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β,γ-Vicinal Dicarbofunctionalization of Alkenyl Carbonyl Compounds via Directed Nucleopalladation

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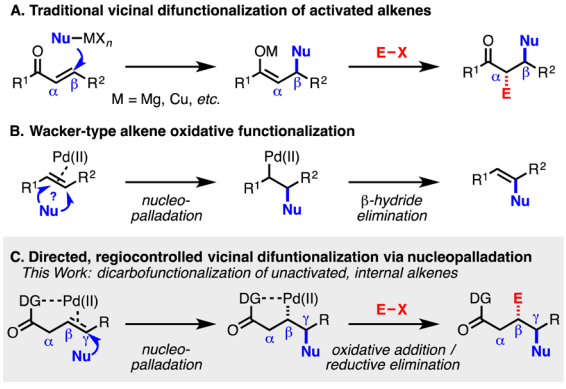
Supporting Information

ABSTRACT: A palladium(II)-catalyzed 1,2-dicarbofunctionalization reaction of unactivated alkenes has been developed, wherein a cleavable bidentate directing group is used to control the regioselectivity and stabilize the putative alkylpalladium(II) intermediate. Under the optimized reaction conditions, a broad range of nucleophiles and electrophiles were found to participate in this transformation, providing moderate to high yields. 3-Butenoic acid derivatives containing internal alkenes and α-substituents were reactive substrates, offering a powerful platform for preparing β,γ-substituted carbonyl compounds with multiple stereocenters.

Alkene dicarbofunctionalization is a powerful synthetic method that enables rapid generation of molecular complexity. The transformation forges two new C−C bonds and up to two stereocenters in a single operation. Traditional vicinal difunctionalization of α,β-unsaturated carbonyl compounds, the archetypal alkene dicarbofunctionalization, consists of two steps (Scheme 1A).[1] After initial conjugate addition of a nucleophile to the β-carbon, the *in situ* generated enolate is trapped with an electrophile, thus functionalizing the α-carbon. Although this reaction has a rich history in synthetic organic chemistry, several limitations remain. First, it is restricted to establishing an α,β-disubstitution pattern relative to the carbonyl group. Second, it often suffers from low functional group tolerance because of the reactive organometallic reagents involved.

π-Lewis acid activation of alkenes by transition metals enables alkene polarization in the absence of an electron-withdrawing group in conjugation with the π-system. Palladium(II) is known to facilitate addition of carbon and heteroatom nucleophiles to alkenes, generating an alkylpalladium(II) species which typically collapses via β-hydride elimination (Wacker oxidation, Scheme 1B). We questioned whether a carbopalladated Wacker-type intermediate could be intercepted with a carbon electrophile as a strategy for alkene dicarbofunctionalization (Scheme 1C). By strategic use of a proximal removable directing group to control the regioselectivity of carbopalladation and stabilize the resulting alkylpalladium(II) intermediate, we envisioned that we could extend classical α,β-vicinal difunctionalization to alternative substitution patterns, namely a β,γ-selective variant. Previous reports spoke to the viability of such an approach. Our group has previously demonstrated that nucleopalladated alkylpalladium(II) species can be sufficiently stabilized by a bidentate directing group such that protodepalladation can outcompete β-hydride elimination.[2,3] Daugulis and others have shown that chelation-stabilized alkylpalladium(II) species formed from C−H cleavage can react with carbon electrophiles in an oxidative addition/reductive elimination sequence.[4] Additionally, several groups have reported high-valent Pd catalysis approaches to alkene difunctionalization, with the vast majority of examples concerning C−heteroatom bond formation.[5] Examples of intermolecular Pd-catalyzed dicarbofunctionalization of unactivated alkenes are rare,[6,7] and to our knowledge, no examples have been reported with internal alkenes to date. Herein, we describe a new catalytic dicarbofunctionalization method for unactivated alkene substrates, wherein a removable bidentate directing group enables regioselective carbopalladation and facilitates subsequent oxidative addition and reductive elimination.

Scheme 1. Background and Project Synopsis



We initiated our study with a series of stoichiometric experiments to validate the elementary steps in the proposed catalytic cycle (see Supporting Information). With this information in hand, we next began optimizing a catalytic protocol using 10 mol % $Pd(OAc)_2$ as the catalyst and 1 equiv of K_2CO_3 as the base (Table 1). Under neat conditions, the addition of AgOAc as an iodide scavenger promoted the reaction to some extent (entries 1−3). We then found that by running the reaction in hexafluoroisopropanol (HFIP) as solvent,[8] the yield increased to 48%. Various alternative inorganic bases were tested (entries 5−7), but none were higher yielding than K_2CO_3. Further optimization revealed that a lower temperature of 80 °C gave a slightly higher yield of 52% (entry 8). With HFIP as solvent, the addition of AgOAc was unnecessary and in fact led to lower yields (entry 9). Finally, we found that by reducing the Pd loading to 5

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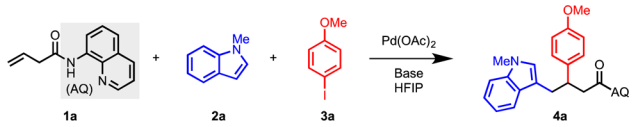
Table 1. Optimization of the Reaction Conditions[a]



1a 2a 3a 4a

entry	additive (equiv)	base	$Pd(OAc)_2$ (mol %)	temp (°C)	yield[b]
1[d]	none	K_2CO_3	10	110	24[c]
2[d]	AgOAc (1)	K_2CO_3	10	110	38[c]
3[d]	AgOAc (2)	K_2CO_3	10	110	28[c]
4	AgOAc (1)	K_2CO_3	10	110	48
5	AgOAc (1)	$KHCO_3$	10	110	30[c]
6	AgOAc (1)	K_3PO_4	10	110	45[c]
7	AgOAc (1)	KF	10	110	trace[c]
8	AgOAc (1)	K_2CO_3	10	80	52
9	none	K_2CO_3	10	80	84
10	**none**	**K_2CO_3**	**5**	**80**	**92**
11[e]	none	K_2CO_3	5	80	26
12	none	K_2CO_3	0	80	0[c]

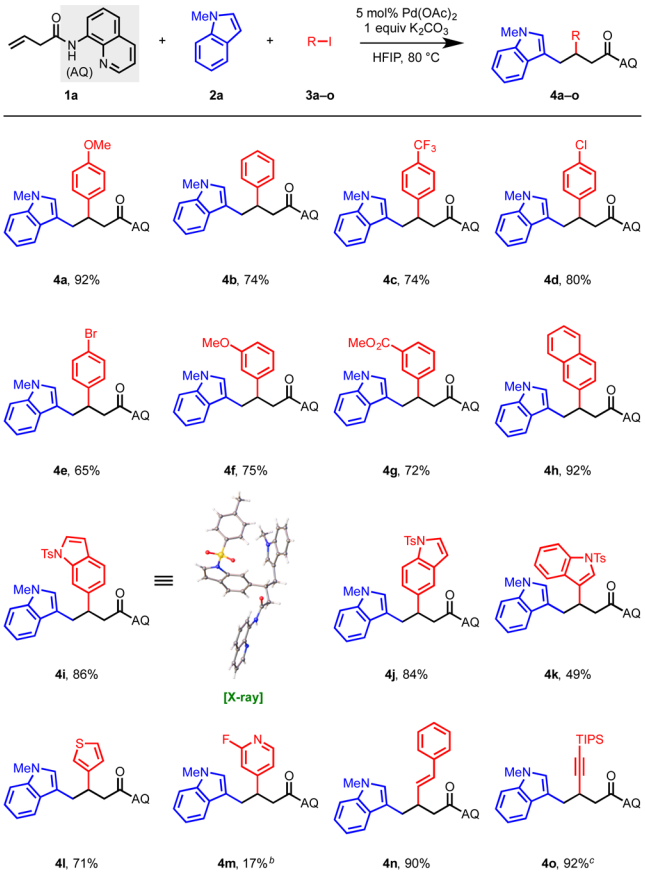
[a]Reaction conditions: **1a** (0.1 mmol), **2a** (1.2 equiv), **3a** (4 equiv), $Pd(OAc)_2$ (5−10 mol %), base (1 equiv), HFIP (0.2 mL), air, 10−12 h. [b]Isolated yield (unless otherwise specified). [c]Yield determined by ^1H NMR analysis of the crude reaction mixture using CH_2Br_2 as internal standard. [d]Neat. [e]Ph_2ICl (3 equiv) was used in place of **4a**.

mol %, product **4a** was generated in 92% yield (entry 10). The more electrophilic reagent diphenyliodonium chloride was also reactive under these conditions but gave a diminished yield of 26% (entry 11). In the absence of the Pd catalyst, no product was formed (entry 12).

Having optimized the reaction conditions, we next investigated the substrate scope of this palladium(II)-catalyzed alkene 1,2-dicarbofunctionalization reaction. First, various carbon electrophiles were tested with alkene substrate **1a** and *N*-methylindole (**2a**) as the nucleophile (Table 2). An array of aryl iodides containing substituents with different electronic properties on the *para* or *meta* position were found to be reactive, providing the corresponding 1,2-dicarbofunctionalized products in moderate to high yields (**4a**−**4h**). Notably, bromide and chloride groups were tolerated, presenting the opportunity for subsequent diversification via cross-coupling. Heteroaryl iodides, namely those containing *N*-tosylindolyl (**4i**−**4k**) and thienyl (**4l**) groups, were also competent coupling partners. We performed the reaction using a series of pyridyl iodides bearing different substitution patterns and found that these were generally not suitable electrophiles in this transformation, presumably because of the coordination strength of the nitrogen atom, which can sequester the palladium catalyst off-cycle. By installing a fluoride group on the 2-position of the pyridine ring and thereby attenuating its coordination ability, however, we were able to obtain 17% of difunctionalized product **4m**.[9] We were encouraged to observe that carbon electrophiles other than aryl iodides also reacted under our optimized conditions. In particular, styrenyl iodide (**3n**) and (bromoethynyl)triisopropylsilane (**3o**) were efficient coupling partners, enabling installation of a vinyl and an alkynyl group, respectively (**4n** and **4o**).

Next, the scope of carbon nucleophiles was studied with alkene substrate **1a** and 4-iodoanisole (**3a**) or styrenyl iodide (**3n**) as the electrophile under the standard reaction conditions (Table 3). First, different substituted indole nucleophiles were tested. Generally, using *N*-protected indoles gave higher yields than free indoles. *N*-Methylindoles bearing substituents on the 4- or 5-

Table 2. Carbon Electrophile Scope[a]



1a 2a 3a−o 4a−o

[a]Reaction conditions: **1a** (0.1 mmol), **2a** (1.2 equiv), **3a**−**o** (4 equiv), $Pd(OAc)_2$ (5 mol %), K_2CO_3 (1 equiv), HFIP (0.2 mL), 80 °C, air, 10−12 h. Percentages refer to isolated yields. [b]10 mol % $Pd(OAc)_2$. See ref 9. [c](Bromoethynyl)triisopropylsilane was used as the electrophile.

position participated in the reaction, providing the corresponding products in excellent yields (**5b**−**5d**). 1,2-Dimethylindole was also a competent coupling partner but gave a lower yield (**5e**). 1-Methyl-7-azaindole (**2g**), containing a pyridine ring, also underwent this transformation in 76% yield, although 10 mol % $Pd(OAc)_2$ was used in this case (**5f**). 1,3-Dicarbonyl compounds were also suitable nucleophiles in this reaction, especially when styrenyl iodide (**3n**) was used as the electrophile (**5g**−**5i**). With this class of nucleophiles, reaction with aryl iodides required slightly modified conditions, using 1 equiv of AgOAc and higher reaction temperature to form the desired product in relatively low yield (**5g**). 2-Naphthol, a representative nonheteroaryl Friedel−Crafts nucleophile, was also reactive, providing the desired product **5j** in moderate yield.

Subsequently, we examined the scope of unactivated alkenes with *N*-methylindole (**2a**) as the nucleophile and styrenyl iodide (**3n**) as the electrophile (Table 4).[10] We were pleased to find that internal alkene (*E*)-**1b** underwent this transformation in good yield, albeit at a slower rate, requiring longer reaction time. Though stereochemically pure (*E*)-alkene was used in the reaction, the diastereomeric ratio of **6a** was observed to be approximately 4:1. This is likely due to rapid *E*/*Z* isomerization of the alkene substrate under the reaction conditions.[11] A variety of α-substituted terminal alkenes were found to be suitable substrates and underwent difunctionalization in moderate to high yields with >20:1 diastereomeric ratio (**6b**−**6e**). The relative

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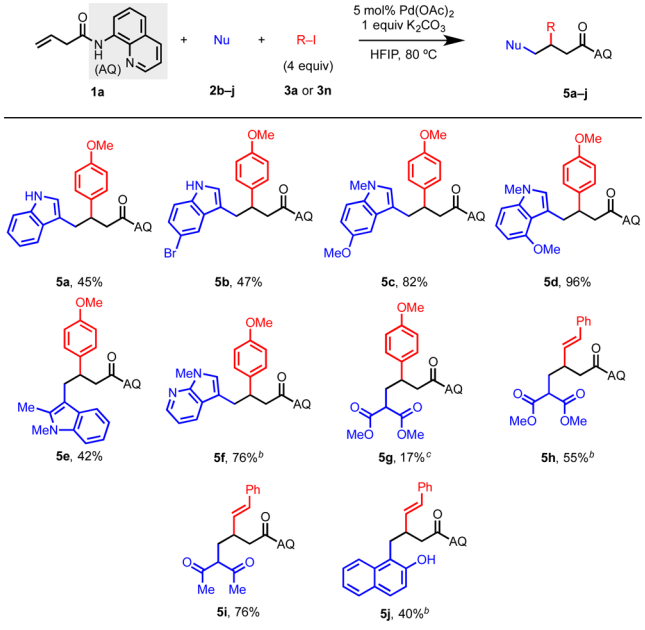
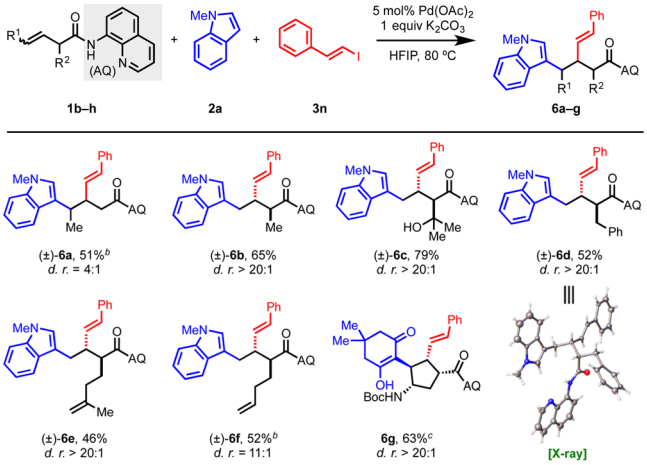
Table 3. Carbon Nucleophile Scope[a]



[a]Unless otherwise specified reaction conditions were as in Table 2. Percentages refer to isolated yields. [b]10 mol % $Pd(OAc)_2$. [c]10 mol % $Pd(OAc)_2$, 1 equiv of K_2CO_3, 1 equiv of AgOAc, 110 °C.

Table 4. Unactivated Alkene Scope[a]

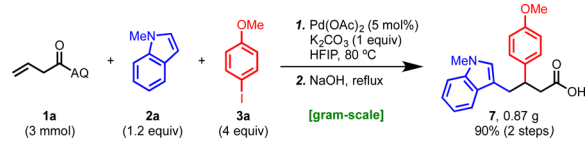


[a]Unless otherwise specified reaction conditions were as in Table 2. Percentages refer to isolated yields. [b]10 mol % $Pd(OAc)_2$, 24 h. [c]5,5-Dimethylcyclohexane-1,3-dione was used as the nucleophile.

stereochemistry of **6d** was determined by X-ray crystallography, consistent with selective formation of a *trans* 5-membered palladacycle intermediate upon nucleopalladation (see Supporting Information for further discussion). In terms of functional group compatibility, the presence of a pendant tertiary alcohol was well tolerated (**6c**). With substrates containing two alkenes, the reaction proved to be chemoselective with preferential functionalization of the β-γ olefin over the more distal δ-ε olefin (**6e** and **6f**). An enantiopure cyclopentenyl substrate was also difunctionalized in good yield with 5,5-dimethylcyclohexane-1,3-dione as the nucleophile (**6g**). Notably, this transformation establishes two new stereocenters and provides expedient access to a highly substituted cyclopentane framework. The *trans* relationship of the two new substituents is consistent with *anti*-nucleopalladation[2,3] and stereoretentive oxidative addition/reductive elimination.[4f]

To demonstrate the practicality and operational simplicity of this Pd(II)-catalyzed alkene dicarbofunctionalization method, we performed the reaction with alkene substrate **1a**, *N*-methylindole (**2a**), and 4-iodoanisole (**3a**) on gram scale (Scheme 2). After

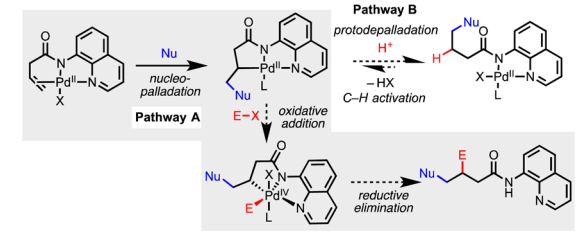
Scheme 2. Scale-Up and Directing Group Removal



difunctionalization, the 8-aminoquinoline directing group was then conveniently cleaved to reveal the free carboxylic acid group. Overall, carboxylic acid **7** was synthesized in 0.87 g via two steps with an overall yield of 90%.

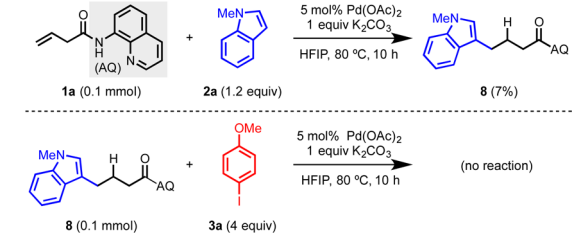
Two possible mechanistic pathways could potentially be envisioned for this catalytic alkene difunctionalization process (Scheme 3). In pathway A, after nucleopalladation, the

Scheme 3. Possible Mechanistic Pathways



alkylpalladium(II) species directly undergoes oxidative addition with the aryl iodide, followed by reductive elimination to generate the final product. In contrast, in pathway B, following nucleopalladation, rapid and reversible protodepalladation generates the hydrocarbofunctionalized intermediate.[3] This intermediate then slowly undergoes C−H cleavage to regenerate a small concentration of the corresponding palladacycle at equilibrium. The palladacycle then reacts with the aryl iodide as above. To disambiguate between these possibilities, several mechanistic experiments were performed (Scheme 4). First, the

Scheme 4. Mechanistic Experiments



reaction between substrate **1a** and *N*-methylindole (**2a**) was run in the absence of the electrophile, and only 7% of the putative hydrocarbofunctionalized intermediate **8** was detected. When we then attempted to expose independently prepared **8**[3] to the standard conditions in the absence of additional nucleophile, no reaction was observed, illustrating that **8** is not a competent intermediate in catalytic dicarbofunctionalization. Lastly, we took note of the connectivity of α-methyl product **6b**; if pathway B

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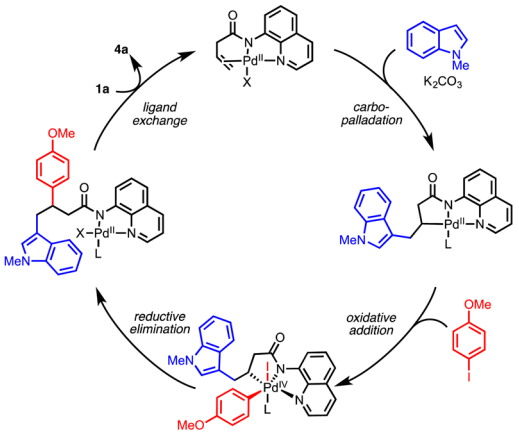
were operative, one would expect the vinyl group to be installed at the α-methyl position since palladium(II) species are known to preferentially activate methyl C(sp^3)−H bonds rather than methylene C(sp^3)−H bonds.[4e,f] Collectively, these results are inconsistent with pathway B, leading us to favor pathway A.

A plausible mechanism for this Pd(II)-catalyzed alkene dicarbofunctionalization reaction is proposed in Scheme 5.

Scheme 5. Proposed Reaction Mechanism



Initially, the palladium catalyst, $Pd(OAc)_2$, coordinates with the directing group, which brings it in close proximity to the alkene, facilitating π-Lewis acid activation. Next, a carbon nucleophile, such as *N*-methylindole, attacks the alkene to generate the alkylpalladium(II) intermediate. Because of the stability and conformational rigidity imparted by the directing group, the palladacycle does not undergo β-hydride elimination and is instead sufficiently long-lived to be intercepted by the aryl iodide via oxidative addition to form a palladium(IV) species. Finally, reductive elimination from the high-valent palladium center gives the palladium(II)−product complex, which can undergo ligand exchange with a new substrate molecule, releasing the product and closing the catalytic cycle.

In conclusion, we have developed a regiocontrolled dicarbofunctionalization reaction of unactivated alkenes using a removable 8-aminoquinoline directing group. By intercepting a chelation-stabilized nucleopalladated intermediate with a carbon electrophile, this reaction has allowed us to extend the classical vicinal-difunctionalization reactivity of α,β-unsaturated carbonyl compounds to β,γ-difunctionalization of 3-butenoic acid derivatives. The reaction proceeded smoothly with a broad range of nucleophiles and electrophiles, including sterically hindered internal and α-substituted alkene substrates. The reaction was amenable to scale up, and clean removal of the 8-aminoquinoline directing group via hydrolysis was demonstrated. Future investigation will focus on elucidating the reaction mechanism and expanding the nucleophile and electrophile scope. These results will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b09170.

Experiment details, spectra data, copies of ^{1}H and ^{13}C NMR spectra, and X-ray crystallographic data (PDF)
Crystallographic data for **4i** (CIF)
Crystallographic data for **6d** (CIF)

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Notes

The authors declare no competing financial interest.

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(9) 1,2-Diarylation byproduct **4m′** was also formed in 20% yield. A plausible mechanism is discussed in the Supporting Information.

(10) Among several carbon electrophiles that were examined, styrenyl iodide was found to be uniquely effective with internal and α-substituted alkene substrates for reasons that remain unclear.

(11) When (*E*)-*N*-(quinolin-8-yl)pent-3-enamide (**1b**) was exposed to the reaction conditions in the absence of a nucleophile and an electrophile, *E*/*Z* isomerization was observed; after 6 h, the *E*/*Z* ratio was ~4:1 based on ^{1}H NMR analysis.

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