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# Ligand-enabled *ortho*-C–H olefination of phenylacetic amides with unactivated alkenes†

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Although chelation-assisted C–H olefination has been intensely investigated, Pd(II)-catalyzed C–H olefination reactions are largely restricted to acrylates and styrenes. Here we report a quinoline-derived ligand that enables the Pd(II)-catalyzed olefination of the C(sp<sup>2</sup>)-H bond with simple aliphatic alkenes using a weakly coordinating monodentate amide auxiliary. Oxygen is used as the terminal oxidant with catalytic copper as the co-oxidant. A variety of functional groups in the aliphatic alkenes are tolerated. Upon hydrogenation, the *ortho*-alkylated product can be accessed. The utility of this reaction is also demonstrated by the late-stage diversification of drug molecules.

## Introduction

The use of inert C–H bonds as coupling partners in diverse carbon–carbon and carbon–heteroatom bond-forming reactions has undergone substantial progress in recent years as it provides a straightforward tool to access a variety of valuable molecules from simple hydrocarbon derivatives.<sup>1</sup> Most notably, Pd(II)-catalyzed C(sp<sup>2</sup>)-H bond olefination reactions have been extensively investigated in terms of both catalyst development and mechanistic understanding.<sup>2</sup> Despite these significant advances, chelation-assisted C–H olefination reactions have been largely restricted to electronically activated alkenes such as acrylates and styrenes.<sup>3</sup> Catalytic C–H olefination reactions with abundant unactivated, aliphatic alkenes remain an unsolved problem because of their intrinsic poor reactivity.<sup>4</sup> It is of great synthetic value to develop robust catalytic systems to address these long-standing issues.<sup>5–7</sup>

Our group has focused on the development of weakly coordinating, monodentate directing groups for a diverse range of C–H activation reactions (*e.g.*, alcohols, ethers, amides and carboxylic acids),<sup>8</sup> for the following reasons: monodentate substrates have the potential to match a wide range of mono and bidentate ligands to achieve ligand-acceleration; secondly, a wide range of readily available chemicals contain

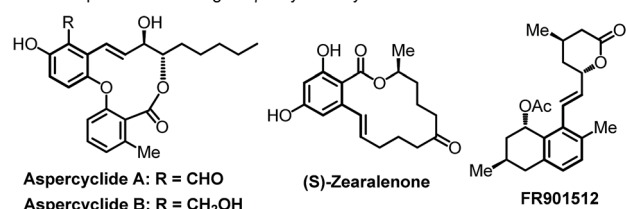
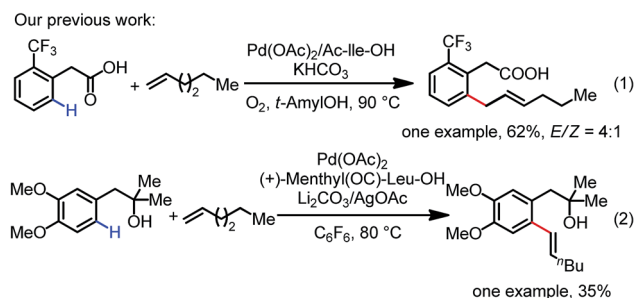
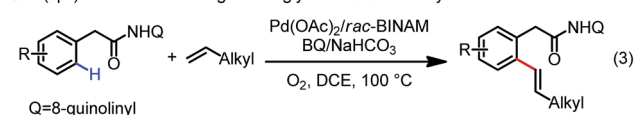
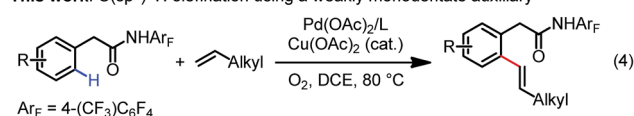
monodentate functional groups that could serve as native directing groups. In 2010, we reported an example of the Pd(II)-catalyzed *ortho*-C–H activation of phenylacetic acid with linear 1-hexene using a mono-*N*-protected amino acid (MPAA) ligand.<sup>9</sup> However, this process predominantly afforded the non-conjugated allylation product allyl benzene (eqn (1)). The successful example of C–H olefination with unactivated 1-hexene was also reported by our group using a weakly monodentate hydroxyl group (eqn (2)).<sup>10</sup> In this case, a mono-*N*-protected amino acid (MPAA) was used as the ligand to promote this transformation, yet the unsatisfactory efficiency as well as the limited substrate scope substantially hampered the utility of this reaction. Recently, a single example of C–H olefination with unactivated olefins using the Daugulis' bidentate directing group was disclosed (eqn (3)).<sup>11</sup> To reach our goal of using versatile ligands and potentially a broad range of monodentate substrates, we pursued further development of the Pd(II)-catalyzed C–H olefination reaction directed by weakly monodentate auxiliaries with unactivated alkenes by identifying an effective ligand. The success of pyridine ligands in C–H activation inspired us to revisit the C(sp<sup>2</sup>)-H olefination with unbiased alkenes.<sup>12</sup> Herein, we report the Pd(II)-catalyzed *ortho*-C–H olefination of phenylacetic amides assisted by a weak amide group (eqn (4)). The identified monodentate quinoline-based ligand is found to be crucial for this olefination to proceed smoothly. This protocol is compatible with a wide range of simple as well as functionalized aliphatic alkenes, leading to diverse synthetically valuable  $\beta$ -alkylated styrenes that are frequently encountered in complex natural products (Scheme 1A).<sup>13</sup> Importantly, the use of molecular oxygen with a catalytic Cu(II) salt as the co-oxidant is a practical advantage compared to the costly silver oxidants required in related palladium chemistry.<sup>14</sup> The utility of this protocol was also demonstrated by the late-stage diversification of drug molecules.

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A: Natural products featuring the  $\beta$ -alkylated styrene scaffoldsB: C(sp<sup>2</sup>)-H activation using a weakly monodentate auxiliaryC: C(sp<sup>2</sup>)-H olefination using a strongly bidentate auxiliaryThis work: C(sp<sup>2</sup>)-H olefination using a weakly monodentate auxiliary

Scheme 1 Pd(II)-catalyzed C–H functionalization with unactivated alkenes.

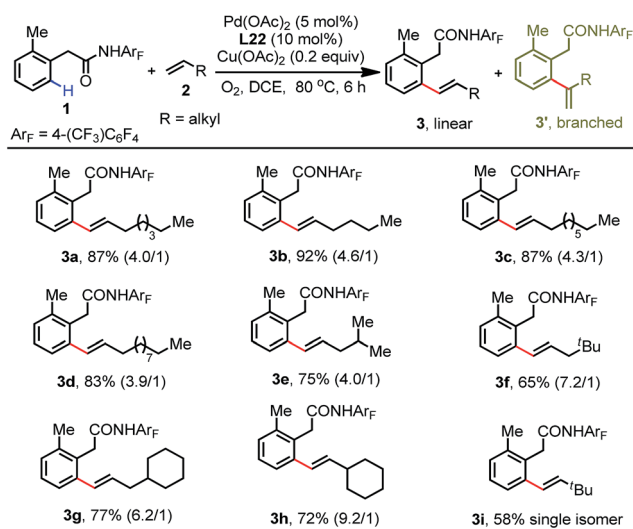
Table 1 Screening of ligands for the *ortho*-C–H olefination of phenylacetic amide<sup>a,b,c</sup>

		3a, linear	3a', branched	
no ligand				
trace	L1, 76% (2.4/1)	L2, 77% (2.1/1)	L3, trace	L4, 55% (2.6/1)
L5, 64% (2.5/1)	L6, 62% (2.5/1)	L7, 83% (2.3/1)	L8, 76% (1.9/1)	L9, 81% (1.3/1)
L10, 63% (2.9/1)	L11, trace	L12, 73% (1.5/1)	L13, 79% (2.3/1)	L14, 42% (2.3/1)
L15, 46% (2.5/1)	L16, 54% (2.9/1)	L17, 60% (2.7/1)	L18, 47% (2.7/1)	L19, 70% (1.8/1)
		<div style="border: 1px solid black; padding: 5px; display: inline-block;">   <b>L22</b> 88% (3.7/1)  87%<sup>d</sup> (4.0/1) </div>		
L20, 46% (2.1/1)	L21, 85% (3.8/1)			
		L23 no reaction		L24 no reaction

the parameters to search for more practical conditions. We were pleased to find that this olefination reaction can also be conducted with a catalytic amount of  $\text{Cu}(\text{OAc})_2$  (0.2 equiv.) under an oxygen atmosphere without any decrease in the isolated yield (Table S7†). Finally, reducing the catalyst loading to 5 mol% did not affect the reactivity, affording the product in 87% yield.

With the optimal conditions established, we next proceeded to explore the substrate scope of this reaction with respect to simple aliphatic alkenes (Table 2). This protocol is compatible with a variety of terminal unactivated alkenes, affording the corresponding olefinated products in excellent yields (83–92%) with moderate linear/branched selectivity (3a–3d). Alkenes bearing branched alkanes are also efficient coupling partners for this process (3e–3h). It is noteworthy that the regioselectivity improved with the increased steric hindrance of branched alkenes. For instance, the sterically bulky 3,3-dimethylbut-1-ene reacted smoothly under standard conditions to give the single isomer olefination product, albeit in moderate yield (3i).

We subsequently proceeded to investigate the generality of this protocol with a wide range of functionalized aliphatic alkenes (Table 3). A variety of aliphatic alkenes can be converted into the corresponding olefination products in modest to excellent yields (5a–5k). Excitingly, the mild conditions allowed for high functional group compatibility, and many synthetically useful functionalities were well-tolerated with these conditions without any compromise (5c–5k). However, substrates containing electron-deficient coordinating groups such as nitrile (5l) and nitro (5m) groups exhibited lower reactivity to produce the products in 45% and 43% yields, respectively. Substrates containing heterocycles were also suitable to generate products in moderate yields (5n–5r). Moreover, olefins derived from

Table 3 Scope of functionalized aliphatic alkenes<sup>a,b,c</sup>Table 2 Scope of simple alkenes<sup>a,b,c</sup>

<sup>a</sup> Reaction conditions: phenylacetamide 1 (0.1 mmol), alkene 2 (3.0 equiv.),  $\text{Pd}(\text{OAc})_2$  (5 mol%), **L22** (10 mol%),  $\text{Cu}(\text{OAc})_2$  (0.2 equiv.), DCE (2.0 mL), 80 °C,  $\text{O}_2$ , 6 h. <sup>b</sup> Isolated yields. <sup>c</sup> The data in parentheses is the ratio of linear and branched isomers determined using  $^1\text{H}$  NMR analysis.

<sup>a</sup> Reaction conditions: phenylacetamide 1 (0.1 mmol), alkene 4 (3.0 equiv.),  $\text{Pd}(\text{OAc})_2$  (5 mol%), **L22** (10 mol%),  $\text{Cu}(\text{OAc})_2$  (0.2 equiv.), DCE (2.0 mL), 80 °C,  $\text{O}_2$ , 6 h. <sup>b</sup> Isolated yields. <sup>c</sup> The data in parentheses is the ratio of linear and branched isomers determined using  $^1\text{H}$  NMR analysis. <sup>d</sup> At 100 °C. <sup>e</sup> 12 h.

coumarin and estrone proceeded smoothly to produce the olefinated products in acceptable yields with excellent regioselectivity (5s and 5t). It should be noted that the *ortho*-C–H allylation products were detected in trace amounts for most of the substrates.

Various phenylacetamide substrates were next subjected to the standard conditions to further evaluate the scope of this protocol (Table 4). A variety of phenylacetamides bearing both electron-donating and -withdrawing substituents at the *ortho*-position were successfully olefinated to give the corresponding products in yields from 57% to 74% (7a–7e). Substrates bearing

Table 4 Scope of phenylacetic amides<sup>a,b,c</sup>

<sup>a</sup> Reaction conditions: phenylacetic amide **6** (0.1 mmol), **2e** (3.0 equiv.), Pd(OAc)<sub>2</sub> (5 mol%), L22 (10 mol%), Cu(OAc)<sub>2</sub> (0.2 equiv.), DCE (2.0 mL), 80 °C, O<sub>2</sub>, 6 h. <sup>b</sup> Isolated yields. <sup>c</sup> The data in parentheses is the ratio of linear and branched isomers determined using <sup>1</sup>H NMR analysis. <sup>d</sup> At 100 °C. <sup>e</sup> 12 h.

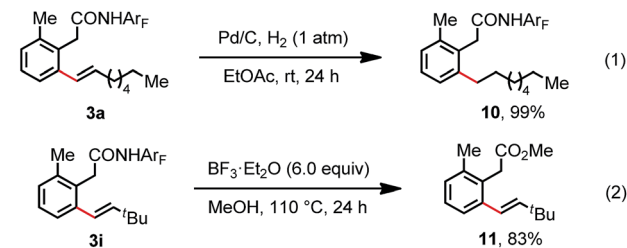
methyl (**6f**), trifluoromethyl (**6g**) and chloro (**6h**) groups at the *meta*-position were well-tolerated with this protocol, providing the less sterically hindered olefination products. The reaction of *para*-substituted phenylacetic amides proceeded smoothly, and the olefination products (**7i–7l**) were isolated in good yields (62–74%). Moreover, the reaction of a 1-naphthalene substrate with the aliphatic olefin occurred to generate **7m** in 68% yield. It is worth noting that the 2-naphthalene substrate showed high site-selectivity in this process, exclusively delivering the β-olefinated product **7n**. Disubstituted phenylacetic amides were also proven to be favorable for this transformation, enabling the formation of desired products **7o–7r** in good yields (68–83%). Lastly, α-substituted substrates underwent this olefination

Table 5 Late-stage diversification of drug molecules<sup>a,b,c</sup>

<sup>a</sup> Reaction conditions: phenylacetic amide **8** (0.1 mmol), 1-octene **2a** (3.0 equiv.), Pd(OAc)<sub>2</sub> (10 mol%), L22 (20 mol%), Cu(OAc)<sub>2</sub> (1.0 equiv.), DCE (2.0 mL), 100 °C, O<sub>2</sub>, 12 h. <sup>b</sup> Isolated yields. <sup>c</sup> The data in parentheses is the ratio of linear and branched isomers determined using <sup>1</sup>H NMR analysis.



Scheme 2 Gram-scale synthesis.



Scheme 3 Hydrogenation and deprotection.



Scheme 4 Plausible mechanism for the formation of olefinated products.

reaction to give the corresponding products in modest yields (**7s–7u**).<sup>16</sup>

To showcase the synthetic utility of this protocol, we sought to apply this method to the late-stage diversification of drug





molecules (Table 5). Gratifyingly, phenylacetic amides derived from ibuprofen **8a**, naproxen **8b** and ketoprofen **8c** were smoothly olefinated to give the corresponding olefination products **9a–9c** in 70%, 63% and 56% yields, respectively.<sup>16</sup>

To further investigate the feasibility of this transformation, we carried out a gram scale *ortho*-C(sp<sup>2</sup>)-H olefination reaction of substrate **1** with 1-octene **2a**. The desired olefination product was isolated in 77% yield when the reaction was performed on a 3.0 mmol scale (Scheme 2). Furthermore, hydrogenation and deprotection reactions were conducted. The hydrogenation of the linear olefination product **3a** at room temperature provided the *ortho* alkylation product **10** in a quantitative yield (Scheme 3). Moreover, the amide auxiliary could be readily removed by treatment with BF<sub>3</sub>·E<sub>2</sub>O in MeOH, affording the methyl ester **11** in 83% yield (Scheme 3).

A plausible mechanism for this Pd(II)-catalyzed *ortho*-C(sp<sup>2</sup>)-H olefination with aliphatic alkenes is proposed (Scheme 4).<sup>4</sup> The C–H activation and further olefin coordination steps form intermediate **A**, which undergoes subsequent 1,2-migratory insertion with the aliphatic olefin to produce the eight-membered palladacycle intermediate **B**. In contrast to the coordination of the carboxylate directing group to generate the allylated product, the amide group may be likely to undergo fast dissociation to afford alkylpalladium species **C**, which makes bond rotation necessary for *syn* elimination. β-Hydride elimination with the benzylic hydrogen atom leads to the formation of kinetically and thermodynamically favored olefinated products.

## Conclusions

In summary, we have developed a Pd(II)-catalyzed *ortho*-C(sp<sup>2</sup>)-H olefination of phenylacetic acid derivatives with unactivated aliphatic alkenes using a monodentate amide coordinating group. The identified quinoline-type ligand is found to be crucial for enabling this transformation. Both simple and functionalized aliphatic alkenes can be converted into the valuable β-alkylated styrene derivatives. Importantly, this catalytic system employs molecular oxygen as the terminal oxidant. We anticipate that the use of monodentate directing groups and ligands will lead to further development of this transformation to include a wide range of readily available monodentate substrates.

## Conflicts of interest

The authors declare no conflict of interest.

## Acknowledgements

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- 16 For substrates **6f-6h**, **6s-6u** and **8a**, the corresponding diolefinated products were detected (<5% yield).

