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Catalytic Multisite-Selective Acetoxylation Reactions at sp^2 vs sp^3 C−H Bonds in Cyclic Olefins

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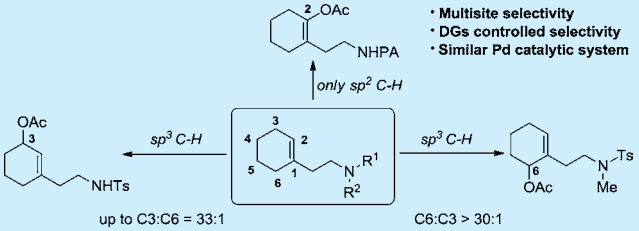
Supporting Information

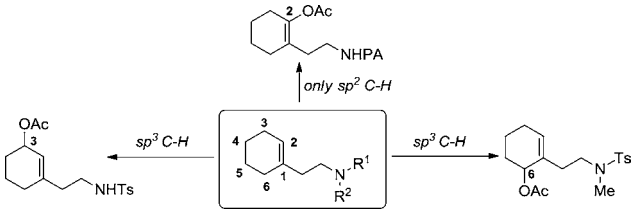
ABSTRACT: The first Pd-catalyzed multisite-selective acetoxylation reactions are disclosed at an unactivated alkene sp^2 C−H bond versus secondary allylic sp^3 C−H bond in cyclic olefins via the modulation of directing groups. The different directing groups overcome the key challenge in differentiating C−H bonds and provide a new controlling approach for site-specific C−H activation. A wide variety of substrates are readily acetoxylated under operationally simple conditions. Mechanistic studies suggest that different Pd (IV) intermediates were involved in the multisite-selective acetoxylation reactions.



Due to the ubiquitous nature of C−H bonds in organic molecules, it is challenging to achieve selective functionalizations among different kinds of C−H bonds.[1−3] The introduction of oxygen functionalities to C−H bonds with site selectivity[4−9] is critically important, and the principles and tactics for achieving vinyl sp^2 C−H[10] and allylic sp^3 C−H acetoxylation,[11−17] respectively, have been established.[18] However, multisite-selective acetoxylation using similar catalytic systems has been scarcely reported in the literature.[1c] One obvious challenge is the formation of intractable mixture of regioisomers due to the similar reactivities. Herein, we disclose the first Pd-catalyzed multisite-selective acetoxylation reactions at the unactivated alkene sp^2 C−H bond versus the secondary allylic sp^3 C−H bond in cyclic olefins via the modulation of directing groups (DGs).[9]

As shown in Scheme 1, our multisite-selective acetoxylation strategy relies on the choice of appropriate directing groups. The chemoselectivity of the vinyl sp^2 C−H bond versus allylic sp^3 C−H bond (2- vs 3- or 6-position) could be achieved in cyclic olefins by using picolinamide (PA)[19] and *p*-toluenesulfonyl (Ts) groups as DGs.[20] Furthermore, by introducing a methyl group on the *N*-Ts group, regioselective acetoxylation was also obtained between the two allylic sp^3 C−H bonds (3- vs 6-position). These three pathways afforded different and complementary site-selectivities in the same cyclic olefins.

Scheme 1. Approaches for Multisite-Selective Acetoxylation



Our initial studies focused on the acetoxylation of sp^2 C−H bond in cyclic olefins. 2-(Cyclohex-1-en-1-yl)ethanamines with different protecting groups were examined (Table 1). Gratifyingly, when PA was used as the directing group, the vinyl acetoxylation product (**2**, entry 1) was obtained in 70% isolated yield with excellent site-selectivity. When Ts was employed (entry 2), the allylic acetoxylation products (C3:6 = 5:1) along with double acetoxylation product (**Di-4**) were observed, while no vinyl acetoxylation product was generated. Moreover, excellent site-selectivity (C3:C6 = 33:1) was realized with 4-(trifluoromethyl)benzenesulfonyl (TFTs) as the directing group (entry 4). Similar site-selectivity was observed when 4-nitrobenzenesulfonyl (4-Ns) or 2-nitrobenzenesulfonyl (2-Ns) was introduced (entries 5 and 6). These results suggest that the selectivity could be enhanced by the electron-withdrawing benzenesulfonyl groups. However, the ratio of the products of allylic acetoxylation (C3:C6) was about 1:1 when the amine was protected by a weaker coordinating group (Boc, Cbz, and Ac) (entries 7−9). It is noteworthy that the substrate underwent acetoxylation with high site selectivity (C6:C3 > 30:1, entry 10) at the proximal sp^3 C−H bond (6-position) when the amine was protected by Ts and Me groups. No acetoxylation occurred if the Ts group was replaced by a Bn group (entry 12). Notably, by employing White's conditions,[13g] the acetoxylation occurred at the 6-position mainly with low yield, as the majority of starting materials remained (entry 3 and 11).

The substrate scope of vinyl sp^2 C−H acetoxylation was explored, and the results are summarized in Scheme 2 (see the Supporting Information for optimization details). The substrates

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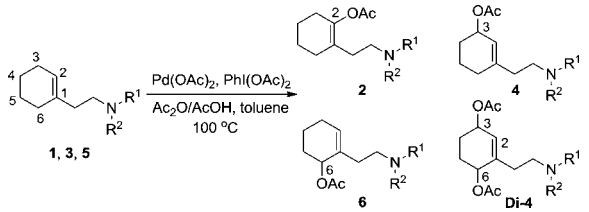
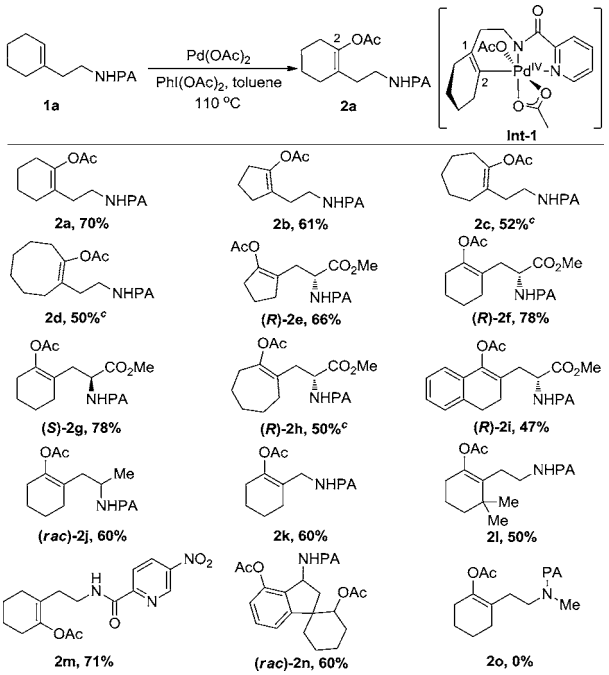
Table 1. Optimization of Acetoxylation Reactions with Different DGs[a−c]



entry	R^1/R^2	yield (%) 2	4	6	Di-4
1	PA/H	70	<2	<2	<2
2	Ts/H	<2	50	10	15
3[d]	Ts/H	<2	3	17	<2
4	TFTs/H	<2	66	2	13
5	4-Ns/H	<2	50	3	18
6	2-Ns/H	<2	60	8	15
7	Boc/H	<2	17	16	<2
8	Cbz/H	<2	19	18	<2
9	Ac/H	<2	18	17	<2
10	Ts/Me	<2	<2	34	<2
11[d]	Ts/Me	<2	<2	12	<2
12	Bn/Me	<2	<2	<2	<2

[a]Reactions conditions: substrate (0.3 mmol), $PhI(OAc)_2$ (0.75 mmol), $Pd(OAc)_2$ (0.03 mmol, 10 mol %), Ac_2O (1.5 mmol), AcOH (1.5 mmol), toluene (4 mL), N_2, 2 h. [b]Yield is that of the isolated product. [c]The site selectivity is determined by ^1H NMR (400 MHz) of the crude reaction mixture. [d]Reactions conditions: substrate (0.3 mmol), 1,4-benzoquinone (0.60 mmol), $Pd(OAc)_2$ (0.03 mmol, 10 mol %), (vinylsulfinyl)benzene (0.03 mmol, 10 mol %), AcOH (1.2 mmol), dioxane (1 mL), 30 h.

Scheme 2. Substrate Scope of sp^2 C−H Acetoxylation[a,b]

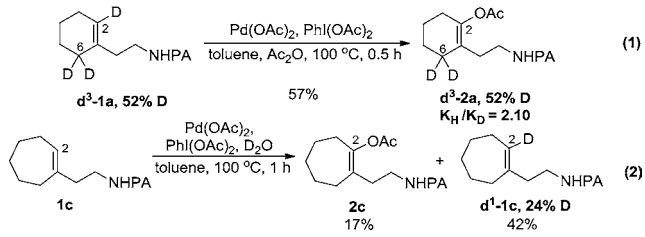


[a]Reactions conditions: **1** (0.3 mmol), $Pd(OAc)_2$ (0.03 mmol), $PhI(OAc)_2$ (0.75 mmol), 2-Chloro-4-cyanopyridine (0.12 mmol), toluene (5 mL), N_2, 2 h. [b]Yield is that of the isolated product. [c]Yield is based on the recovered starting material.

possessing five-, six-, seven-, and eight-membered rings afforded the desired products **2a−d** in moderate to good yields. In particular, optically pure amino acid derivatives also produced the target products in moderate to high yields without erosion of enantiopurities (**2e−i**). The derivatives with an α-methyl group or one carbon shorter chain proceeded smoothly with satisfactory yields (**2j,k**). The cyclohexene with bulky 6,6-dimethyl groups provided the desired product in moderate yield (**2l**). Moreover, the electron-withdrawing group on PA had no effect on this transformation (**2m**). Surprisingly, a spirocyclic product (**2n**) via an Friedel−Crafts alkylation and double acetoxylation was isolated in moderate yield when an α-phenyl group was introduced into the substrate. Furthermore, introduction of a methyl group to the N-PA group completely inhibited this transformation (**2o**), suggesting that N−H as the coordination group plays a key role in these reactions.

To gain an understanding of the site-selectivity in the vinyl sp^2 C−H acetoxylation reaction, **d^3-1a** (52% deuterium) was prepared to distinguish acetoxylations at the 2- and 6-positions (eq 1, Scheme 3). Under the optimized reaction conditions, **d^3-**

Scheme 3. Deuterium-Labeling Experiments of sp^2 C−H Acetoxylation



2a was obtained in 57% yield at C2 of the cyclohexene, and no C6 acetoxylation product was generated. Comparison of the initial acetoxylation rates of **1a** versus its deuterated analogue **d^3-1a** provided a K_H/K_D of 2.10 in toluene. These data suggest that the sp^2 C−H(D) bond breaking to form the cyclopalladium is rate limiting in the system. Significant deuteration occurred at the C2 position and acetoxylation product **2c** was formed when the reaction was carried out with excess D_2O (2.0 equiv) under the standard conditions (eq 2, Scheme 3). This result suggests that acetoxylation occurs through an sp^2 C−H activation process via the postulated intermediate (**Int-1**, Scheme 2)[21,22] at the 2-position of the cyclohexene. The exchange of deuterium between the alkene and D_2O was observed. The H/D exchange also implied that the process occurred through the cyclopalladated intermediate.

To date, there are only a few examples of Pd-catalyzed C−H functionalization at secondary sp^3 C−H bonds.[13f,14] Therefore, we turned our attention to the development of acetoxylation of secondary allylic sp^3 C−H bonds and achieved C3-selectivity when proper sulfonyl groups were employed as the directing groups (Scheme 4; see the Supporting Information for optimization details). For the cyclohexene derivative with a Ts group, the ratio of the products of C3 and C6 acetoxylation (**4a** and **4a′**) was improved with $PdCl_2(PhCN)_2$ instead of $Pd(OAc)_2$. The substrate with an Ns group led to the C3-selective product (**4b**) and double-acetoxylation product (Di-**4b**) in 53% and 18% yields, respectively, while no C6-acetoxylation occurred. The structure of **4b** was confirmed by X-ray diffraction of its hydrolysate (**4b-OH**).[23] Furthermore, when TFTs was used as the directing group, better yield and

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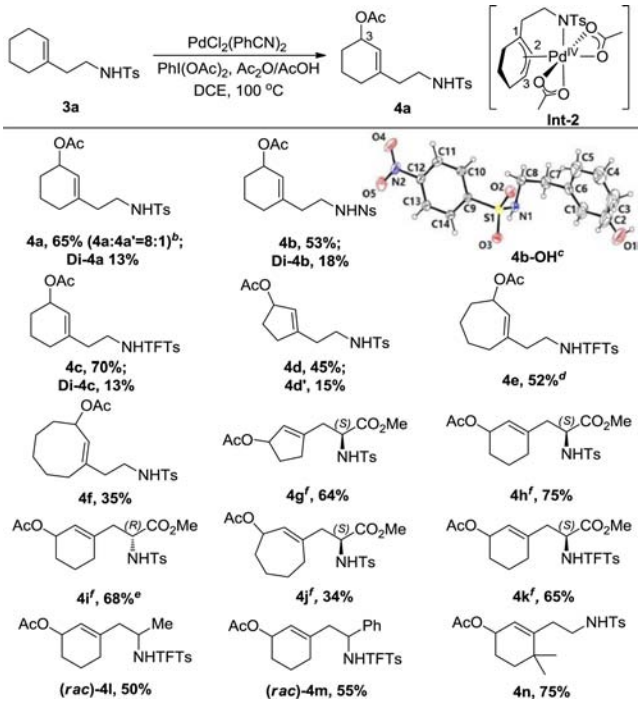
Scheme 4. Substrate Scope of sp^3 C−H Acetoxylation 1[a]

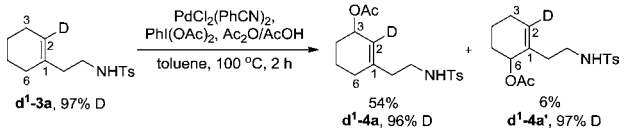


[a]Reactions conditions: **3** (0.3 mmol), $PdCl_2(PhCN)_2$ (0.015 mmol), $PhI(OAc)_2$ (0.75 mmol), Ac_2O (1.5 mmol), AcOH (1.5 mmol), DCE (4 mL), N_2, 2 h. [b]C6-acetoxylation products **4a**′ and **Di4a** were found. [c]X-ray structure of **4b-OH**. For simplicity, one of the two configurations has been omitted. [d]Yield is based on the recovered starting material. [e]At 80 °C. [f]The dr value is about 1:1.

selectivity were achieved. In addition, a five-membered ring substrate with TFTs gave a mixture of C3- and C6-acetoxylation products (**4d** and **4d**′) with a ratio of 3:1. The substrates with seven- and eight-membered rings also worked, providing only the C3 acetoxylation products **4e** and **4f** with lower yields, respectively. Interestingly, the substrates of chiral amino acid ester proceeded smoothly (**4g**−**k**). The substrates with α-methyl or phenyl group also performed well (**4l**,**m**). When two methyl groups were introduced into the six-membered ring, the corresponding acetoxylation product was still obtained in good yield (**4n**). The steric hindrance on the ring had negligible impact on the cyclohexene C3-selectivity acetoxylation.

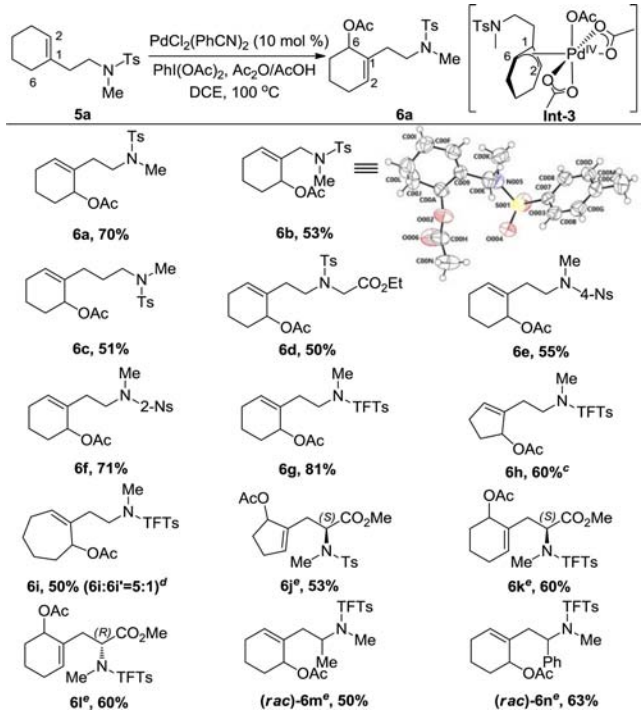
2-Deuterated (cyclohex-1-en-1-yl)ethanamine (**d^1-3a**, 97% deuterium) was prepared to determine if this sp^3 C−H bond acetoxylation occurred at the 3- or 6-position as shown in Scheme 5. Under the optimized reaction conditions, **d^1-4a** was obtained in 54% yield at the 3-position, and the acetoxylation product at the 6-position was formed in 6% yield. This result indicates that acetoxylation occurs through the postulated π-(1,2,3)-allylpalladium species (**Int-2**, Scheme 4).[14]

Scheme 5. Deuterium-Labeling Experiments of sp^3 C−H Acetoxylation



Moreover, introduction of a methyl group into the substrates of the C3-acetoxylation led to C6-acetoxylation. A series of sulfonamides **5** were surveyed (Scheme 6). The model C6-

Scheme 6. Substrate Scope of sp^3 C−H Acetoxylation 2[a,b]

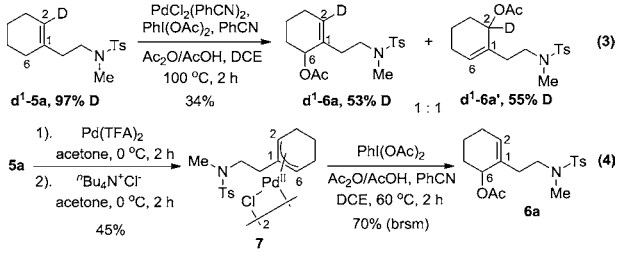


[a]Reactions conditions: **5** (0.3 mmol), $PdCl_2(PhCN)_2$ (0.03 mmol), $PhI(OAc)_2$ (0.75 mmol), Ac_2O (1.5 mmol), AcOH (1.5 mmol), DCE (4 mL), N_2, 2 h. [b]Yield is that of the isolated product. [c]At 80 °C. [d]C3-side product **6i**′. [e]The dr value is about 1:1.

acetoxylation product (**6a**) was formed in 70% yield. The substrates with one less or more carbon on the side chain compared with **5a** afforded the corresponding products (**6b**[23] and **6c**). The ester group in **6d** was well tolerated. Additional protecting groups were also screened (**6e**−**g**), and the TFTs group provided the highest yield. The substrates with five- and seven-membered rings generated the products in moderate yields with good site selectivities (**6h**,**i**). The amines with different α-substituents (ester, methyl, phenyl) also furnished the C6-acetoxylation (**6j**−**n**) with satisfactory yields.

2-Deuterated (cyclohex-1-en-1-yl)ethanamine (**d$_1$-5a**, 97% deuterium) was synthesized to examine the possibility of the double-bond migration (Scheme 7). Under the optimized reaction conditions, **d^1-6a** and **d^1-6a**′ were obtained in 34% yield with a ratio of 1:1 (eq 3). The possible palladium(II)

Scheme 7. Deuterium-Labeling and Palladium(II) Intermediate Experiments



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complex **7**[23] was prepared from the alkene **5a** and $Pd(TFA)_2$ (eq 4),[24] and the isolated complex could be converted into the desired product **6a** when heated to 60 °C with $PhI(OAc)_2$. These results suggest that acetoxylation occurs through the postulated π-(6,1,2)-allylpalladium species (**Int-3**, Scheme 6).[14,21]

In summary, a straightforward strategy for the multisite-selective acetoxylation of vinyl sp^2 versus secondary allylic sp^3 C−H bonds in cyclic olefins has been developed using a Pd(II/IV) catalysis system via the modulation of directing groups. Mechanistic studies and deuteration experiments suggest that different Pd(IV) intermediates were involved in the acetoxylations. Efforts toward to the development of asymmetric allylic acetoxylation as well as applications of the methodologies in the synthesis of natural and designed products of biological importance are currently ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02458.

Experimental procedures, characterization of the products, X-ray analysis, and NMR spectra (PDF)

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Author Contributions

†Z.-L.Z. and S.Z. contributed equally.

Notes

The authors declare no competing financial interest.

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