C–H Activation

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Easily Accessible Auxiliary for Palladium-Catalyzed Intramolecular Amination of C(sp^2)–H and C(sp^3)–H Bonds at δ- and ε-Positions**

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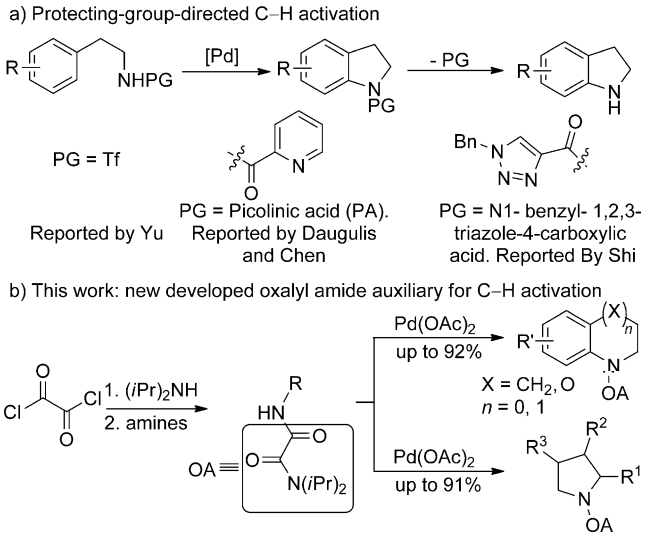
Abstract: *An easily synthesized and accessible N,O-bidentate auxiliary has been developed for selective C–H activation under palladium catalysis. The novel auxiliary showed its first powerful application in C–H functionalization of remote positions. Both C(sp^2)–H and C(sp^3)–H bonds at δ- and ε-positions were effectively activated, thus giving tetrahydroquinolines, benzomorpholines, pyrrolidines, and indolines in moderate to excellent yields by palladium-catalyzed intramolecular C–H amination.*

Transition-metal-catalyzed functionalization of C–H bonds has emerged as an efficient methodology for carbon–carbon and carbon–heteroatom bond formation, and the directing group plays an important role for selective C–H functionalization.[1] Especially in recent years, significant progress in palladium-catalyzed intramolecular C–N amination through C–H activation has been achieved.[2] Among the reports, the groups of Yu, Daugulis, Chen, and Shi have described different types of N-protected amides (NH-PG) as the directing groups, which have a the ability to direct palladium-catalyzed functionalization of C–H bonds (Scheme 1 a).[3–5] The group of Yu showed that N-triflated phenethylamines could be converted into indolines using a range of oxidants with palladium as a catalyst.[3b] Later, the groups of Daugulis and Chen used picolinicamide-directed intramolecular amination to synthesize azetidines, pyrrolidines, and indolines.[2f,g] Recently, the group of Shi reported a similar intramolecular C–N bond formation reaction using 1,2,3-triazole acids as an auxiliary.[5]

The synthesis of azetidine, indoline, and carbazole derivatives through directed C–H functionalization, via five- or six-membered palladacycles, is well developed.[6] However, there have been few reports of directed C–H functionalizations, via seven-membered palladacycles, to synthesize six-membered heterocycles,[7] because the formation of a seven-membered palladacycle intermediate during the catalytic cycle is more difficult than that of five- or six-membered palladacycles. Herein, we report the first example of the use of oxalyl amide derivatives as a newly discovered directing group in the synthesis of tetrahydroquinolines (THQs), benzomorpholines (BMPs), pyrrolidines, and indolines by palladium-catalyzed intramolecular amination of C(sp^2)–H and C(sp^3)–H bonds at the δ- and ε-positions of amine substrates (Scheme 1 b).



Scheme 1. Protecting-group-directed intramolecular C–H amination

THQs, BMPs, and pyrrolidines are widely used in the pharmaceutical and agrochemical industries.[8] We envisioned that THQs and BMPs could be synthesized by directed C–H functionalization reactions from phenylpropylamine substrates via seven-membered palladacycles.[9] We first tested Boc, Cbz, Ac, and picolinamide as auxiliaries under the general palladium-catalyzed intramolecular C–N amination conditions (Table 1). All failed to give any intramolecular amination products. The triflamide of phenylproylamine gave the desired product, but the maximum yield was 25% when using 1-fluoro-2,4,6-trimethylpyridinium triflate as the oxidant.[3b]

The weakly coordinating directing group could assist at the δ-position for C–H functionalization under mild reaction conditions which were disclosed by the group of Yu.[10] Inspired by these works, we hypothesized that a new auxiliary, with weaker coordination to the palladium center than that of picolinamide and stronger coordination than that of trifla-

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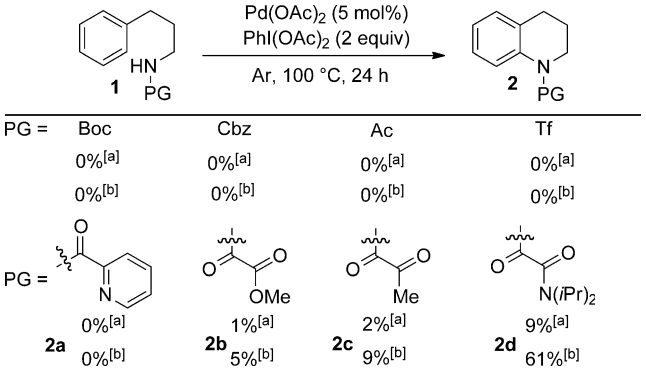
Table 1: Screening of directing groups.[a,b]

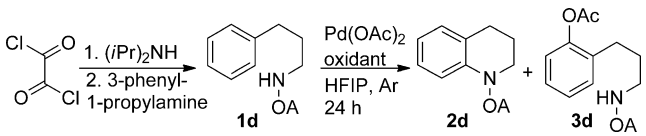


[a] Reactions were carried out on a 0.2 mmol scale under argon (1 atm), using toluene (2 mL) as the solvent. Yields were based on GC-MS. [b] Using HFIP (2 mL) as the solvent. Boc = *tert*-butoxycarbonyl, Cbz = benzyloxycarbonyl, Tf = trifluoromethansulfonyl.

mide, might give THQ and BMP derivatives through remote C–H activation.[11] To this end, we examined the effect of a range of N,O bidentate directing groups with $Pd(OAc)_2$ (0.05 equiv), $PhI(OAc)_2$ (2 equiv), and either toluene or hexafluoroisopropanol (HFIP) as the solvent at 100 °C (Table 1, **2b–d**).[12] To our delight, with the oxalyl amide as the auxiliary (**2d**), the desired cyclized product was obtained in 61 % yield, accompanied by a 19 % yield of the acetoxylated byproduct **3d** when HFIP was used as the solvent.

The substrate **1d** could be easily synthesized on large scale (27.5 g, 93 %) from oxalyl chloride and diisopropylamine. We next investigated the reactions of allyl amide (**1d**) with different additives in HFIP (Table 2). The addition of a carboxylic acid such as PivOH or AcOH reduced the yield (Table 2, entries 2 and 3). Oxygen inhibited cyclization and increased the byproduct yield. To our surprise, lowering

Table 2: Palladium-catalyzed amination of ε C(sp^2)–H bonds.



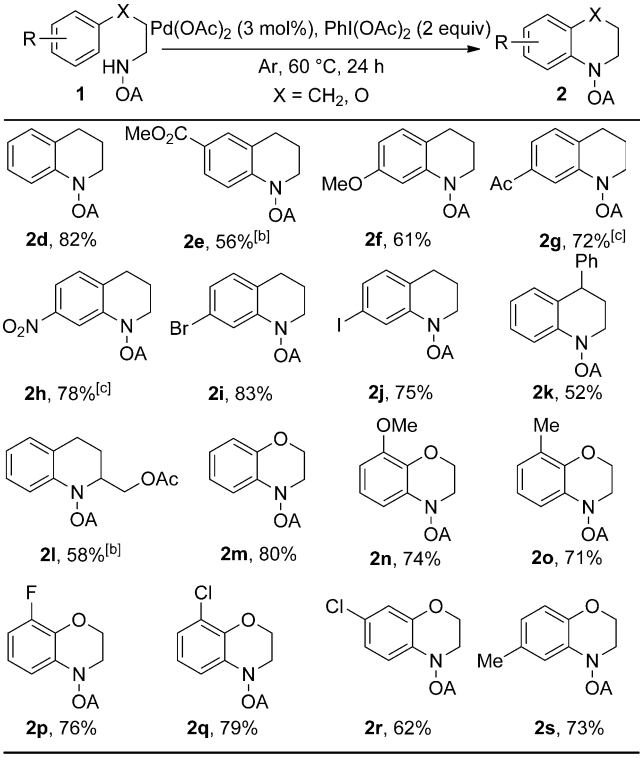
Entry	$Pd(OAc)_2$ (mol %)	Oxidant (equiv)	Additive (equiv)	*T* [°C]	Yield [%][a,b] **2d**, **3d**
1	5	$PhI(OAc)_2$ (2)	DMF (2)	100	60, 18
2	5	$PhI(OAc)_2$ (2)	AcOH (2)	100	56, 23
3	5	$PhI(OAc)_2$ (2)	PivOH (2)	100	59, 21
4	5	$PhI(OAc)_2$ (2)	Air	100	54, 20
5	5	$PhI(OAc)_2$ (2)	O_2	100	39, 25
6	5	$PhI(OAc)_2$ (2)	O_2	60	68, 13
7	3	$PhI(OAc)_2$ (2)	O_2	60	73, 9
8	1	$PhI(OAc)_2$ (2)	O_2	60	42, 6
9[c]	3	$PhI(OAc)_2$ (2)	O_2	60	84(82), 7
10	3	$PhI(OAc)_2$ (2)	TEMPO (0.2)	60	50, 19
11	0	$PhI(OAc)_2$ (2)	TEMPO (0.2)	60	0, 0

[a] Reactions were carried out on a 0.25 mmol scale under argon (1 atm), using HFIP (4.2 mL) as the solvent. Yield was based on GC using tridecane as the internal standard. [b] Yield of isolated product given within parentheses. [c] Using 12.5 mL HFIP as solvent.

the reaction temperature led to an increase of the chemoselectivity and the yield increased under otherwise identical reaction conditions (entry 6). Compared with many known C–H functionalization protocols, low catalyst loading was necessary for the cyclization reaction to proceed well.[3c] Slightly improved results were achieved using 3 mol % of $Pd(OAc)_2$ at 60 °C. When the concentration of the reaction mixture was lowered, a satisfactory yield and selectivity were obtained (entry 9). No reaction occurred without $Pd(OAc)_2$, and only starting material was recovered from the reaction.

Once we had identified the optimal reaction conditions for the intramolecular amination of phenylproplyamine oxalyl amide, we next studied the substrate scope of the cyclization reaction (Table 3). Overall, THQ derivatives were

Table 3: Synthesis of THQ and BMP by intramolecular amination.[a]



[a] Yields based on isolated products on a 0.25 mmol scale, using 12.5 mL HFIP (0.02 M). [b] Used 10 mol % $Pd(OAc)_2$. [c] At 80 °C.

generated in fair to good yields (**2d–l**) for a range of substituted phenylproplyamine oxalyl amides with tolerance to a variety of functional groups including Ac, NO_2, Br, and I. Notably, the substrate **1l**, bearing an α substituent, gave the cyclized product **2l** in only 58 % yield with 10 mol % $Pd(OAc)_2$. Under standard reaction conditions, a set of substituted 2-phenoxyethylamine oxalyl amides were converted into the corresponding BMPs in good yields (**2m–s**).

We also expanded the substrate scope, and found that a range of β-arylethyamines were cyclized under milder reaction conditions (Table 4). Both electron-donating and electron-withdrawing groups were tolerated. The cyclized products were obtained in good to excellent yields. Excellent regioselectivity at the least sterically hindered position was

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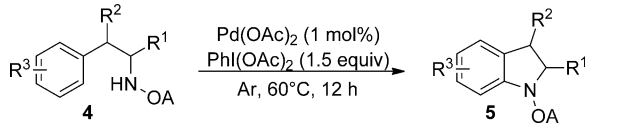
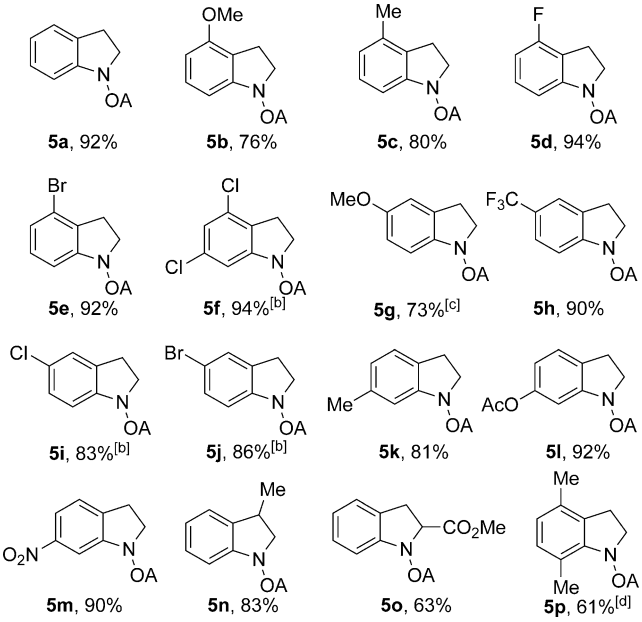
Table 4: Synthesis of indolines by intramolecular amination.[a]

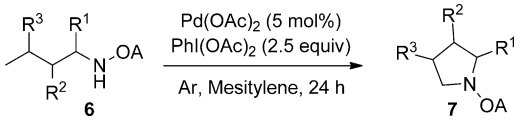


4 → 5

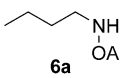
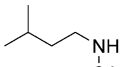
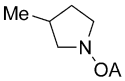
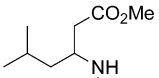
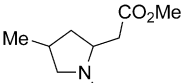
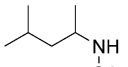
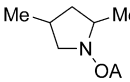
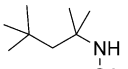
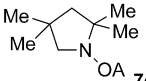
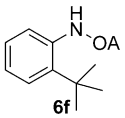
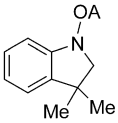
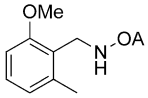
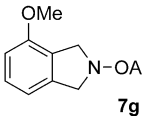


[a] Yields based on isolated products on a 0.5 mmol scale, using 3 mL HFIP (0.17 M). [b] At 80 °C. [c] PhCl as solvent. [d] Used 3 mol% $Pd(OAc)_2$.

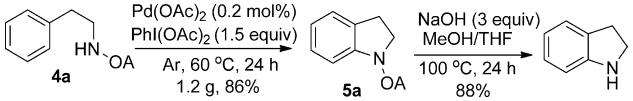
Table 5: Synthesis of pyrrolidines by intramolecular amination.[a]



6 → 7

Entry	Substrates	Temperature	Products
1	 **6a**	140 °C	 **7a** (25%)
2	 **6b**	140 °C	 **7b** (60%)
3	 **6c**	120 °C	 **7c** (62%)
4	 **6d**	120 °C	 **7d** (64%)
5	 **6e**	100 °C	 **7e** (91%)
6	 **6f**	80 °C	 **7f** (72%)
7	 **6g**	80 °C	 **7g** (73%)

[a] Yields based on isolated products on a 0.25 mmol scale, using 5 mL mesitylene (0.17 M).



4a → 5a

Scheme 2. Scaling up and auxiliary removal. THF = tetrahydrofuran.

also observed. Moreover, the challenging 2,5-disubstituted product **5p** was also observed in 61% yield with a slight increase in the loading of the catalyst.

Encouraged by the success with the oxalyl-amide-assisted intramolecular amination of a remote C(sp^2)–H bond, we went on to explore the more challenging intramolecular C(sp^3)–H/N–H cyclizations to synthesize pyrrolidines (Table 5). The cyclization of the substrates bearing two or three primary δ C(sp^3)–H bonds proceeded smoothly to give the corresponding pyrrolidine products in good to excellent yields. To our delight, even the oxalyl-amide-protected *n*-butylamine, could be cyclized in 25% yield, with 50% recovery of the starting material. The substrates **6b–d**, with or without an α substituent, gave the cyclized products **7b–d** in around 60% yield. The *tert*-octylamine oxalyl amide **6e**, having three primary δ C(sp^3)–H bonds, was cyclized in nearly quantitative yield. Furthermore, the 2-*tert*-butylaniline derivative **6f** is cyclized in a much better yield than that of previous reports.[2f,g] Cyclization of the substrate **6g** also gave a satisfactory yield.[2f] In addition, the oxalyl-amide-protected valine was prepared as a substrate to form azetidine. Unfortunately, the acetoxylated product was observed in 49% yield without any cyclized product.

For the reaction to be synthetically useful, the directing group must be easily introduced and removed from the substrate. Indeed, oxalyl amides fulfill these requirements as shown in Scheme 2.[13] For a gram-scale reaction, the catalyst loading was reduced (0.2%) and the product **5a** was obtained in 86% yield with a slightly longer reaction time.

In an attempt to gain deeper insight into the reactivity of oxalyl-amide-directed intramolecular amination, deuteration experiments were performed to show the different reactivities of the C–H bonds (Scheme 3a).[14] It turned out that more than 60% deuteration incorporation occurred at the ε-positions with less than 2% at the γ-position of **1d**. This outcome explains why there is no formation of four-membered azetines or acetoxylated byproducts at the γ-position in the reaction.

A primary kinetic isotope effect (3.0) was observed under general reaction conditions (see the Supporting Information), thus implicating that C–H bond activation should be the rate-determining step.[15] To get a better understanding on the reaction mechanism, we tried to isolate and identify the

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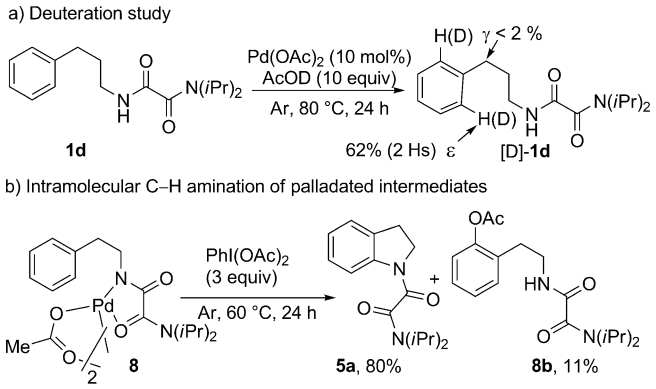

Scheme 3. Primary mechanism studies.

palladium intermediate. The compound **4a**, with 1 equivalent of palladium diacetate in toluene afforded the palladium complex **8** at 40 °C. The X-ray structure of **8** shows that an N,O-bidentate palladacycle intermediate is formed and is consistent with our hypothesis (Figure 1). We then tried to

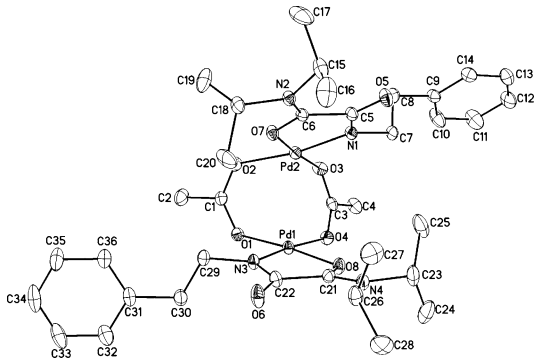

Figure 1. Crystal structure of **8**. Thermal ellipsods are shown at the 20% probability level.[17]

prepare the rare seven-membered palladacycle at a higher temperature in toluene with acetonitrile. Unfortunately, only palladium black was observed. It might be that the seven-membered palladacycle was not stable.[7,16] Furthermore, when **8** was heated with 3 equivalents of iodobenzene diacetate, 80% of cyclized product **5a** and 11% of acetoxylated byproduct **8b** were obtained. All the results reveal that oxalyl-amide-directed intramolecular C(sp^2)–H amination occurred by a $Pd^{II/IV}$ catalytic cycle, involving a sequence of C–H palladation, $Pd^{II/IV}$ oxidation, and C–N reductive elimination.

In conclusion, we have developed palladium-catalyzed C(sp^2)–H and C(sp^3)–H activations directed by new N,O-bidentate oxalyl amide groups. The new method provides efficient, economical, and practical syntheses of THQs, BMPs, and indolines under mild reaction conditions by palladium-catalyzed intramolecular C–H amination. The newly developed directing group could be easily introduced and removed under mild reaction conditions, and can be considered a new amine-protecting group. More detailed mechanistic studies and the investigation of new applications of oxalyl amides as directing groups in the construction of C–C, C–O, and C–F bonds at remote positions are now being undertaken in our laboratory.

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Keywords: amination · C–H activation · cyclization · heterocycles · palladium

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[17] CCDC 1013832 (**8**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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