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Copper catalyzed benzylic sp^3 C–H alkenylation†Ting-An Chen,^{ab} Richard J. Staples^b and Timothy H. Warren^{b*}

The prenyl group is present in numerous biologically active small molecule drugs and natural products. We introduce benzylic C–H alkenylation of substrates Ar–CH₃ with alkenylboronic esters (CH₂)₃O₂B–CH=CMe₂ as a pathway to form prenyl functionalized arenes Ar–CH₂CH=CMe₂. Mechanistic studies of this radical relay catalytic protocol reveal diverse reactivity pathways exhibited by the copper(II) alkenyl intermediate [Cu^{II}]-CH=CMe₂ that involve radical capture, bimolecular C–C bond formation, and hydrogen atom transfer (HAT).

Introduction

The prenyl group (–CH₂CH=CMe₂) is a prevalent functionality found in natural products and biologically active small molecules.^{1–6} Prenyltransferase, an essential enzyme involved in prenylation, enhances protein stability and anchors proteins to cell membranes due to the hydrophobic nature of the prenyl group.^{7–10} The addition of a prenyl group to molecules can influence their biological activities.^{11–14} For instance, the prenyl group is the primary inhibitory component of the HIV inhibitor Osthol (Fig. 1a).¹⁵ Additionally, both experimental and computational methods have been used to determine that prenylated chrysin functions as a more potent inhibitor for P-glycoprotein, a determinant of drug accumulation in leukemia cells.^{16,17}

Methods for installing prenyl groups onto aromatic rings typically involve C–C coupling through allylation of an aryl halide (or pseudohalide) (Fig. 1b). For instance, Pd catalyzed Suzuki or Negishi coupling reactions produce prenylated aryl derivatives.^{18–20} Alternatively, sp^2 C–H prenylation of arene C–H bonds with 1,1-dimethylallene also leads to aryl prenyl derivatives.^{21–24}

This report presents an alternative strategy to prenyl-functionalized molecules through C–H alkenylation of benzylic C–H bonds *via* the alkenylboronic ester (CH₂)₃O₂B–CH=CMe₂ (Fig. 1d). Previous examples of direct sp^3 C–H alkenylation with alkenylboronic esters required highly acidic C–H bonds in aryl difluoromethyl derivatives Ar–CF₂H.²⁵ Alternatively, benzylic sp^3 C–H styrenylation occurs with styrenyl carboxylates and nitrites in the presence of ^tBuOO^tBu (Fig. 1c).^{26–30}

This report utilizes the dimethylethenyl (–CH=CMe₂) group as the alkenyl source for sp^3 C–H functionalization. Our research team and other groups have employed radical relay approaches for C–H functionalization (Fig. 2a).^{31–35} Based on sp^3 C–H alkynylation,³⁶ arylation,^{37–39} and methylation⁴⁰ that proceed *via* [Cu^{II}]-C≡CAr, [Cu^{II}]-Ar, and [Cu^{II}]-Me intermediates, respectively (Fig. 2b), we anticipated that [Cu^{II}]-CH=CMe₂ intermediates (Fig. 2c) could lead to benzylic sp^3 C–H alkenylation. This would convert an Ar–CH₂–H group to Ar–CH₂–CH=CMe₂, enabling net prenylation (Fig. 1d).

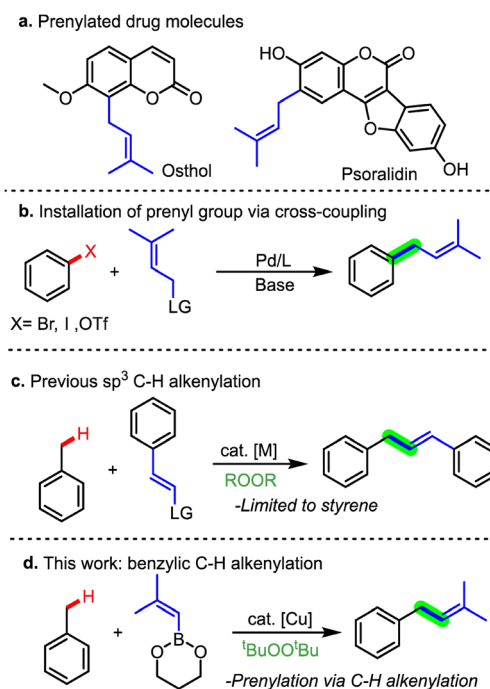


Fig. 1 (a) Prenylated natural products and drug molecules. (b) Prenylation *via* cross-coupling. (c) sp^3 C–H styrenylation. (d) Net prenylation *via* benzylic C–H alkenylation.

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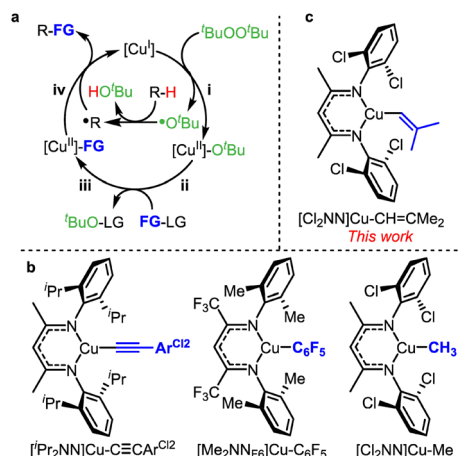


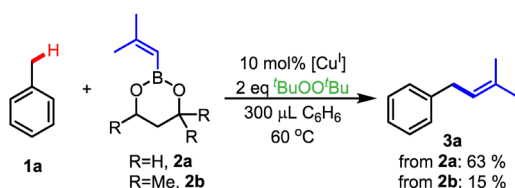
Fig. 2 (a) Radical relay mechanism for C-H functionalization. (b) β-Diketiminato copper(II) intermediates in C-H alkenylation, arylation and methylation. (c) Proposed copper(II) alkenyl intermediate for C-H alkenylation.

Results and discussion

Reaction discovery and optimization

We sought to enable benzylic C-H alkenylation, employing toluene as a representative benzylic substrate using Cu(I) β-diketiminato complexes as catalysts along with di-*tert*-butyl peroxide (^tBuOO^tBu) as the oxidant. We chose alkenylboronic esters as the alkenyl source but recognized that the nature of the boronic ester backbone could play an important role (Scheme 1). For example, 4,4,6-trimethyl-2-phenyl-1,3,2-dioxaborinane exhibited a higher yield in sp³ C-H arylation compared to phenylboronic acid pinacol ester.³⁹ Therefore, we investigated 2-alkenyl-1,3,2-dioxaborinane (**2a**) and 4,4,6-trimethyl-2-alkenyl-1,3,2-dioxaborinane (**2b**) as possible alkenyl group transfer reagents for C-H alkenylation of toluene (Scheme 1). Use of the less sterically hindered boronic ester **2a** produced a higher C-H alkenylation yield of product **3a** than with the more sterically hindered boronic ester **2b** (63% vs. 15%, respectively). Importantly, the more hindered boronic ester **2b** led to toluene C-H etherification to give PhCH₂O^tBu that signals capture of the benzyl radical PhCH₂• by the [Cu^{II}]-O^tBu intermediate (Scheme S1†).⁴¹ We hypothesize that a higher rate of transmetalation between the [Cu^{II}]-O^tBu intermediate and the less sterically hindered alkenylboronic ester **2a** to form a [Cu^{II}]-C=CMe₂ intermediate inhibits the formation of PhCH₂O^tBu (Scheme S1†).

Employing boronic ester **2a**, we explored various parameters including the solvent, catalyst loading (Table S1†), oxidant (Table S2†), temperature (Table S4†). Using optimized



Scheme 1 Size of alkenylboronic ester impacts alkenylation yield.

Table 1 Catalyst optimization for C-H alkenylation^a

Entry	X	R	R'	Product
1	CH ₃	Cl	H	63%
2	CF ₃	Cl	H	6%
3	CH ₃	Me	H	41%
4	CH ₃	Me	Me	29%
5	CH ₃	OMe	H	21%

^a Conditions: 20 equiv. R-H, 2 equiv. ^tBuOO^tBu, 60 °C, 1 h. Yield determined by GCMS analysis.

conditions (10 mol% [Cu], 2 equiv. ^tBuOO^tBu, 20 equiv. R-H, 300 μL benzene, and 60 °C), we also examined different copper β-diketiminato catalysts with diverse electronic and steric properties (Table 1). Among the tested catalysts, [Cl₂NN]Cu (Table 1, entry 1) gave the highest product yield. Interestingly, a very electron-poor catalyst (Table 1, entry 2) gave a very low yield, yet catalysts with electron-donating groups on the β-diketiminato *N*-aryl rings also decreased the product yield.

Benzylic C-H alkenylation leading to net prenylation

We systematically examined a range of benzylic R-H substrates, assessing reaction yields *via* GCMS analysis (Table 2). We initially focused on sp³ C-H alkenylation of commercially available 1° benzylic substrates Ar-CH₃ that lead to prenyl derivatives ArCH₂-CH=CMe₂ (**3a-3i**) in 42–92% yield. Slightly higher yields result in more electron-rich substrates Ar-CH₃ (**3b**, **3d**, **3e**; 64–92%). This method tolerates aryl halides Ar-X (**3f-3h**) that typically serve as substrates in more traditional cross-coupling reactions. The method also tolerates ortho-substitution as illustrated by the use of *o*-chlorotoluene and *o*-xylene (**3i** and **3j**) for C-H alkenylation. Secondary benzylic C-H sites in ethylbenzene also undergo C-H alkenylation (**3l**), yet exhibit lower yields due to the formation of styrene in 20% yield *via* β-H-atom abstraction from the ethylbenzene radical (PhCH(•)Me) (ESI, Section 4 and Scheme S5†). Additionally, *N,N*-dimethyl aniline (**3o**) proved amenable to α-*N* C-H functionalization, albeit in lower yield (22%). We also examined indoles with heteroaryl-Me groups, but unfortunately no C-H alkenylation occurs, even with *N*-Boc protected indoles.

To highlight potential advantages of prenylation *via* benzylic C-H alkenylation, we performed C-H alkenylation on three pharmaceutically relevant compounds (**3p-3r**). Notably, our method exhibited high selectivity for benzylic C-H bonds. For example, in the case of nabumetone (**3p**) which possesses multiple sp³ C-H bonds, exclusive benzylic C-H functionalization occurs. Entry **3r** yielded a product closely related to its *o*-OMe derivative with HIV inhibitory properties, highlighting the

Table 2 Cu catalysed C–H alkenylation^a

$\text{R-H} + \text{2a} \xrightarrow[60^\circ\text{C}]{10\text{ mol\% } [\text{Cl}_2\text{NN}]\text{Cu}, 2\text{ eq } ^t\text{BuOO}^t\text{Bu}, 300\text{ }\mu\text{L C}_6\text{H}_6} \text{R-CH=CHMe}$			
Benzylic CH₃			
R = H, 3a , 63 %	R = Me, 3d , 92 % (75%)	X = F, 3f , 50 % (22%)	R = Me, 3i , 70 % (22%)
Me, 3b , 64 % (40 %)	R = OMe, 3e , 69 %	Cl, 3g , 52 % (38 %)	Cl, 3j , 53 % (31%)
^t Bu, 3c , 51 % (21 %)		Br, 3h , 43 % (34 %)	
Benzylic CH₂R			
3k[†] , 42 % (28 %)	R = Me, 3l , 39 %	3n , 64 % (25 %)	3o[*] , 22 %
	Ph, 3m , 65 % (19 %)		
Drug-related molecules			
3p[*] , 35 % (15 %)	3q^{**} , 29 % (6 %)	3r^{**} , (8 %)	
Nabumetone	Psoralidin related structure	HIV inhibitor	

^a Detailed reaction conditions in ESI. Yields determined by GCMS. Isolated yield in parenthesis. [†]80 °C. ^{*}100 °C. ^{**}10 equiv. R–H substrate used.

potential of this direct C–H alkenylation method to condense lengthy syntheses.¹⁵ Yet we recognize the rather modest yields for the C–H functionalization step with these compounds (Table 2, entries **3p–3r**); some substrates lead to relatively strong binding with the [Cu^I] catalyst that impedes C–H functionalization (Scheme S2 and Fig. S4[†]).

Mechanistic investigations

To gain more insight into the interaction between the alkenylboronic ester and the [Cu^I] catalyst as well as the formation and reactivity of the proposed [Cu^{II}]-CH=CMe₂ intermediate, we examined facets of the reaction mechanism by integrating both experimental and computational analyses.

Alkenylboronic ester binding to copper(i) catalyst

Given the need for mild heating to encourage C–H alkenylation, we considered the possibility of equilibrium binding of the dimethylethenylboronic ester **2a** with the [Cu^I] catalyst (Fig. 3a). The crystal structure of the [Cu^I](η²-**2a**) adduct reveals an interaction between the π electrons of the alkene and the [Cu^I] catalyst (Fig. 3b). Higher temperatures promote the dissociation of this adduct, leading to increased concentrations of the dissociated species. A van't Hoff plot reveals thermodynamic parameters corresponding to this equilibrium: Δ*G*_{exp} (298) = 6.7 ± 1.0, Δ*H*_{exp} = 11.1 ± 0.5 kcal mol^{−1}, and Δ*S*_{exp} = 14.4 ± 1.6 e.u. (Fig. 3c and S2[†]).

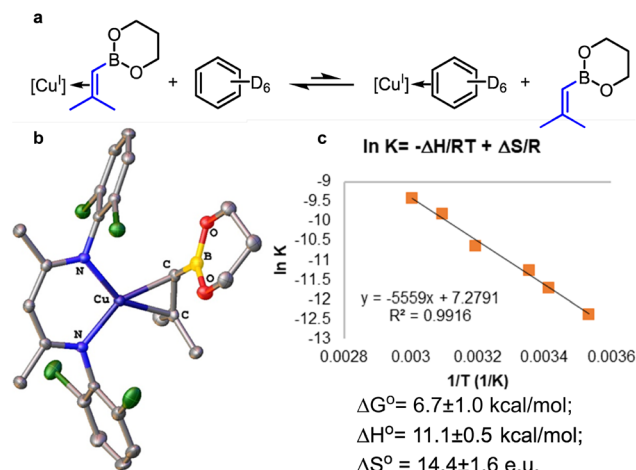


Fig. 3 (a) Reversible binding of **2a** to [Cu^I] catalyst in benzene, (b) X-ray structure of alkenylboronic ester adduct, and (c) van't Hoff plot.

Formation and reactivity of alkenyl intermediate [Cu^{II}]-C=CMe₂

Mixing [Cu^{II}]-O^tBu with **2a** in fluorobenzene produces a substantial amount of 2,5-dimethylhexa-2,4-diene (alkenyl dimer) (84% yield, Fig. 4a). This could proceed *via* a [Cu^{II}]-CH=CMe₂ intermediate that undergoes bimolecular C–C coupling to give the observed alkenyl dimer, much as [Cu^{II}]-C≡C–Ar and [Cu^{II}]-Ar intermediates readily form ArC≡C–C≡C–Ar³⁷ and Ar–Ar³⁸ species. *In situ* UV-vis analysis was employed to monitor the reaction intermediate of [Cu^{II}]-O^tBu and **2a** (Fig. S6[†]). Upon introducing **2a** into the [Cu^{II}]-O^tBu solution at −38 °C, a rapid reaction occurred, leading to a decrease in the absorption band of [Cu^{II}]-O^tBu without the detection of any newly generated [Cu^{II}] species. Based on previous bimolecular C–C bond formation *via* [Cu^{II}]-C≡C–Ar³⁷ and [Cu^{II}]-Ar³⁸ species, we propose that the [Cu^{II}]-CH=CMe₂ intermediate similarly undergoes rapid bimolecular C–C coupling to form Me₂C=CH–CH=CMe₂. Indeed, it is possible for a conjugated diene to bridge between two β-diketiminato [Cu^I] to form a [Cu^I]₂(μ-diene) species (Fig. S8[†]).

To further confirm the reaction intermediate obtained upon addition of alkenylboronic ester **2a** with [Cu^{II}]-O^tBu as [Cu^{II}]-CH=CMe₂, reaction in the presence of Gomberg's dimer (that

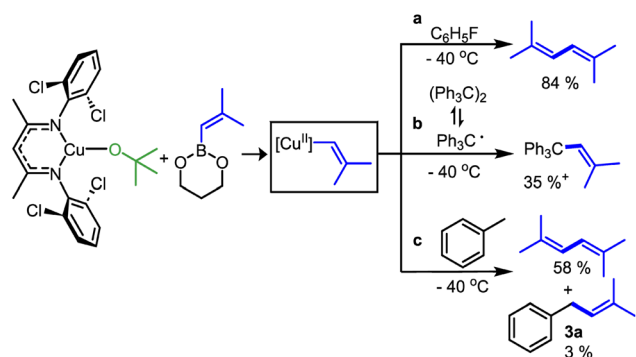


Fig. 4 Reaction of [Cl₂NN]Cu–O^tBu and **2a** (a) in C₆H₅F, (b) in the presence of Gomberg's dimer in C₆H₅F, and (c) in toluene. [†]isolated yield.

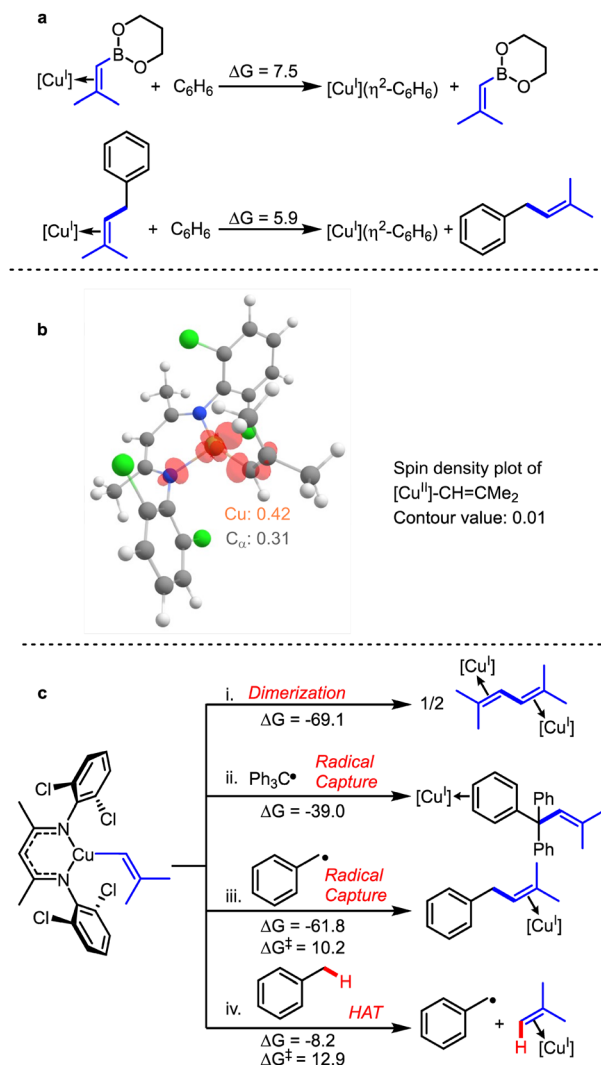


Fig. 5 DFT calculation of (a) [Cu^I] binds to alkenes, 2a and 3a. (b) spin density plot of [Cu^{II}]-CH=CMe₂. (c) Possible reaction pathways for [Cu^{II}]-CH=CMe₂. Free energies in kcal mol⁻¹ at 298.15 K. For more details, see Schemes S3 and S4.

dissociates to produce the trityl radical Ph₃C•) provides Ph₃C-CH=CMe₂ in 35% yield (Fig. 4b). Additionally, a minimal amount of 3a also forms when the reaction occurs in toluene (Fig. 4c). Product 3a can arise from the sequential steps of toluene radical formation through HAT, followed by subsequent radical capture (Fig. 5c).

Computational analysis and insights

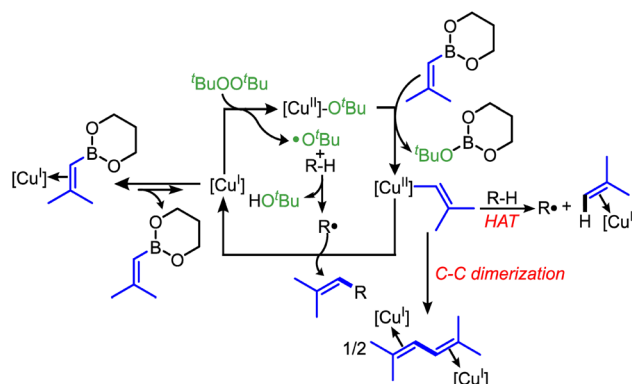
We employed density functional theory (DFT) to better understand and interpret the above experimental findings. Remarkably, the experimental thermodynamic parameters derived from the van't Hoff plot for the binding of the alkenylboronic ester to [Cu^I], closely correspond to the predictions from density functional theory (DFT), with $\Delta G_{\text{DFT}} = 7.5$ kcal mol⁻¹, $\Delta H_{\text{DFT}} = 11.5$ kcal mol⁻¹, and $\Delta S_{\text{DFT}} = 12.1$ e.u. (Fig. 5a). The strong agreement between experimental data ($\Delta G_{\text{exp}} = 6.7 \pm 1.0$ kcal mol⁻¹) and DFT results supports the reliability of the

thermodynamic data from calculations. Furthermore, the alkenylated product 3a exhibits a lower affinity for binding to [Cu^I] compared to 2a ($\Delta G_{\text{DFT}} = 5.9$ kcal mol⁻¹) (Scheme S4†).

This result is consistent with the need for mild heating (60 °C) to disrupt the interaction between alkenyl precursors or products 2a or 3a and the [Cu^I] catalyst, thereby initiating the catalytic cycle. Upon dissociation of the alkene from the [Cu^I] complex, the [Cu^I] complex undergoes oxidation by ^tBuOO^tBu which requires on an accessible coordination site. Furthermore, the formation of [Cu^{II}]-CH=CMe₂ via transmetalation of [Cu^{II}]-O^tBu with 2a is exergonic ($\Delta G = -3.5$ kcal mol⁻¹) with a modest reaction barrier ($\Delta G^\ddagger = 13.6$ kcal mol⁻¹) (Scheme S3†).

A spin density plot of the [Cu^{II}]-CH=CMe₂ intermediate indicates 31% localization on C_α (Fig. 5b). The radical nature of the alkenyl group bound to the copper(II) center in [Cu^{II}]-CH=CMe₂ also accounts for its propensity to dimerize to form Me₂C=CH-CH=CMe₂, a highly favorable reaction ($\Delta G_{\text{rxn}} = -69.1$ kcal mol⁻¹). A relaxed energy scan for dimerization further reveals essentially no barrier for this process (Fig. S22†). Similarly, the radical capture by trityl radical pathway is also a highly favourable reaction ($\Delta G = -39.0$ kcal mol⁻¹) (Fig. 5c(ii)). We note that loss of the alkenyl radical [•]CH=CMe₂ from [Cu^{II}]-CH=CMe₂ is significantly uphill in free energy ($\Delta G = 36.0$ kcal mol⁻¹; Fig. S21†); accordingly we do not anticipate the direct involvement of the [•]CH=CMe₂ radical in these copper-catalyzed reactions.

Due to the radical character on C_α, we investigated whether [Cu^{II}]-CH=CMe₂ could abstract a H-atom from a benzylic C-H bond. This HAT process is favourable with a relatively low reaction barrier ($\Delta G = -8.2$ kcal mol; $\Delta G^\ddagger = 12.9$ kcal mol; Fig. 5v(iv)). This calculation result is consistent with the experiment, where a trace amount of alkenylation product, 3a, was observed in the absence of ^tBuO[•] (Fig. 4c). After [Cu^{II}]-CH=CMe₂ abstracts an H atom from toluene, the resulting toluene radical undergoes capture by [Cu^{II}]-CH=CMe₂ to form 3a (Fig. 5c(iii)). Calculations also rationalize the formation of styrene as a byproduct in the C-H alkenylation of ethylbenzene. Both radical capture and H-atom abstraction of a β-H of the 2° ethylbenzene radical PhCH(•)Me are extremely favorable ($\Delta G = -55.0$ and -48.3 kcal mol⁻¹, respectively; Scheme S5†).



Scheme 2 Catalytic cycle for sp³ C-H alkenylation with competing pathways via the [Cu^{II}]-CH=CMe₂ intermediate.

Conclusions

This report illustrates the use of alkenylboronic esters in catalytic benzylic C–H functionalization for sp^3 – sp^2 C–C bond construction. The $Me_2C=CH-B(OR)_2$ reagent **2a** exhibits a broad C–H substrate scope across typical 1° benzylic C–H bonds. Importantly, it significantly expands the scope for benzylic C–H alkenylation as it does not require highly acidified $ArCF_2$ –H bonds.²⁵ Importantly, this study illustrates how sp^3 C–H alkenylation can lead to formation of the prenyl group known to engender biological activity in small molecules.

A combination of experimental and computational studies support that this sp^3 C–H alkenylation protocol proceeds *via* a copper(II) alkenyl intermediate $[Cu^{II}]-CH=CMe_2$ (Scheme 2). This $[Cu^{II}]-CH=CMe_2$ intermediate promotes C–C bond formation to form $R-CH=CMe_2$ products in the capture of an alkyl radical $R^\cdot$ derived from H-atom abstraction from R–H *via* the $^tBuO^\cdot$ radical generated upon reaction of $^tBuOO^tBu$ with $[Cu^I]$. Facile bimolecular C–C coupling between $[Cu^{II}]-CH=CMe_2$ species results in a competing pathway to form the diene $Me_2C=CH-CH=CMe_2$. Yet, the copper(II) alkenyl intermediate can also directly transform substrates R–H into $R-CH=CMe_2$, albeit in low yield, due to the ability of the $[Cu^{II}]-CH=CMe_2$ intermediate to abstract a H-atom from substrates R–H to form $R^\cdot$. This unusual chemical pathway available uncovered for copper(II) alkenyls offers additional opportunities to construct catalytic C–H alkenylation protocols *via* selective H-atom abstraction of substrates R–H *via* metal-centred intermediates en route to functionalized species $R-CH=CRR'$.

Data availability

All synthetic procedures, characterization data, spectroscopic data, computational data, supplementary figures and tables, and detailed crystallographic information can be found in the ESI. Crystallographic data are available *via* the Cambridge Crystallographic Data Centre (CCDC): 2268882 and 2329536.

Author contributions

T.-A. C. and T. H. W. conceived project. T.-A. C. carried out experimental and computational works. T.-A. C. and R. J. S. collected, solved, and refined crystallographic data. T. H. W. supervised the experimental and computational work. T.-A. C. and T. H. W. wrote the manuscript. All authors have given approval to the final version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

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