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Synthesis of isoindolinones *via* palladium-catalyzed C–H activation of *N*-methoxybenzamides†

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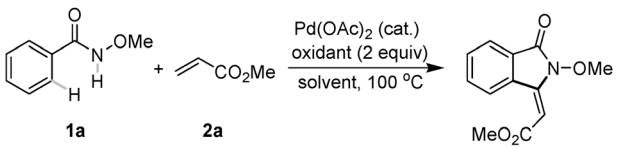
The synthesis of isoindolinones from *N*-methoxybenzamides and alkenes has been achieved by Pd-catalyzed *ortho* sp^2 C–H activation and intramolecular oxidative amidation, which involve the cleavage of four bonds and formation of two bonds.

Palladium-catalyzed C–H activation has become one of the most important methods to construct C–C and C–X (X = heteroatom) bonds in recent years.[1] A directing group is frequently required to achieve high regioselectivity in a C–H activation reaction. The CONHOMe group was first exploited by the Yu group as a directing group in the Pd-catalyzed arylation of sp^3 C–H bonds[2] and lactamization of sp^2 C–H bonds.[3] We have reported the alkoxylation of *N*-methoxybenzamides *via* Pd-catalyzed sp^2 C–H bond activation,[4a] and the synthesis of phenanthridinones from *N*-methoxybenzamides and aryl iodides by intermolecular C–C bond formation and subsequent intramolecular C–N bond formation through Pd-catalyzed sequential C–H bond activation.[4b] The same CONHOMe group could act as both a directing group and an internal oxidant when a rhodium catalyst was used.[5] The Rh-catalyzed reaction of *N*-methoxybenzamides with acrylates/styrenes gave *ortho*-olefinated products with concurrent N–O bond cleavage.[5a] In contrast, replacing the *N*-methoxy group with the *N*-pivalate group led to the formation of 3,4-dihydroisoquinolone derivatives *via* a sequence of *ortho*-olefination and intramolecular cyclization, concomitant with the N–O bond rupture.[5a,b] Intriguingly, we found that the same reaction of *N*-methoxybenzamides with acrylates/acrylamides/styrenes selectively afforded another type of products, *i.e.*, isoindolinones, without N–O bond cleavage when catalyzed by $Pd(OAc)_2$. Herein, we report this novel result.

Our success in the Pd-catalyzed C–H activation reactions of *N*-methoxybenzamides with alcohols[4a] and aryl iodides[4b] prompted us to examine their olefination reactions with activated alkenes such as acrylate esters. The Pd-catalyzed reaction of *N*-methoxybenzamide (**1a**) with methyl acrylate (**2a**) was chosen as the model reaction to screen for optimal conditions. No cross-coupling reaction occurred when $Cu(OAc)_2$ was used as the oxidant under Miura's[6] or Yu's[7] conditions (Table 1, entries 1 and 2). Gratifyingly, we found that the reaction of **1a** with 2.0 equiv. of **2a** in the presence of 5 mol% of $Pd(OAc)_2$ and 2.0 equiv. of $Cu(OAc)_2$ in AcOH at 100 °C for 10 h gave product **3aa** in 9% yield (Table 1, entry 3). If Ag_2O was employed as the oxidant, the yield could be increased to 23% (Table 1, entry 4). Other silver salts such as AgOAc and Ag_2CO_3 could also promote the reaction, albeit in slightly lower yields (Table 1, entries 5 and 6 *vs.* entry 4). However, $K_2S_2O_8$, $PhI(OAc)_2$ and O_2 were unsuitable for the reaction (see ESI†). *p*-Benzoquinone (BQ) is a well-established oxidant for Pd^0 and a promoter for C–C bond formation in a wide range of palladium-catalyzed reactions.[8] To our delight, the yield of **3aa** could be improved to 74% yield when BQ was used as the oxidant (Table 1, entry 7). Prolonging or shortening the reaction time did not provide higher yield (Table 1, entries 8 and 9 *vs.* entry 7). Disappointedly, when

Table 1 Screening conditions for the Pd-catalyzed reaction of *N*-methoxybenzamide and methyl acrylate[a]



1a **2a** **3aa**

Entry	Oxidant	Solvent	Time/h	Yield (%)
1[b]	$Cu(OAc)_2$	DMF	10	0
2[c]	$Cu(OAc)_2$	DMF	10	0
3	$Cu(OAc)_2$	AcOH	10	9
4	Ag_2O	AcOH	10	23
5	AgOAc	AcOH	10	21
6	Ag_2CO_3	AcOH	10	17
7	**BQ**	**HOAc**	**10**	**74**
8	BQ	HOAc	8	73
9	BQ	HOAc	12	70

[a] Unless otherwise specified, all reactions were carried out with **1a** (0.5 mmol), **2a** (1.0 mmol), $Pd(OAc)_2$ (0.025 mmol), oxidant (1.0 mmol), solvent (5 mL), 100 °C. [b] $Pd(OAc)_2$ (0.025 mmol), $Cu(OAc)_2$ (0.025 mmol), KOAc (0.25 mmol), 4 Å MS (400 mg), DMF (5 mL), 100 °C. [c] $Pd(OAc)_2$ (10 mol%), $Cu(OAc)_2$ (2.0 equiv.), LiCl (2.0 equiv.), DMF (5 mL), 120 °C, N_2.

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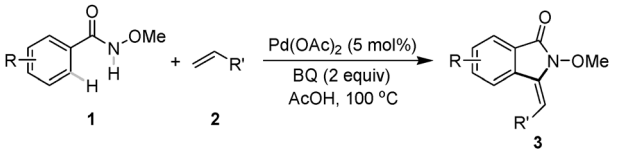
DMF, DCE, 1,4-dioxane, CH_3CN and toluene were employed as the solvent, either no or a trace amount of product was formed (see ESI†). Therefore, 1.0 equiv. of **1a**, 2.0 equiv. of **2a**, 5 mol% of $Pd(OAc)_2$ and 2.0 equiv. of BQ were chosen as the optimized conditions for the Pd-catalyzed reaction of **1a** with **2a** in refluxing AcOH.

With the optimized reaction conditions in hand, we then investigated the synthesis of isoindolinones by utilizing various *N*-methoxybenzamides and acrylates/acrylamides/styrenes. The results are listed in Table 2. *N*-Methoxybenzamides with either electron-donating or electron-withdrawing groups afforded isoindolinones **3ba–3ma** in moderate to good yields. *N*-Methoxybenzamides having electron-donating groups at the *meta*-position and/or *para*-position of the phenyl ring were generally more reactive and gave higher yields than those bearing electron-withdrawing groups (62–75% for **3ba–3ha** *vs.* 40–53% for **3ia–3la**). 3,5-Dimethylated benzamide **1m** gave much lower yield than its counterpart **1e** due to steric hindrance. *n*-Butyl acrylate (**2b**) could replace methyl acrylate to react with *N*-methoxybenzamides **1a–k** and afforded products **3ab–3kb** in slightly better yields than the corresponding counterparts of **3aa–3ka**. *ortho*-Substitution on phenyl rings is known to retard the Pd-catalyzed *ortho* C–H activations.[4,8a] Nevertheless, the *o*-Me on the phenyl ring of **1d** afforded only slightly lower product yields (67% for **3da** and 69% for **3db**) relative to those (71% for **3ba**, 72% for **3ca**, 75% for **3bb** and 77% for **3cb**) of their *p*- and *m*-substituted counterparts. The reaction could be extended to acrylamides such as *N*,*N*-dimethyl acrylamide (**2c**). For example, the reaction of **1a**, **1c**, and **1d** with **2c** generated **3ac**, **3cc** and **3dc** in 80%, 67% and 82% yields, respectively. Finally, alkenes with an electron-withdrawing group was not mandatory, styrene could also be employed, and **3da** was obtained in 46% yield. It should be noted that the chloro, bromo, ether, nitro and ester groups in the phenyl ring were tolerated under our conditions, and can be further manipulated for the functionalization of the corresponding isoindolinone products. For the *meta*-substituted *N*-methoxybenzamides (**1c**, **1e**, **1g** and **1h**), only one regioisomer was obtained due to the steric factor.

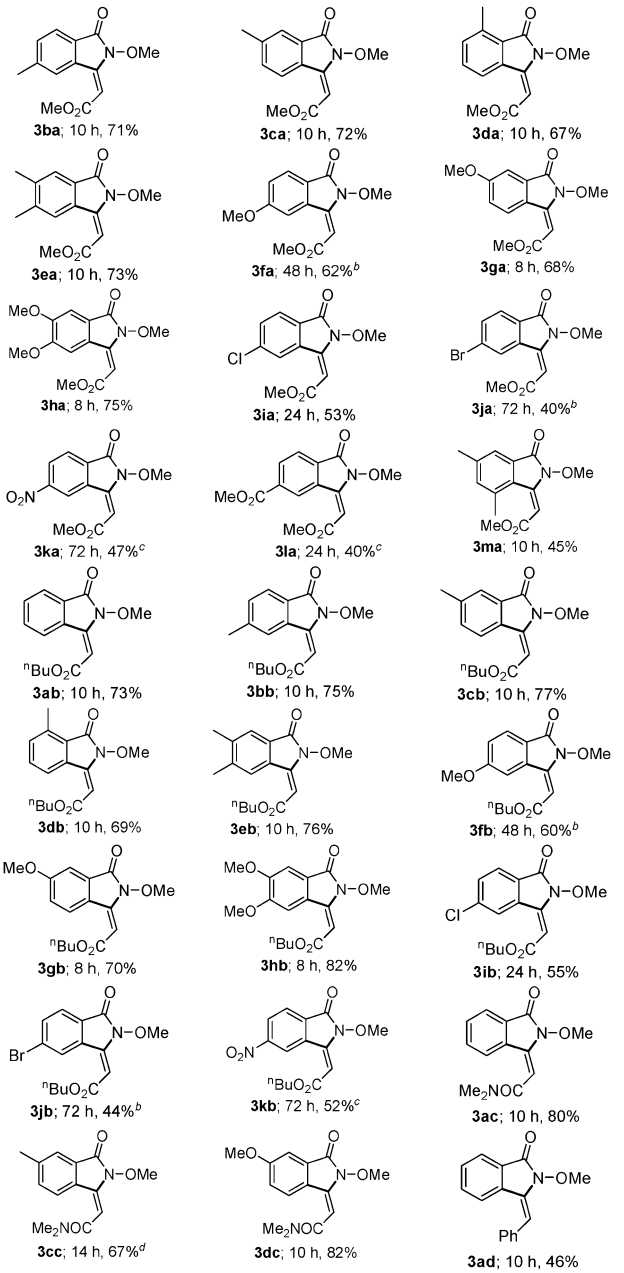
Additional experiments were performed to gain insights for the reaction mechanism. In our previous work, we found that the reaction of *N*-methoxybenzamides **1** with $Pd(OAc)_2$ generated palladacycles **4**.[4b] The reaction of palladacycle **4** with an acrylate ester could generate either **5** or **6** as the precursor of the final product *via* C–C and C–N bond formation, respectively. When **5aa** and **6aa** were treated with $Pd(OAc)_2$ (5 mol%) and BQ (2 equiv.) in AcOH at 100 °C, only **5aa** could successfully afford isoindolinone **3aa** (Scheme 1). In addition, Michael adduct **7aa** could not cyclize to **3aa** under the same conditions. Thus the reaction of *N*-methoxybenzamides **1** with acrylate esters did not give **6** and **7**, instead generated **5** as the intermediate. Intermediate **5** may undergo intramolecular aza-Michael addition to produce **8**, which is then oxidized to **3**. However, treatment of **8aa** with $Pd(OAc)_2$ (5 mol%) and BQ (2 equiv.) failed to produce **3aa**, thus ruling out the intermediacy of **8** in the formation of **3**. The molecular structure of product **3** was established by the X-ray crystallography of representative **3aa**.

Based on the aforementioned results, a plausible reaction mechanism is proposed and shown in Scheme 2. Palladation of benzamide **1** with $Pd(OAc)_2$ produces the five-membered palladacycle **4**.[4b] Olefin insertion into **4** generates the seven-membered palladacycle **9**, which undergoes β-hydride elimination to give *ortho*-olefinated intermediate **5** together with Pd^0. Coordination of **5** with $Pd(OAc)_2$ furnishes **10**, and subsequent

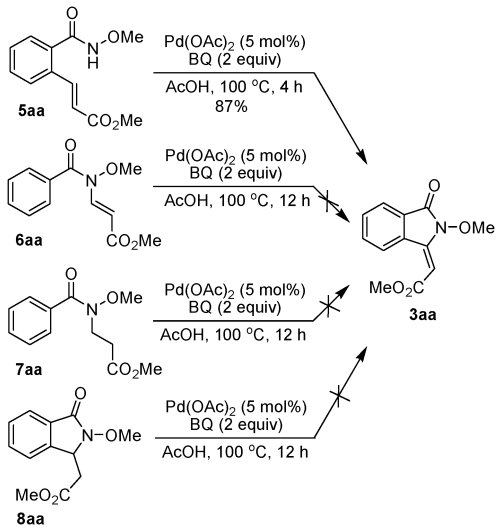
Table 2 Synthesis of isoindolinones by Pd-catalyzed reaction of *N*-methoxybenzamides with alkenes[a]



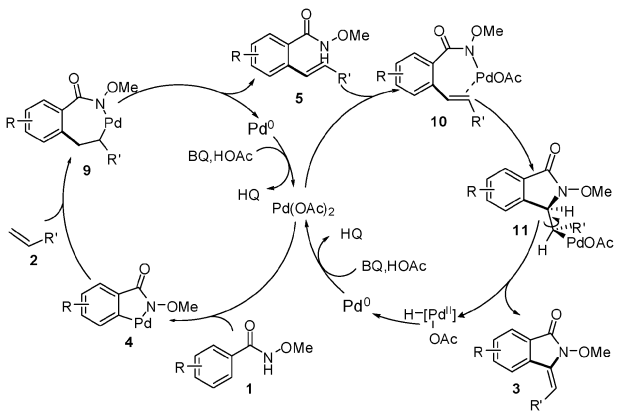
1 2 3



[a] Unless otherwise specified, all reactions were carried out with **1** (0.5 mmol), **2** (1.0 mmol), $Pd(OAc)_2$ (0.025 mmol), and BQ (1.0 mmol) in AcOH (5 mL) at 100 °C. [b] 0.05 mmol of $Pd(OAc)_2$ was employed. [c] 120 °C was employed. [d] 1.5 mmol of **2c** was used.



Scheme 1 Attempted Pd-catalyzed cyclization of **5aa**, **6aa**, **7aa** and **8aa**.



Scheme 2 Proposed reaction mechanism.

syn-aminopalladation produces **11**. β-Hydride elimination from **11** after bond rotation provides the final isoindolinone **3** as the *E*-isomers along with Pd^0. Pd^0 is oxidized by BQ to Pd^{II}, which re-enters the catalytic cycle. The fact that BQ behaves as an oxidant is confirmed by observation and isolation of *p*-hydroquinone (HQ).

Yu and co-workers reported the palladium-catalyzed olefination of sp^3 C–H bonds directed by *N*-arylamide (CONHAr), followed by cyclization to give lactams.[7] More recently, Li, Zhu, and their co-workers described the reaction of benzamides (ArCONHAr′ and ArCONHTs) with electron-deficient alkenes such as acrylate esters to afford isoindolinones *via* sp^2 C–H olefination and subsequent cyclization.[9] In these reactions, the cyclization step is an intramolecular aza-Michael addition,[7,9] which is mechanistically distinct from the intramolecular oxidative amidation step generating an *E*-configured exocyclic C=C bond in our case (see Scheme 2). It is noteworthy that the CONHOMe group was not a suitable directing group in the above-mentioned reactions because the acidic N–H was essential and dramatically improved the reactivity under the employed conditions.[7,9] More importantly, the Rh-catalyzed reaction of **1a** with **2b** gave a Heck-type product accompanied by the N–O bond cleavage.[5a] In sharp contrast, our Pd-catalyzed reaction afforded an isoindolinone with retention of the OMe group. The Pd- or Rh-catalyzed reaction of primary benzamides with **2b** gave isoindolinones as the *Z*-isomers resulting from the intramolecular *anti*-aminometallation in low to moderate yields.[10] A similar *anti*-addition process led to cyclized products with *Z* geometry for the Pd-catalyzed hydroxy-directed *ortho* C–H olefination.[11] Clearly, the CONHOMe group under our conditions directs the intramolecular cyclization step in a different pathway.[7,9–11]

In summary, we have achieved the synthesis of isoindolinones by a palladium-catalyzed cascade reaction, which involves the cleavage of three C–H bonds and one N–H bond as well as the formation of one C–C bond and one C–N bond. The reaction proceeds initially through the palladium-catalyzed *ortho* sp^2 C–H activation directed by the CONHOMe group of benzamides, followed by an intramolecular oxidative amidation with acrylates/acrylamides/styrenes, leading to the isoindolinone products as the *E*-isomers rather than the *Z*-isomers reported in the literature.[10,11] Intriguingly, replacing the Rh-catalyzed system[5a] with our Pd-catalyzed system switches the reaction pathway leading to different products for the reaction of *N*-methoxybenzamides with acrylate esters.

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Notes and references

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