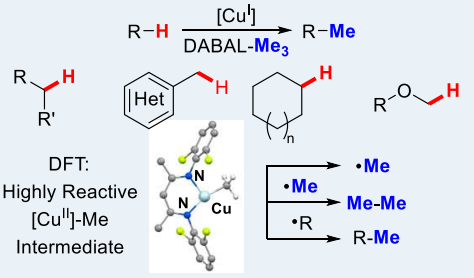
ABSTRACT: The methyl moiety is a key functional group that can result in major improvements in the potency and selectivity of pharmaceutical agents. We present a radical relay C−H methylation methodology that employs a β-diketiminate copper catalyst capable of methylating unactivated C(sp^3)−H bonds. Taking advantage of the bench-stable DABAL-Me_3, an amine-stabilized trimethylaluminum reagent, methylation of a range of substrates possessing both activated and unactivated C(sp^3)−H bonds proceeds with a minimal amount of overmethylation. Mechanistic studies supported by both experiment and computation suggest the intermediacy of a copper(II) methyl intermediate reactive toward both the loss of the methyl radical as well capture of radicals R$^\bullet$ to form R−Me bonds.



KEYWORDS: *C−H functionalization, methylation, copper, radical relay, DFT*

The methyl group is one of the smallest, yet most common, functional groups in chemistry. The addition of a methyl group has the ability to alter steric and conformational properties without significantly affecting the electronic characteristics of a molecule.[1] In some cases, large conformational changes occur upon addition of this functional group, leading to greater efficacy of pharmaceutical agents.[2] This effect, dubbed the "magic methyl" effect, creates an increased demand for protocols to install a methyl group, especially for both weaker as well as nonactivated C−H bonds.

C−H functionalization has enabled the installation of the methyl groups in a wide variety of settings via directed C(sp^2)−H activation[3,4] or radical-generating mechanisms.[5,6] Oxidative C(sp^3)-H methylation, however, has been far less explored and typically requires directing groups.[7−9] Recently undirected C(sp^3)−H methylation has been reported employing activated C−H bonds α to heteroatoms (Figure 1a).[10,11] In these protocols, C(sp^3)−H bonds are selectively oxidized to C−OH or C−OR moieties that serve as synthetic handles for subsequent methylation to provide products with C−Me bonds. Since these methods typically target activated, weaker C−H bonds, methylation of nonactivated C(sp^3)−H bonds poses a considerable challenge.

Employing a substrate-bound directing group, Sharma utilized a [Cp*Rh^{III}] catalyst to methylate 8-methylquinolines with organoboron reagents (Figure 1b).[12] The undirected methylation of simple substrates has been recently performed by Li, using p-type doped gallium nitride nanowires to methylate simple hydrocarbons via methylene intermediates such as cyclopentane and *n*-hexane (Figure 1c).[13] Recently, Stahl has realized C(sp^3)−H methylation using Ni and Ir catalysts under photoredox catalysis with ^{t}BuOO^{t}Bu serving as a HAT reagent and a source of CH_3 radicals (Figure 1d).[14] While recent reports have begun to address nonactivated C(sp^3)−H methylation,[13] new approaches are still needed for this important synthetic opportunity.

Building upon the Kharasch−Sosnovsky reaction,[15−17] we have developed various C−H functionalization protocols that convert sp^3 C−H bonds to C−N and C−O bonds employing amides,[18] anilides,[19,20] and acyl-protected phenols[21] that result in β-diketiminate-stabilized [Cu^{II}]-FG intermediates in radical relay catalysis[22] (Figure 2a). Recently, we have shown that copper(II) complexes with Cu−C bonds also function in this radical relay protocol. For instance, terminal alkynes can be utilized in the alkynylation of sp^3 C−H substrates RH to give RC≡CAr via the isolable three-coordinate copper(II) alkynyl intermediate [^{i}Pr$_2$NN]CuC≡CAr (**1**) (Figure 2b) capable of capture of radicals such as $Ph_3C^\bullet$ to give Ph_3C−C≡CAr.[23] This enables C−H alkynylation of benzylic substrates R-H with ^{t}BuOO^{t}Bu as oxidant to give products RC≡CAr in good yield that competes with bimolecular coupling to give the diynes ArC≡CC≡CAr.

Thus, copper(II) organometallic complexes can serve in radical relay catalysis for C−C bond formation. DFT studies in support of a recently developed C−H arylation protocol that converts benzylic sp^3 C−H bonds in substrates R-H to R-C_6F_5 suggests the formation of [Cu^{II}]-C_6F_5 intermediates via an acid−base exchange between [Cu^{II}]-O^{t}Bu and the mildly acidic C−H bond in HC_6F_5.[24] Earlier synthetic studies enabled the isolation of the β-diketiminato copper(II) aryl complex [Me_2NN_{F6}]CuC_6F_5 (**2**) via transmetalation between [Cu^{II}]-

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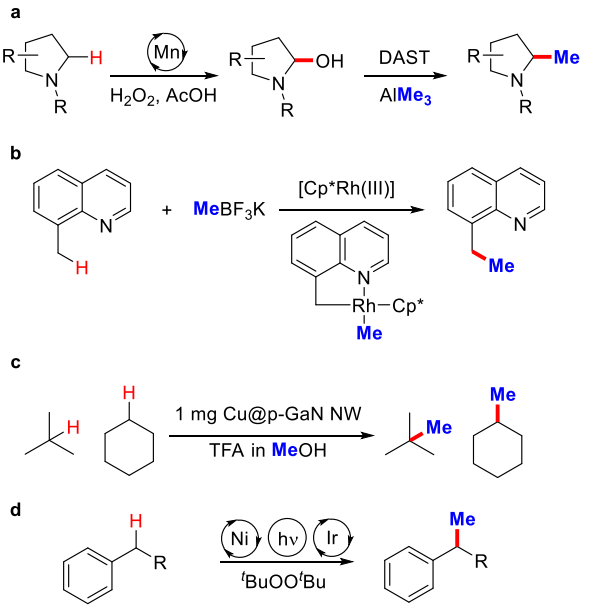


Figure 1. (a) Activated C(sp^3)–H methylation. (b) Directed C(sp^3)–H methylation. (c) Unactivated C(sp^3)–H methylation. (d) Photoredox C(sp^3)–H methylation.

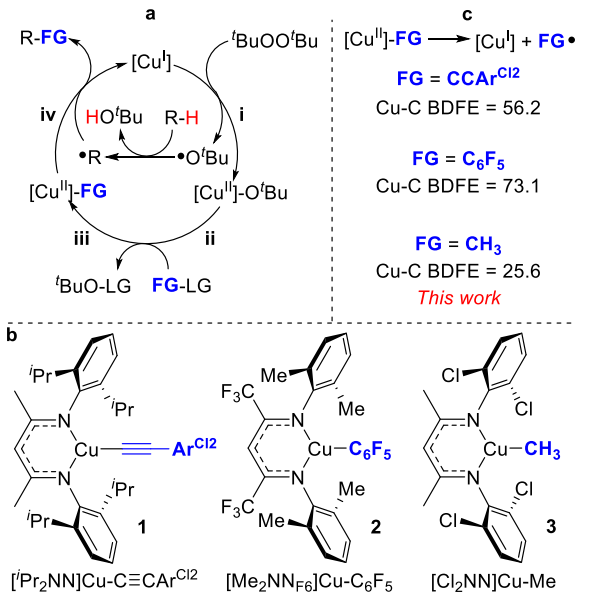
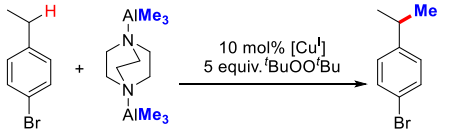


Figure 2. (a) Radical relay mechanism for C–N, C–O, and C–C bond forming reactions. (b) Proposed Cu-alkynyl, Cu-aryl, and Cu-methyl intermediates in C_{sp}–C_{sp3}, C_{sp2}–C_{sp3}, and C_{sp3}–C_{sp3} bond forming reactions. (c) Calculated Cu–C bond free energies (kcal/mol) for proposed Cu-alkynyl, Cu-aryl, and Cu-methyl intermediates.

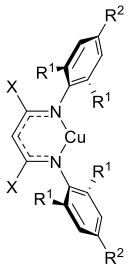
O^tBu and $B(C_6F_5)_3$.[25] These studies reveal that $[Cu^{II}]$-C_6F_5 intermediates such as **2** are more stable than nonfluorinated $[Cu^{II}]$-C_6H_5 with higher Cu–C BDFEs being calculated by DFT (56.2 vs 30 kcal/mol) (Figure 2b,c). Each decomposes to the corresponding biaryl Ar–Ar, likely via a redox disproportionation pathway that enables formation of $[Cu]Ar_2$ species with low barriers to Ar–Ar coupling.[25]

To enable a related copper-catalyzed sp^3 C–H methylation methodology via a copper(II) methyl intermediate such as $[Cl_2NN]$Cu-Me (**3**), we began by exploring Lewis acidic methylating reagents capable of reaction with copper(II) *tert*-butoxide intermediates $[Cu^{II}]$-O^tBu formed upon activation of copper(I) β-diketiminates with $^tBuOO^tBu$ (Figure 2a, step i.[26] During the screening of various reagents that included $AlMe_3$ and $ZnMe_2$ (Table S1), we identified 1,4-diazabicyclo[2.2.2]-octane (DABAL-Me_3)[27,28] as an attractive methylating reagent. Initial investigations showed an 80% yield for methylation of 4-bromotoluene based on 1 equiv of DABAL-Me_3 that includes 20 equiv of C–H substrate and 5 equiv of $^tBuOO^tBu$ oxidant with 10 mol % of $[Cl_2NN]Cu^I$ (henceforth denoted $[Cu^I]$), a commercially available β-diketiminate catalyst (Table S1). Heating the reactions to 100 °C also improved yields. With our methylation source in hand, we began screening a range of copper(I) β-diketiminate catalysts (Table 1). Utilizing the

Table 1. Copper-Catalyzed C–H Methylation of 4-Bromotoluene by DABAL-Me_3



Entry	Catalyst		(X, R^1, R^2)	Yield (%)
1.	$[Cl_2NN]Cu$	**1a**	(Me, Cl, H)	80
2.	$[Me_3NN]Cu$	**1b**	(Me, Me, Me)	60
3.	$[(OMe)_2NN]Cu$	**1c**	(Me, OMe, H)	25
4.	$[Cl_2NN_{F6}]Cu$	**1d**	(CF_3, Cl, H)	49
5.	$[iPr_2NN_{F6}]Cu$	**1e**	(CF_3, iPr, H)	29
6.	$[Me_2NN_{F6}]Cu$	**1f**	(CF_3, Me, H)	49
7.	No catalyst			9



Conditions: 20 equiv. R-H, neat, -35 °C then heated to 100 °C, 16 h. All yields were determined by ^1H NMR.

more electron rich catalysts **1b,c** did not improve yields, whereas the more electron poor catalysts **1d–f** also showed a diminished product formation. Focusing on $[Cl_2NN]Cu$ as catalyst, we find that increasing the catalyst loading from 1 to 10 mol % increases the yield of C–H methylation with ethylbenzene (Table S2). While DABAL-Me_3 could potentially deliver multiple Me groups in the presence of excess oxidant, we report yields relative to the use of 1 equiv of DABAL-Me_3.

We then began to investigate the efficacy of this methodology with various C(sp^3)–H substrates. For consistency, we report NMR and GC yields directly measured from the reaction mixtures (Table 2). Primary benzylic substrates are particularly good substrates for this methylation protocol (**4a,d,f,h**). Despite their lower C–H bond strengths, secondary and tertiary benzylic substrates often exhibited lower yields (**4b,e,g,I**). Accordingly, we see very little overmethylation of primary benzylic substrates (<2%). A modest range of substrates possessing sp^3 C–H bonds α to heteroatoms gave moderate to good yields of C–H methylation products **4m–p**. Notably, nonactivated sp^3 C–H substrates such as cyclohexane and cyclooctane provided methylated cycloalkanes **4k,l** in good to moderate yields. Use of DABAL-Me_3-d_{18} derived from $Al(CD_3)_3$ in the C–H methylation of toluene results in $PhCH_2CD_3$, confirming that the added methyl group in the product is derived from the DABAL-Me_3 reagent (Figure S36).

Based on previous synthetic studies with copper(II) β-diketiminato *tert*-butoxide complexes $[Cu^{II}]$-O^tBu, we anticipated that the reaction of $[Cu^{II}]$-O^tBu and DABAL-Me_3 would result in a transmetalation leading to the $[Cu^{II}]$-CH_3 intermediate **3**. Addition of DABAL-Me_3 to $[Cl_2NN]$Cu-O^tBu results in rapid decay of the band at λ = 470 nm without the observation of any new optical band consistent with a long-lived copper(II) species. Thus, any $[Cl_2NN]$Cu-Me (**3**)

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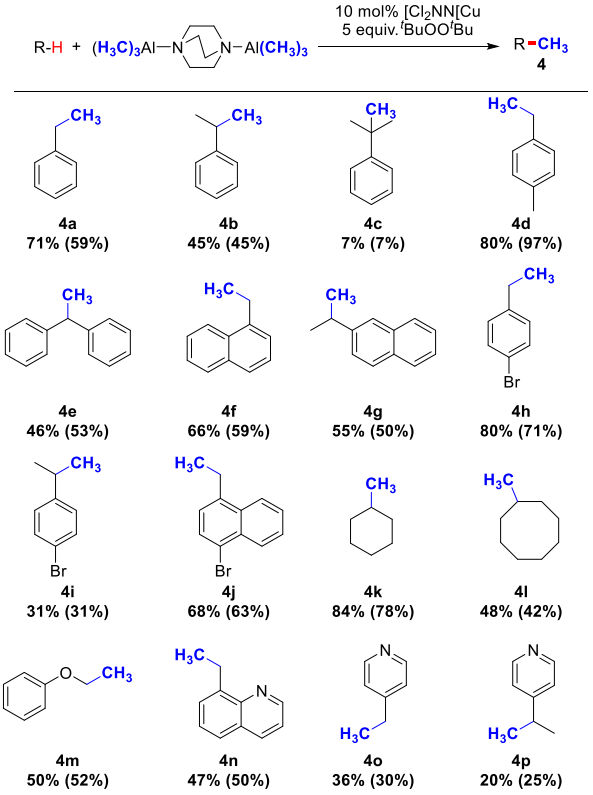
Table 2. Copper-Catalyzed C−H Methylation of Various C−H Substrates by DABAL-Me$_3$[a]



[a]Conditions: 20 equiv of R-H, neat, −35 °C then heated to 100 °C, 16 h. All yields were determined by ^{1}H NMR. GC/MS yields are noted in parentheses.

intermediate would have a very short lifetime. Additionally, we note the copious generation of gas upon addition of DABAL-Me$_3$ to [Cu^{II}]-O^{t}Bu when the reaction carried out on synthetic scales at room temperature.

We studied the formation of these gases through stoichiometric reaction of [Cu^{II}]-O^{t}Bu with DABAL-Me$_3$ in toluene (Figure 3a). We observe significant generation of methane and ethane that could proceed via Me$^\bullet$ radicals. Moreover, the formation of ethylbenzene suggests that Me$^\bullet$ radicals could engage in H atom transfer with PhCH$_2$-H to generate methane (Me-H) and a toluene radical (PhCH$_2^\bullet$); previous studies have demonstrated that [Cl$_2$NN]C-O^{t}Bu is unreactive toward benzylic C−H bonds.[20] Inclusion of

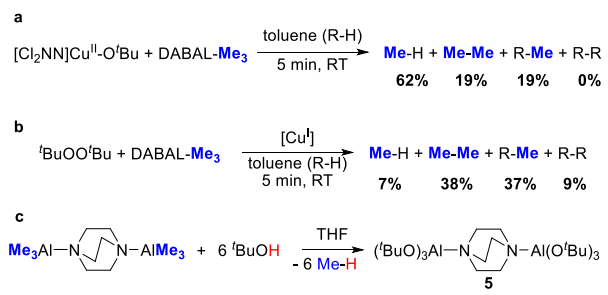


Figure 3. Analyzing the reactivity of DABAL-Me$_3$ under catalytically relevant conditions: (a) reactions between [Cu^{II}]-O^{t}Bu and DABAL-Me$_3$, (b) catalytic C−H methylation with toluene; (c) alcoholysis of DABAL-Me$_3$.

^{t}BuOO^{t}Bu enhances the sp^3 C−H methylation of toluene, though Me$^\bullet$ and PhCH$_2^\bullet$ radical homocoupling also occurs (Figure 3b). We speculate that the generation of benzylic radicals through HAT from toluene to the ^{t}BuO$^\bullet$ radical facilitates benzylic C−H methylation through more efficient production of benzyl radicals for capture via [Cu^{II}]-CH$_3$ intermediates. An additional route for Me-H formation involves the alcoholysis of DABAL-Me$_3$ with ^{t}BuOH generated in HAT reactions via ^{t}BuO$^\bullet$. Addition of excess ^{t}BuOH to a solution of DABAL-Me$_3$ results in quantitative formation of DABAL-(O^{t}Bu)$_3$ (**5**) (Figure 3c), isolated as colorless crystals and identified by X-ray crystallography (Figure S39).

To investigate organometallic intermediates suggested to be highly reactive via our experimental studies, we employed DFT methods at the BP86+/6-311G(d,p)/SMD-benzene//BP86/6-311+G(d) level of theory. We began by examining the stability of [Cu^{II}]-Me intermediate **3** toward homolytic cleavage of its Cu−Me bond to give the methyl radical (Figure 4a). Release of Me$^\bullet$ from the T-shaped d^9 complex[29] [Cu^{II}]-Me (Figure 4d and Figure S73) is uphill by 26.0 kcal/mol, disfavored by the instability of the two-coordinate β-diketiminato copper(I) fragment [Cu^I]. Noting the affinity of copper(I) β-diketiminates for η^2-arene coordination,[30,31] we considered the concerted displacement of the methyl radical by an incoming molecule of benzene. This results in a much less endergonic release of the methyl radical Me$^\bullet$ (+7.2 kcal/mol) with a free energy of activation of only 12.4 kcal/mol (Figure 4a).

Recognizing that the [Cu^{II}]-Me intermediate can readily generate Me$^\bullet$ radicals, we briefly computationally compared activation barriers for H atom abstraction (HAA) from sp^3 C−H substrates R-H by Me$^\bullet$ and ^{t}BuO$^\bullet$ generated in the presence of [Cu^I] and ^{t}BuOO^{t}Bu (Figure 4b and Table S8).[26] At this level of theory, thermodynamic and activation parameters for abstraction of a benzylic hydrogen atom from ethylbenzene by a methyl radical (ΔG = −20.3 kcal/mol, $\Delta G^\ddagger$ = 8.9 kcal/mol) are greater in magnitude than those for the *tert*-butoxy radical (ΔG = −17.8 kcal/mol, $\Delta G^\ddagger$ = 4.8 kcal/mol). These computational finding reflect the experimentally observed trend of more favorable benzylic C-H abstraction by the ^{t}BuO$^\bullet$ vs the Me$^\bullet$ radicals.[32,33] HAT by Me$^\bullet$ represents one pathway for experimentally observed methane formation (Figure 3a), while HAT by ^{t}BuO$^\bullet$ forms ^{t}BuOH.

Computational studies reveal that the copper(II) methyl intermediate [Cu^{II}]-Me captures alkyl radicals R$^\bullet$ extremely efficiently to provide distorted square planar [Cu^{III}](Me)(R) intermediates with τ_4 values between 0.30 and 0.60 (τ_4 = 0, square planar; τ_4 = 1, tetrahedral)[34] susceptible to reductive elimination of R-Me products (Figure 4c, 4e). While the capture of a Me$^\bullet$ radical by [Cu^{II}]-Me to form [Cu]Me$_2$ is thermodynamically most favored (ΔG = −31.9 kcal/mol), capture of 1°, 2°, and 3° benzylic radicals decreases in exergonicity (ΔG = −20.7, −17.2, −7.2 kcal/mol, respectively) with increasing size and stability of the alkyl radical R$^\bullet$.

Relaxed potential energy scans reveal no significant barrier for radical capture by [Cu^{II}]-Me. The T-shaped geometry of [Cu^{II}]-Me (Figure 4d), similar to that of [Cu^{II}]-C$_6$F$_5$, leaves the copper center poised for capture of alkyl radicals R$^\bullet$ to form the square-planar [Cu^{III}](Me)(R) (Figure 4e). In each case, reductive elimination from [Cu^{III}](Me)(R) species to form [Cu^I] and Me-R is facile with minute barriers of 2.8−5.4 kcal/mol.

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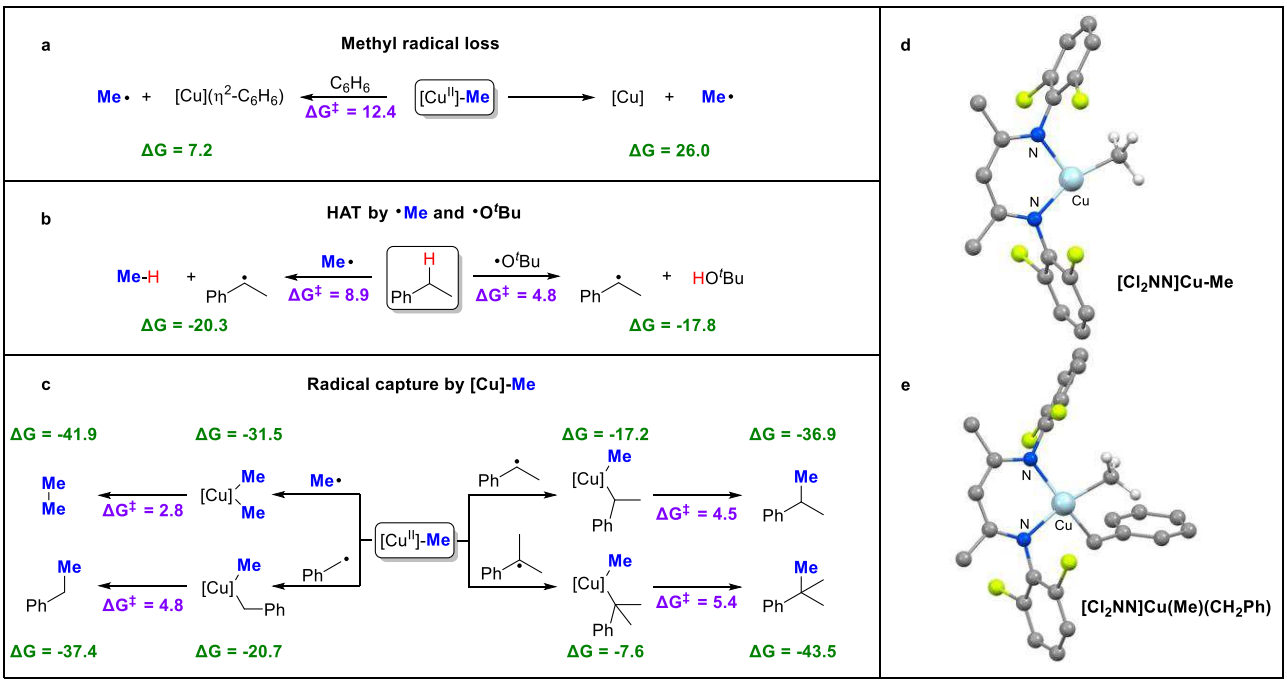

Figure 4. DFT calculated thermodynamics and activation barriers for (a) methyl loss from [Cu]-Me, (b) H atom transfer from ethylbenzene by Me• and •O^{t}Bu, (c) radical capture by [Cu]-Me along with DFT structures of (d) [Cu]-Me and (e) [Cu](Me)(CH$_2$Ph) calculated at the BP86+/6-311G(d,p)/SMD-benzene//BP86/6-311+G(d) level of theory. Free energies are given in kcal/mol.

C(sp^3)−H methylation can occur via copper-catalyzed radical relay employing ^{t}BuOO^{t}Bu as oxidant similar to other C−H functionalization reactions that form C−N, C−O, and C−C bonds (Figure 2).[18−22] In contrast to other protocols that involve relatively stable [Cu^{II}]-FG intermediates, experimental and computational studies suggest that [Cu^{II}]-Me generates the Me• radical capable of H atom abstraction of sp^3 C−H substrates R-H to form radicals R•.[35] At the same time, Me• radicals generated may compete with R• for capture by [Cu^{II}]-Me (**3**) to form [Cu](Me)(R) intermediates (R = Me, alkyl) that undergo facile reductive elimination which can lead to nonproductive methyl group usage (R = Me). Solely based on sterics, we would anticipate slower capture of bulky 3° radicals such as PhC(•)Me$_2$ as compared to 1° radicals PhCH$_2$• that could result in lower experimental yields of PhCMe$_3$ vs PhCH$_2$Me, especially if these radicals are competing for capture at [Cu^{II}]-Me with the small, reactive Me• radical. Thus, the decreasing exergonicity of radical capture for larger radicals such as the 3° benzylic PhC(•)Me$_2$ (Figure 4c) may contribute to the lower experimental yields observed (Table 2, entry 4c).

Since H atom abstraction can occur via either ^{t}BuO• or Me• radicals that form strong ^{t}BuO−H and Me−H bonds (BDE = 105 and 104 kcal/mol, respectively); this system methylates unactivated 2 °C−H bonds of cycloalkanes (BDE = 95−99 kcal/mol).[36] One pathway to consider in catalyst optimization is to decrease the ability of an incoming arene to associatively displace a Me• radical from [Cu^{II}]-Me to give [Cu^{I}](η^2-arene) and Me•. Nonetheless, the volatility of the methane and ethane byproducts coupled with the ease of handling of DABAL-Me$_3$ results in a system that allows for the use of excess methylating reagent that generates easily separable gaseous products.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.2c02474.

Experimental, X-ray structure and DFT calculation details (PDF)

X-ray data for DABAL-(O^{t}Bu)$_3$ (**5**) (CIF)

XYZ coordinates of DFT calculated structures (TXT)

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Author Contributions

B.C.F. performed all experimental and most computational work; T.-A. C.carried out some computational work. B.C.F. and J.A.B. collected, solved, and refined crystallographic data. T.H.W. supervised the experimental and computational work. B.C.F. and T.H.W. wrote the manuscript. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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