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Communication

General Regio- and Diastereoselective Allylic C−H Oxygenation of Internal Alkenes

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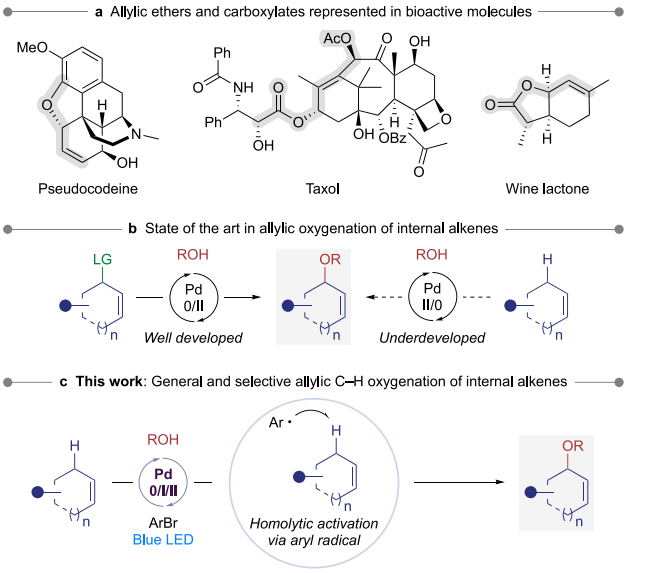
ABSTRACT: Branched allylic esters and carboxylates are fundamental motifs prevalent in natural products and drug molecules. The direct allylic C−H oxygenation of internal alkenes represents one of the most straightforward approaches, bypassing the requirement for an allylic leaving group as in the classical Tsuji−Trost reaction. However, current methods suffer from limited scope—often accompanied by selectivity issues—thus hampering further development. Herein we report a photocatalytic platform as a general solution to these problems, enabling the coupling of diverse internal alkenes with carboxylic acids, alcohols, and other *O*-nucleophiles, typically in a highly regio- and diastereoselective manner.

Allylic ethers and carboxylates are valuable motifs in organic molecules as both end products and synthetic intermediates.[1] In particular, branched allylic ethers and carboxylates are frequently found in natural products, bioactive molecules, and FDA-approved medicines (Scheme 1a). Thus, various methods have been developed toward branched allylic oxygenated molecules.[2] Among them, the palladium-catalyzed Tsuji−Trost reaction represents one of the most powerful and robust methods, offering high levels of regio- and stereocontrol with numerous applications in synthesis (Scheme 1b, left).[3] However, accessing prefunctionalized alkenes bearing a leaving group at the allylic position often requires extra synthetic effort and sometimes can be challenging, eventually limiting the scope of this approach. The direct intermolecular allylic C−H functionalization of alkenes has therefore become a topic of broad interest. In this regard, terminal alkenes have been extensively utilized over the years toward the coupling with carboxylic acids, alcohols, and other *O*-nucleophiles such as ketoximes, typically leading to linear products.[4,5] However, much less progress has been made with respect to internal alkenes, which are much more common and important (Scheme 1b, right). While nonfunctionalized alkenes, for instance cyclohexene, have been routinely employed as substrates, the incorporation of more complex alkenes is met with challenges, such as low functional group tolerance and product decomposition.[6,7] Besides, these methods rely on an electrophilic Pd(II) catalyst to activate the allylic C−H bond, rendering the engagement of electron-deficient substrates much more challenging. Regarding the nucleophile coupling partner, feedstock carboxylic acids, such as acetic acid, were first utilized, often in the form of a solvent in allylic C−H oxygenation. However, the requirement of harsh conditions has prevented further development toward more complex carboxylic acids or other nucleophile classes.[6]

In addition to their narrow scope, selectivity issues have also hampered the advance of the field. Thus, substituted alkenes often yield products with unsatisfactory regio- and diastereoselectivities, which is likely a consequence of competing

Scheme 1. Background and Methods for Allylic C−O Bond Formation via Palladium Catalysis



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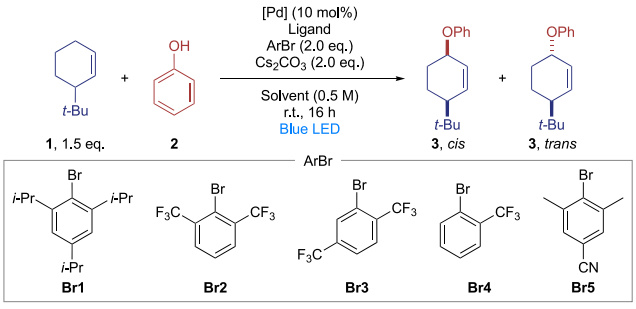
Wacker mechanism or alkene isomerization.[6c,d] Taken together, these drawbacks have largely restricted the chemical space accessible through the current approaches. Herein we report a general solution to the above-mentioned limitations empowered by homolytic activation of alkenes via photocatalytically generated aryl radical (Scheme 1c). Our protocol provides a platform for the coupling of carboxylic acids, phenols, and other *O*-nucleophiles with a wide range of alkenes with varied substitution patterns and electronic properties. Notably, cyclic substituted alkenes can be functionalized in a regio- and stereoselective fashion, thus offering an expedient approach toward complex scaffolds.

Recently, we developed an intermolecular allylic C−H amination reaction of internal alkenes[8] via palladium photocatalysis.[9] While this protocol proved to be efficient with amines, it was unclear whether the less nucleophilic oxygen-based counterparts could be employed. Besides, cyclopentene and cyclohexene represent the only cyclic substrates studied in our previous work.[8] We commenced our studies with 3-*tert*-butylcyclohexene (**1**) using phenol as the nucleophile toward allylic ether **3** (Table 1).[10] This substrate was selected to probe

Table 1. Optimization Studies[a]



entry	[Pd]	ligand (mol %)	ArBr	solvent[e]	yield (%), *dr*
1[b]	$Pd(PPh_3)_4$	–	**Br1**	PhCN/SFL 2:1	35, 6:1
2	$Pd(PPh_3)_4$	–	**Br2**	PhCN/SFL 2:1	66, 6:1
3[b]	$Pd(PPh_3)_4$	Xantphos (4)	**Br2**	PhCN/SFL 2:1	71, 6:1
4[b]	$Pd(PPh_3)_4$	Xantphos (4)	**Br3−5**	PhCN/SFL 2:1	<30
5	$Pd(TFA)_2$	PPh_3 (40)	**Br2**	PhCN/SFL 2:1	89, 5:1
6	$Pd(TFA)_2$	PPh_3 (40)	**Br2**	PhCN	73, 9:1
7[c]	**$Pd(TFA)_2$**	**PPh_3 (40)**	**Br2**	**PhCN**	**82 (74[d]), 15:1**

[a]0.1 mmol scale; yields and *dr* determined by GC-MS. [b]2.0 equiv of **1**. [c]Reaction run at 5 °C. [d]Isolated yield. [e]SFL, sulfolane.

the efficiency as well as regio- and diastereoselecontrol of the C−O bond formation reaction. Using $Pd(PPh_3)_4$ as the catalyst and **Br1** as the aryl radical source, we observed the formation of **3** in a promising yield of 35%, albeit with moderate diastereomeric ratio (entry 1). Additional screening revealed electron-deficient **Br2** as the most efficient hydrogen atom transfer (HAT) agent, while introduction of an additional ligand was found to be ineffective (entries 2−4). Employment of another palladium precursor led to higher yield (entry 5). Finally, switching the solvent to benzonitrile (entry 6) and lowering the reaction temperature (entry 7) substantially improved the diastereoselectivity. Notably, in all cases, the reaction of **1** with **2** proceeded with perfect regiocontrol.

With the optimized conditions in hand, we embarked on investigation of the alkene scope (Scheme 2). Simple cyclic alkenes of different ring sizes reacted efficiently to deliver the corresponding cyclic ethers (**4**−**6**). Styrene derivatives also underwent smooth transformation under reaction conditions modified from our previous work (**7**−**10**).[8] Likewise, a benzothiophene core could also be incorporated (**11**). Notably, electron-deficient alkenes could also be chemoselectively functionalized at the allylic position, despite a potential Michael addition side reaction (**12**). Encouraged by these results, we moved on to probe the regioselectivity of this process in systems possessing multiple allylic C−H sites. To our delight, both activated and unactivated cyclic alkenes furnished products with good to exclusive regioselectivity, likely due to a site-selective HAT step (**13**−**16**). Likewise, linear alkenes **17** and **18** delivered the respective allylic ethers as single regioisomers (**19**, **20**). Interestingly, a site-selective HAT/regioselective etherification cascade of azacycle **21** led to enamine derivative **22** as the sole product in good yield. Subsequently, the ring size and substituent effects on the diastereomeric outcome were examined. The cyclopentene analogue of substrate **1** was equally reactive and afforded product **23** with improved diastereoselectivity. A substrate bearing a tertiary alcohol moiety underwent selective C−H etherification to give **24** as a single diastereomer. However, reactions employing phenyl- and cyclopentyl-substituted cyclohexenes provided products with diminished selectivity, presumably due to lower steric hindrance (**25**, **26**). Notably, N-based substitutents were also compatible, thereby providing entry to various 1,4-amino ethers in a stereocontrolled manner (**27**, **28**). Doubly substituted alkenes were also found to be viable reaction partners. Thus, allylic ethers derived from fused rings (**29**), tertiary allylic alcohols (**30**−**32**), and a bisamide (**34**) were obtained in moderate to good yields and diastereoselectivities. Last but not least, a highly both regio- and diastereoselective reaction was achieved through the sequence of site-selective HAT and diastereoselective C−O bond formation (**35**). As a general observation, switching the aryl bromide did not affect the regioselectivity of the reaction.[10] A brief survey of phenol scope (**34**−**41**) revealed that a high level of stereocontrol could be maintained upon introduction of either electron-donating or -withdrawing substituents (**36**−**39**). An example of a heterocycle was also demonstrated (**43**). In cases where moderate yields were obtained, unreacted phenols were typically observed, indicating good mass balance. Since prolonged reaction time did not improve phenol conversion, the moderate yields could be due to catalyst deactivation/decomposition. It is also worth mentioning that alkenes could undergo consecutive HAT leading to desaturation side products.

In addition to phenols, both aliphatic and aromatic carboxylic acids were found to be competent reaction partners (**44**−**55**). Notably, carboxylic acids bearing other pendent nucleophiles underwent chemoselective allylic C−H carboxylation (**49**, **50**). As in the case of phenols, regio- and/or diastereoselective processes could be achieved (**53**−**55**).

The moderate yields could be explained by competitive HAT from dioxane solvent, eventually leading to side product formation via a radical−polar crossover (RPC) scenario.[11] Our preliminary results also validated the possibility of employing other *O*-nucleophiles, such as aliphatic alcohols and oximes

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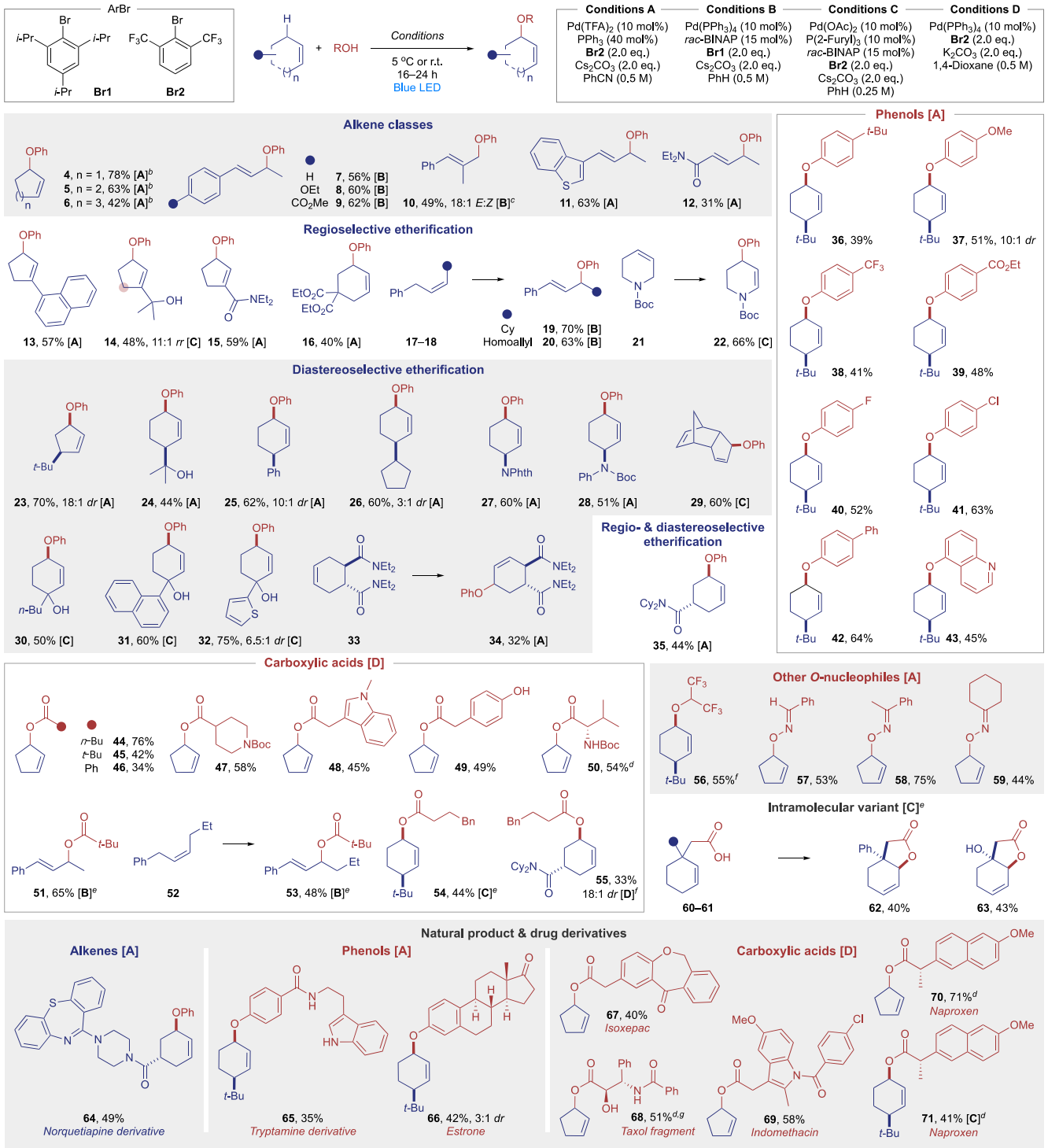
Scheme 2. Allylic C−H Oxygenation of Internal Alkenes[a]



[a]Conditions: 0.2−0.4 mmol scale, 1.0−3.0 equiv of alkene. Isolated yields are reported. *dr* ≥ 20:1 unless otherwise specified. [b]PhH instead of PhCN. [c]Without *rac*-BINAP; **Br2** instead of **Br1**. [d]1:1 dr. [e]K_2CO_3 instead of Cs_2CO_3. [f]SFL as the solvent. [g]5.0 equiv of alkene.

(**56**−**59**). Importantly, the intramolecular variant was also feasible, thus enabling access to highly functionalized bicyclic lactones (**62**, **63**).

To verify whether the efficiency and the highly selective nature of this process could be translated to more complex settings relevant to late-stage functionalization, we tested our protocol using bioactive molecules or their derivatives. Thus, allylic ether **64** was obtained as the exclusive isomer from the corresponding complex alkene. Likewise, a tryptamine-derived phenol and estrone were allylated with high to moderate diastereocontrol (**65**, **66**). Finally, several complex carboxylic acids proved to be reactive coupling partners (**67**−**70**) and were amenable to stereoselective transformations (**71**).

Several experiments were performed to elucidate the mechanism of this transformation. Thus, the role of aryl bromide as a quencher was confirmed by Stern−Volmer

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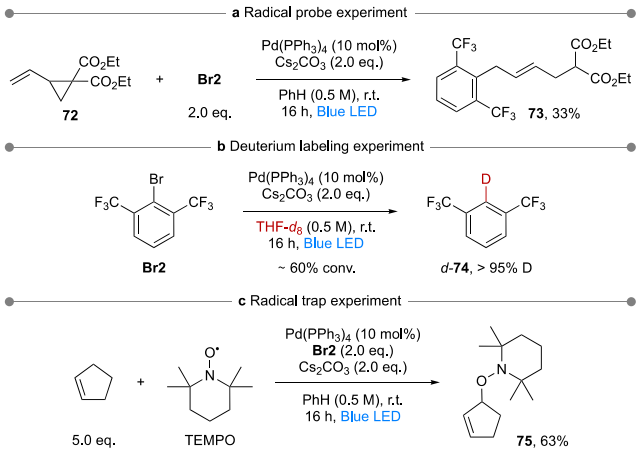
studies.[10] Interestingly, **Br2** was a significantly better quencher of photoexcited Pd(0) compared to **Br1**, clearly indicating that the reactivity of the aryl bromide could be tuned by varying the steric and electronic parameters. The subsequent aryl radical formation from **Br2** was supported by a radical probe experiment using vinylcyclopropane **72**, which underwent radical ring opening to give **73** upon aryl radical addition (Scheme 3a). Furthermore, HAT to aryl radical was

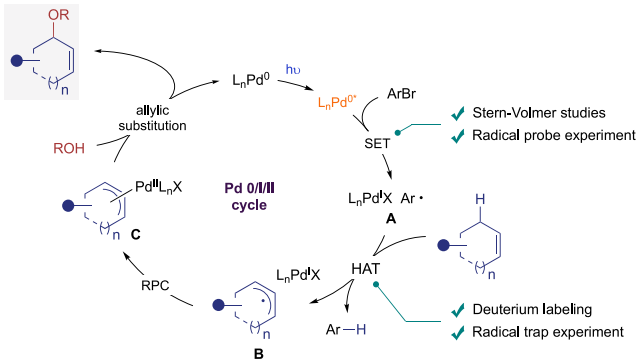
Scheme 3. Mechanistic Studies



established by a deuterium labeling experiment (**Br2** → *d*-**74**) using THF-d_8 as the solvent (Scheme 3b). Additionally, the formation of TEMPO-trapped adduct **75** provided further support for involvement of radical intermediates (Scheme 3c).

Based on the preliminary mechanistic studies and literature precedents, we propose the following mechanism for this allylic C−H oxygenation reaction (Scheme 4). First, the photoexcited

Scheme 4. Proposed Reaction Mechanism



Pd(0) catalyst engages the aryl bromide in a single electron transfer (SET) event to generate hybrid aryl Pd(I) radical **A**,[8,12] which is capable of HAT from the alkene substrate to produce more stable allyl radical species **B**.[8,12,13] A subsequent RPC event leads to the formation of classical, closed-shell π-allyl Pd(II) complex **C**,[14] which upon allylic substitution with an *O*-nucleophile furnishes the desired product, meanwhile regenerating the Pd(0) catalyst.[3]

In conclusion, we have developed a versatile platform for the allylic C−H oxygenation of internal alkenes. Through switching from the conventional electrophilic mode to a photoinduced homolytic activation mode, the alkene scope was substantially expanded with respect to both substitution patterns and electronic properties. It also allows for the employment of *O*-nucleophiles beyond carboxylic acids, such as phenols and derivatives, which remains unprecedented to date. The high variability in both coupling partners enables the assembly of a broad range of differently substituted allylic ethers and carboxylates, typically in highly regio- and diastereoselective fashion.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.4c06421.

Additional experimental data, experimental procedures, and compound characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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