

Letter

Copper-Catalyzed Dehydrogenative Formal [4 + 2] and [3 + 2] Cycloadditions of Methylnaphthalenes and Electron-Deficient Alkenes

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Supporting Information

ABSTRACT: Higher π -extended naphthalene, contained in methylnaphthalenes, which could capture alkyl radicals via SOMO–LUMO interactions, enabled the development of Cucatalyzed formal [4 + 2] and [3 + 2] cycloadditions between methylnaphthalenes and electron-deficient alkenes. Under copper catalysis, a series of electron-deficient alkenes and methylnaphthalenes with different substituents were success-



fully incorporated with di-tert-butyl peroxide (TBP) as an oxidant and radical initiator, providing a wide range of cycloadducts.

C arbocycles are ubiquitous structural motifs found in many natural products and synthetic pharmaceutical agents. In light of their wide existence, carbocycle construction is one of the enduring and crucial goals of organic synthesis.¹ The classic Diels–Alder reaction and dipolar cycloaddition have been extensively utilized as powerful cyclization approaches to sixand five-membered carbocycles (Scheme 1a).^{2,3} However, since these reactions are enslaved by the HOMO–LUMO gap between the coupling partners,⁴ active dienes and special active 1,3-dipoles are generally required, limiting their broader use in

Scheme 1. New Strategy for Constructing Carbocycles via Radical-Redox Relay



the synthesis of complex targets. With new concepts continually emerging for radical-involved transformations,⁵ an intriguing alternative approach to carbocycles could involve considering the possibility of radical-triggered cycloaddition reactions with simple and easily obtained hydrocarbons as starting materials. In this context, we reasoned that the radical addition/trapping/ oxidative termination sequence would be a promising strategy for cycloaddition (Scheme 1b).

Benzyl-type radicals are versatile reactive species that can be generated from simple toluene and its analogues. The electronrich property enables benzylic radicals to be excellent electron donors and moderate acceptors, rendering them ready to be added to electron-deficient alkenes to give rise to new alkyl radical species for establishing a series of radical-oxidative relay transformations.^{6,7} As shown in Scheme 1c, a newly formed alkyl radical such as II could be oxidized by an appropriate oxidant to furnish an oxidative coupling reaction between two C-H bonds.^{7c} Building upon these findings, we reasoned that the appropriate aromatics inherent in the benzyl-type radicals could act as electron acceptors to capture the newly formed alkyl radical II to furnish an intermolecular cycloaddition reaction between alkenes and simple hydrocarbons. On the basis of the resulting mechanistic insight, the key point to realize the above-mentioned idea is the identification of an appropriate hydrocarbon that not only can produce benzyl-type radicals but also contains an arene possessing lower-energy antibonding π orbitals to facilitate single-electron transfer via the SOMO-LUMO interaction.⁸ In this context, we surmised that methylnaphthalenes containing a higher π -extended

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naphthalene would be suitable substrates to fulfill such requests, since their relatively lower-energy antibonding π orbitals could capture II quickly to suppress the oxidative coupling.⁹ Herein we disclose novel Cu-catalyzed formal radical [4 + 2] and [3 + 2] cycloadditions of simple methylnaphthalenes and electron-deficient alkenes that lead to functionalized polycyclic compounds, structural motifs common in natural products and synthetic compounds (Scheme 1d).¹⁰

Our studies began with the formal [4 + 2] cycloaddition for the formation of **3aa** using (E)-N-methoxy-N-methylcinnamamide (1a) and 1-methylnaphthalene (2a) as model substrates. In the presence of 10 mol % Cu(*i*-PrCO₂)₂, 20 mol % HOAc, and 3.0 equiv of TBP at 120 °C, the desired cycloaddition adducts 3aa and 4aa were isolated in 70% yield as a mixture with 90/10 regioselectivity. The structure of the major product 3aa was directly corroborated by single-crystal X-ray diffraction analysis.¹¹ Moreover, the structure of the minor adduct 4aa was also confirmed by X-ray diffraction analysis of the corresponding aldehyde obtained through simple functional group transformation (see the Supporting Information (SI)). The reaction proceeded in a highly diastereoselective way with complete trans diastereoselectivity. Carboxylic acids were found to be effective in promoting the desired transformation, with 2acetoxybenzoic acid (A_1) serving as the most effective additive at 120 °C (Table 1, entries 1-5). 2-Acetoxybenzoic acid may facilitate the genernation of tert-butoxyl radical by accelerating the decomposition of TBP. Upon examination of different copper salts (entries 5-15), Cu(OAc)₂/2-acetoxybenzoic acid was found to be the most general and efficient catalytic system and was chosen as the standard conditions (entry 15). Only lower yields were obtained when the reaction was conducted in

	O N CH ₃ CH ₃ +	H ₃ C _N ,C TBP, 120 °C	DCH ₃ + O ₂ H ₃ CO	N _{CH3}
entrv	[Cu]	acid ^b	vield (%) ^c	4aa 3aa/4aa ^d
1	$Cu(i-PrCO_2)_2$	CH ₂ CO ₂ H	70	90/10
2	$Cu(i-PrCO_2)_2$	Cl ₃ CCO ₂ H	43	88/12
3	$Cu(i-PrCO_2)_2$	$(CH_2CO_2H)_2$	28	89/11
4	$Cu(i-PrCO_2)_2$	PhCO ₂ H	71	91/9
5	$Cu(i-PrCO_2)_2$	\mathbf{A}_{1}	74	91/9
6	CuCl	\mathbf{A}_{1}	62	88/12
7	CuF ₂	A ₁	54	88/12
8	CuCl ₂	A_1	27	88/12
9	$Cu(TFA)_2$	A_1	66	87/13
10	$Cu(OAc)_2$	A_1	75	89/11
11	$Cu(HCO_2)_2$	A ₁	71	88/12
12	$Cu(acac)_2$	A_1	66	88/12
13	$Cu(tfacac)_2$	A ₁	67	89/11
14	$Cu(hfacac)_2$	A_1	43	87/13
15 ^e	$Cu(OAc)_2$	A ₁	76	92/8
16	$Cu(OAc)_2$	-	63	91/9
17	-	A ₁	25	87/13
18 ^e	-	-	17	89/11

Table 1. Optimization of the Reaction Conditions^a

^{*a*}Reaction conditions: **1a** (0.4 mmol), TBP (3.0 equiv), [Cu] (10 mol %), additive (20 mol %), and **2a** (4.0 mmol) at 120 °C under N₂ for 24 h. ^{*b*}A₁ = (2-CH₃CO₂)PhCO₂H. ^{*c*}Isolated yields. ^{*d*}Determined by GC and GC–MS analysis. ^{*e*}2-Acetoxybenzoic acid (10 mol %) was used.

the absence of either copper catalyst or 2-acetoxybenzoic acid (entries 16-18), indicating the importance of the copper catalyst and acid additive to promote the reaction.

With the practical catalyst system identified, we examined the alkene scope of this cycloaddition with 2a as the standard methylnaphthalene (Scheme 2). α,β -Unsaturated Weinreb





^aReaction conditions: 1 (0.4 mmol), 2 (4.0 mmol), TBP (3.0 equiv), $Cu(OAc)_2$ (10 mol %), and 2-acetoxybenzoic acid (10 mol %) at 120 °C under N₂ for 24 h. Isolated yields for 3 and 4 are shown; the data in parentheses are 3/4 ratios, which were determined by GC–MS or ¹H NMR analysis. ^bIsolated yield of 3.

amides, such as 1a-n, all underwent formal [4 + 2] cycloaddition and readily afforded the desired cycloadducts (3aa-na) in 35-78% yield with good to excellent selectivities. The efficient formation of the desired adducts illustrated that either electron-rich or electron-deficient substituents were tolerated on the aryl ring. In general, alkenes bearing electron-withdrawing groups provided higher yields than those containing electron-donating substituents. For example,

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the reactions of substrates with electron-withdrawing substituents such as $-CF_3$ and $-NO_2$ at the 4-position of the benzene ring proceeded smoothly to provide the cycloadducts in >70% yield (3ka and 3la). Typical functional groups such as alkyl (1b-d), alkoxy (1e), fluoro (1f), chloro (1g-i), bromo (1j), trifluoromethyl (1k), and nitro (1l) were well-tolerated under the optimized reaction conditions. In addition to phenylsubstituted alkenes, a naphthyl-substituted α,β -unsaturated Weinreb amide (1m) and a pyridine-substituted $\alpha_{,\beta}$ -unsaturated Weinreb amide (1n) were also compatible with this new reaction, generating the corresponding carbocycles (3ma and 3na) in moderate to good yields with good regioselectivities. The cycloaddition reaction is not limited to $\alpha_{,\beta}$ -unsaturated Weinreb amides, as cinnamates (10 and 1p), cinnamamide (1q), and enones (1r-w) could also be used as coupling partners in these reactions, giving the corresponding cycloaddition products (30a-wa) in 45-57% yield. Notably, the two regioisomers produced from the reactions of 10-w can be easily separated to provide the pure cycloadducts for further elaboration.¹¹ We next examined the scope of methylnaphthalenes in the Cu-catalyzed cycloaddition reactions (Scheme 2). Various types of 1-methylnaphthalenes 2 were readily employed and afforded the desired cycloadducts in moderate to good yields (48-70%) with good regioselectivities (>95/5). Interestingly, a second methyl group at the 2-, 4-, or 5-position of the naphthalene ring could be tolerated. Moreover, a labile substituent such as a bromo group (3le) was tolerated under the present reaction conditions, thus offering an additional opportunity for further manipulation of the products obtained. Meanwhile, we were pleased to observe that 2-methylnaphthalene could also be used as a coupling partner to react with enones and cinnamates to establish a formal [3 + 2]cycloaddition reaction. However, compared with the formal [4+2] cycloaddition reaction, the formal [3+2] cycloaddition reaction afforded the corresponding products with relatively lower yields (7uf, 22%; 7tf, 39%; 7xf, 32%) under otherwise identical reaction conditions. The solid-state structure of 7uf was also confirmed by single-crystal X-ray diffraction analysis, from which we found that the acyl group appears to be trans to the phenyl ring.¹¹

To gain insight into the mechanism of this new cycloaddition reaction, control experiments were conducted under the standard reaction conditions. When the radical scavenger TEMPO was introduced into the reaction system, no desired product was obtained. Instead, the menaphthyl radical trapping product 8 was observed in 32% isolated yield based on TEMPO. These results support the idea that the menaphthyl radical intermediate was most likely involved in the transformation (see the SI). Moreover, kinetic isotope effect experiments were conducted under the standard reaction conditions (Scheme 3; see the SI). The competition reaction of 2a and 2a-d₃ revealed a significant isotope effect $(k_{\rm H}/k_{\rm D} =$ 4.6), indicating that cleavage of the $C(sp^3)$ -H bond might be involved in the rate-limiting step of this cycloaddition reaction. On the other hand, the competition reaction of 2a and $2a-d_7$ showed a small isotope effect $(k_{\rm H}/k_{\rm D} = 1.1)$, indicating that cleavage of the C-H bond of the naphthalene is a fast process.

On the basis of the current results and computational studies,⁹ a plausible reaction pathway for the formation of the cycloadducts is depicted in Scheme 4. Initially, homolytic fission of TBP by Cu(I) affords *tert*-butoxyl radical and Cu(II) species with the assistance of the carboxylic acid.¹² Hydrogen abstraction from the methylnaphthalene by *tert*-butoxyl radical







generates *t*-BuOH and a menaphthyl radical, which then adds to the alkene, giving radical intermediate **A**. The radical in **A** site-selectively adds to the α -position of the naphthalene, affording intermediate **B**.¹³ Finally, direct hydrogen-atom transfer from **B** to *tert*-butoxyl radical forms the product, or single-electron oxidation of **B** by Cu(II) generates a cation that is then deprotonated by *t*-BuO⁻ to deliver the desired product **3** and *t*-BuOH. Meanwhile, Cu(I) is regenerated to enter the next catalytic cycle. Additionally, we assume that the mechanism of the formal [3 + 2] cycloaddition is similar to that of the formal [4 + 2] cycloaddition.

We then attempted to perform further derivatization of the obtained products **3** to demonstrate their synthetic utility. In the presence of $Pd(OAc)_2/PCy_3/Cs_2CO_3$, **3wa** can be easily converted to the polycyclic compound **9**, a polycondensed odd-alternant hydrocarbon,¹⁴ in 72% yield (Scheme 5). Interest-

Scheme 5. Synthetic Applications



ingly, the configuration of the acyl and phenyl groups is changed from *trans* to *cis* in this transformation, most likely as a result of keto–enol tautomerization initiated by Cs_2CO_3 . The solid-state structures of **3wa** and **9** were unambiguously determined by single-crystal X-ray diffraction analysis.¹¹

In summary, we have identified that methylnapthenes not only can be used as benzyl-type radical precursors for initiating the radical addition reaction with electron-deficient alkenes but also can function as radical acceptors to furnish a cycloaddition reaction. This unique feature enables novel copper-catalyzed highly diastereoselective and regioselective formal [4 + 2] and [3 + 2] cycloadditions of simple methylnaphthalenes and electron-deficient alkenes. These transformations offer a unique and efficient approach to directly access a wide range of polycyclic compounds with a wide range of functional groups that are of great value in organic synthesis.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.or-glett.7b03194.

Experimental details and full spectroscopic data for all new compounds (PDF)

Accession Codes

CCDC 1570579, 1570581, 1570583, 1570587, 1570588, 1570590, 1570596, and 1570597 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by e-mailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

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The authors declare no competing financial interest.

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