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Geometry Driven Intramolecular Oxidative Cyclization of Enamides: An Umpolung Annulation of Primary Benzamides with Acrylates for the Synthesis of 3-Methyleneisoindolin-1-ones

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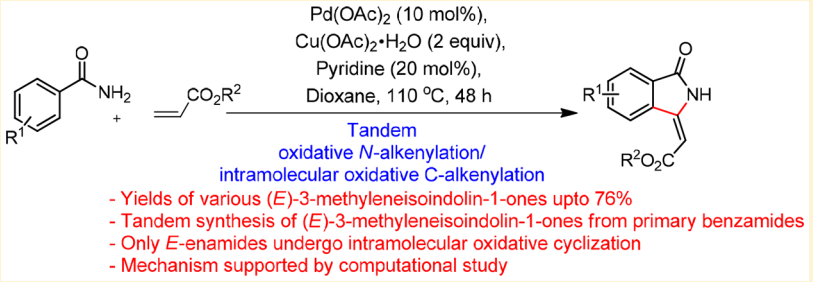
Supporting Information



ABSTRACT: A palladium-catalyzed tandem oxidative annulation of primary benzamides with acrylates via intermolecular *N*-alkenylation followed by intramolecular C-alkenylation yielded a stereoselective synthesis of (*E*)-3-methyleneisoindolin-1-ones. The study unveils, for the first time, that only *E*-enamides could undergo intramolecular oxidative cyclization under the optimized conditions to give isoindolinones. The current strategy represents an umpolung strategy when compared to the literature approaches that use benzamides.

INTRODUCTION

Despite their structural simplicity, 3-methyleneisoindolin-1-ones (**1**) bearing a free (NH) group display unique structural features: for example, (a) their exocyclic double bond adopts a preferred geometry, (b) they can be readily converted to saturated isoindolinones by hydrogenation of the double bond, (c) by virtue of their use as Michael acceptors, they undergo nucleophilic addition forming a quaternary center at C-3, and (d) they offer late-stage functionalization at nitrogen (Figure 1). While pharmaceutical relevance of 3-methyleneisoindolin-1-ones is yet to be investigated,[1] the corresponding saturated isoindolin-1-ones represent a class of privileged medicinal agents with significant therapeutic potentials as rennin inhibitor (**2**), antibiotic (pestalachloride A **3**), anxiolytic drug (pazinaclone **4**), TNF-α inhibitor, 5-HT antagonistic/antidepressant, PARP-1 inhibitor, and as histone deacetylase inhibitor.[2] Noticeably, isoindolin-1-ones that contain a free (NH) group have been demonstrated to contribute a major role in pharmacophoric activities. These structural features, coupled with their promise to assume pharmaceutical significance, make compounds **1** viable synthetic targets.

3-Methyleneisoindolin-1-ones have been synthesized using phthalimides,[3] by ruthenium-catalyzed annulation of benzimidates,[4] and various metal-catalyzed annulation of *ortho*-alkynyl benzamides.[5] However, the control of regioselectivity, competitive formation of byproducts, and the requirement of using preactivated aryl halides could limit the practice of these protocols. More recently, metal-catalyzed oxidative annulations of benzamides with alkenes have appeared to be elegant for the synthesis of isoindolinone derivatives (Scheme 1).[6] While these methods avoid using any preactivated substrates, many of them require a directing group yielding N-substituted isoindolin-1-ones. Therefore, development of an approach that largely avoids an elaborated synthetic strategy, including installation and subsequent removal of the directing group, and stepwise preparation of 3-methyleneisoindolin-1-ones, would be beneficial for the preparation of 3-methyleneisoindolin-1-ones that have a free NH-group. Remarkably, Rh-[6d] or Ru-catalyzed[6e] oxidative annulations of primary benzamides (or, generated in situ from aryl nitriles[6e]) to the synthesis of (NH)-3-methyleneisoindolin-1-ones are available. However, they suffer from limited substrate scope and the requirement of an acidic condition. More importantly, these annulations are reported to occur by oxidative *ortho*-C-alkenylation via C−H bond activation followed by intramolecular oxidative *N*-alkenylation.

From this perspective, a complementary tandem approach to 3-methyleneisoindolin-1-ones, involving oxidative *N* alkenylation of primary benzamides[7,8] followed by intramolecular oxidative cyclization of enamides, would be a subject of further

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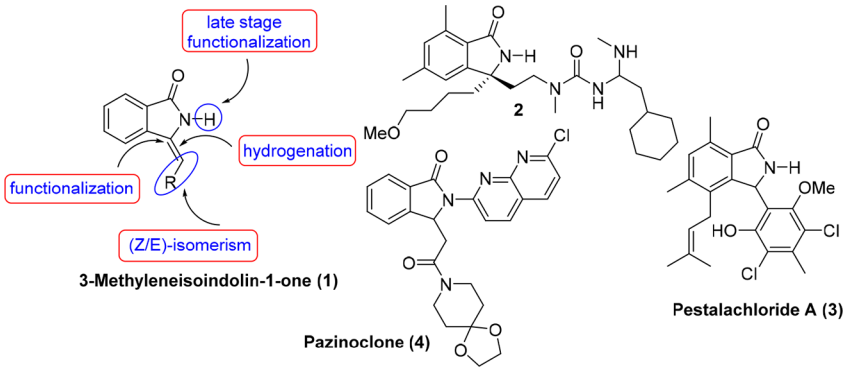


Figure 1. Pharmacophores containing an isoindolin-1-one moiety.

Scheme 1. Tandem Oxidative Annulations of Benzamides for the Synthesis of Isoindolinones

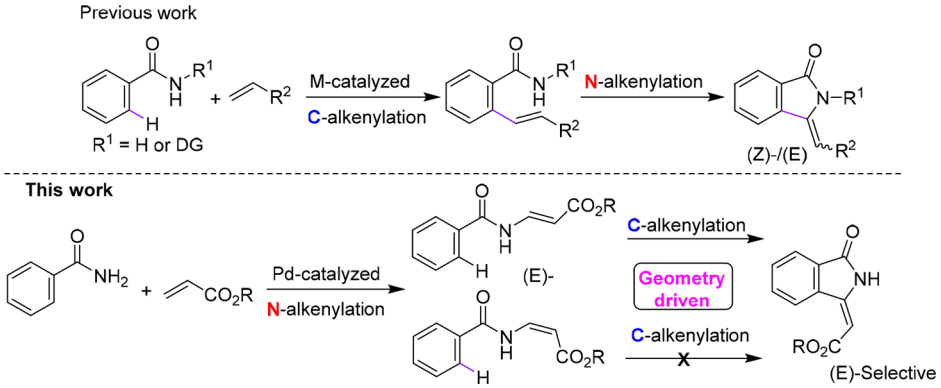
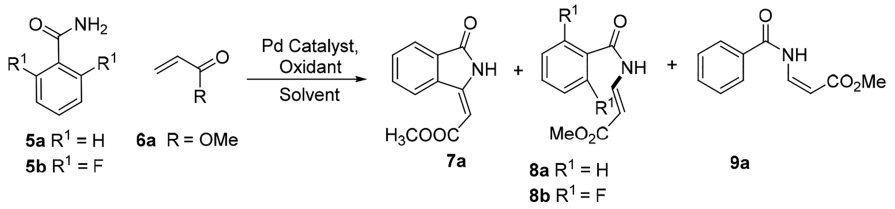


Table 1. Optimizations Study[a]



				yields (%)		
entry	catalyst	oxidant	additive	7a	8a	9a
1[b]	$PdCl_2(CH_3CN)_2$	Air	CuCl		68	21
2[c]	$Pd(OAc)_2$	AgOAc			50	40
3[d]	$Pd(OAc)_2$	AgOAc		40	35	18
4[e]	$Pd(OAc)_2$	AgOAc		42	30	20
5	$Pd(OAc)_2$	AgOAc		71	5	20
6[f]	$Pd(OAc)_2$	AgOAc	$K_2S_2O_8$	42	32	17
7[g]	$Pd(OAc)_2$	AgOAc	$Cu(OAc)_2$	42	25	20
8[h]	$Pd(OAc)_2$	$Cu(OAc)_2$		42	26	23
9[i]	$Pd(OAc)_2$	$Cu(OAc)_2$	PivOH	64		
10[j]	$Pd(OAc)_2$	$Cu(OAc)_2$	Pyridine	87	5	
11[k]	$Pd(OAc)_2$	$Cu(OTf)_2$	$PhI(OAc)_2$			60

[a] **5** (0.25 mmol), **6** (0.5 mL), Pd-catalyst (10 mol%), oxidant (2 equiv), additive (if any), 1,4-dioxane (250 mM), 110 °C., 48 h. [b] $PdCl_2(CH_3CN)_2$ (5 mol%), air, CuCl (10 mol%), DME (250 mM), 70 °C. [c] Room temperature. [d] 70 °C. [e] 24 h. [f] AgOAc (50 mol%), $K_2S_2O_8$ (3 equiv). [g] AgOAc (50 mol %), $Cu(OAc)_2$ (3 equiv). [h] $Cu(OAc)_2$ (3 equiv). [i] PivOH (1 equiv), DMF/DMSO (9:1). [j] Pyridine (20 mol%). [k] $Cu(OTf)_2/PhI(OAc)_2$ (0.02/2 equiv), 24 h.

investigation. Our previous experiences on regio- and chemoselective direct *ortho*-benzylation of primary benzamides,[9] oxidative C-alkenylations in indole and 7-azaindoles,[10] and renewed interest in the concise synthesis of fused nitrogen-containing heterocycles[11] prompted us to develop a workable access to 3-methyleneisoindolinones with a free NH group. Herein, we describe a complementary approach that includes palladium-catalyzed oxidative *N*-alkenylation of primary benzamides followed by intramolecular oxidative cyclization of enamides, providing access to 3-methyleneisoindolin-1-ones

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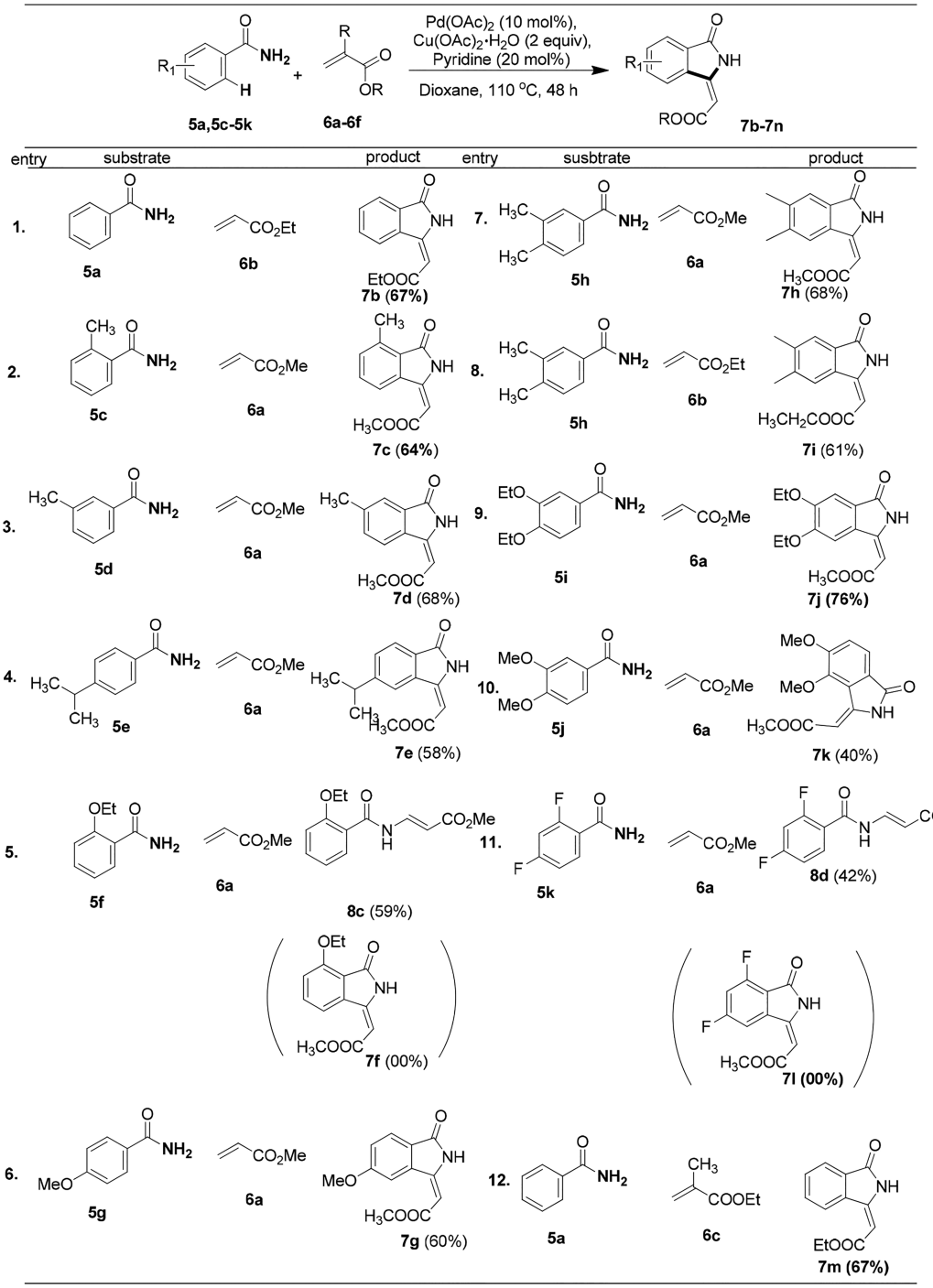
Scheme 2. Substrate Scope for the Synthesis of 3-Methyleleisoindolin-1-ones



with a free NH group that are amenable to functionalization at nitrogen. The key features that are clearly distinct from the current literature include (a) the formation of *N*-alkenylated product exclusively over C-alkenylated product under the optimized conditions, (b) the exclusive formation of *E*-enamides as opposed to *Z*-enamides, and (c) only *E*-enamides could undergo intramolecular oxidative cyclization to give isoindolinones.

RESULTS AND DISCUSSION

Our initial investigations were directed to identify a condition for tandem one-pot synthesis of 3-methyleneisoindolin-1-one **7a** from the reaction of primary benzamide **5a** and methyl acrylate **6a**. Our efforts were primarily focused on utilizing a palladium-catalyst and a sacrificial oxidant, which could form **7a** via intermolecular oxidative *N*-alkenylation of **5a** followed by intramolecular oxidative cyclization of enamides formed in situ in the reaction. Unlike a previous report,[7] reaction of **5a** and methyl acrylate (**6a**, 3 equiv) in the presence of $PdCl_2(CH_3CN)_2$ (5 mol%) and CuCl (10 mol%) in DME at 70 °C for 48 h gave **8a** (*E*-isomer) in 68% yield (Table 1, entry 1). A more frequently used palladium-catalyst, $Pd(OAc)_2$ in the presence of AgOAc as oxidant in dioxane at room temperature resulted in *E*/*Z* mixture of enamides (entry 2). Interestingly the

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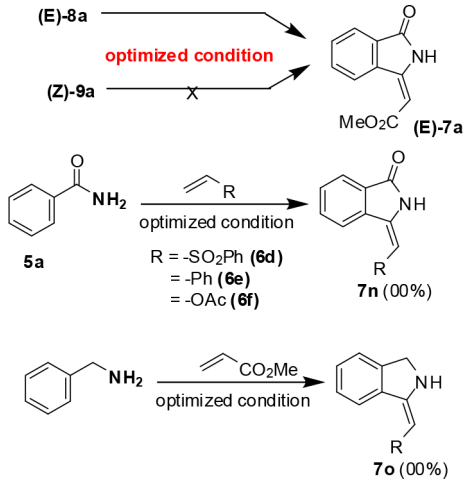
reaction, when conducted at an elevated temperature (70 °C), afforded isoindolin-1-one **7a** in 40% yield in addition to *E*- and *Z*-enamides (entry 3). Further increasing the temperature to 110 °C, however, reducing the time from 48 to 24 h, resulted in a similar distribution of products (entry 4). The formation of **7a** was markedly increased upon continuing the reaction for a longer time (48 h, entry 5). The catalytic effect of AgOAc in combination with a terminal oxidant [$K_2S_2O_8$ or $Cu(OAc)_2$] is similar to that observed in entry 4 (entries 6−7). $Cu(OAc)_2$ alone produced the similar result (entry 8). However, improvement in the formation of **7a** occurred when **5a** and **6a** were reacted in the presence of an additive, PivOH or pyridine, affording **7a** in 64 and 87% yields, respectively (entries 9 and 10). Notably, the formation of *Z*-enamide is largely suppressed under these conditions. Predictably, the reaction of 2,6-disubstituted benzamide **5b** and methyl acrylate **6a** gave only *E*-enamide **8b** in 43% yield, as intramolecular oxidative cyclization is prohibited. A marked difference in reactivity of **5a** and **6a** was observed under a condition described in entry 11, resulting in the formation of **9a** as the exclusive product. Central to this investigation was the identification of reaction conditions that control the formation of isoindolin-1-one **7a**, *E*-enamide **8a**, or *Z*-enamide **8b** exclusively.

Next, we investigated the substrate scope that could participate in the tandem one-pot synthesis of isoindolin-1-ones. Under our optimized conditions, reaction of benzamide **5a** and ethyl acrylate **6b** gave **7b** in 67% yield (Scheme 2, entry 1). An alkyl group at the *ortho*-, *meta*-, or *para*-position of primary benzamides **5c**−**5e** also produced isoindolin-1-ones **7c**−**7e** in 58−68% yield. It is interesting to note that *meta*-substituted benzamide **5d** gave only one regioisomer **7d**, adding value to the current protocol. While benzamide **5f** containing an electron-donating alkoxy group at the *ortho*-position did not give isoindolin-1-one **7f**, benzamide **5g** with an alkoxy group at the *para*-position resulted in the isolation of isoindolin-1-ones **7g** in 60% yield. However, benzamide **5f** reacted with acrylate to give *N*-alkenylated product **8c** in 59% yield.

Similar to *meta*-substituted benzamide **5d**, reaction of 3,4-dimethylbenzamide **5h** and **6a** or **6b** gave isoindolin-1-ones **7h**−**7i** regioselectively in 61−68% isolated yield. 3,4-Diethoxybenzamide **5i** reciprocated the reactivity as that of 3,4-dimethylbenzamide **5h** affording isoindolin-1-one **7j** in 76% yield. However, reaction of 3,4-dimethoxybenzamide **5j** and methyl acrylate **6a** gave isoindolin-1-one **7k** although in moderate yield. Notably, the oxidative cyclization occurred at the *ortho*-position to the OMe group, which is in contrast to the other examples. While the moderate yield in this reaction could be explained on the basis of sluggish reactivity of benzamide, intramolecular oxidative cyclization to the *ortho*-position of OMe group is especially interesting. When 2,4-difluorobenzamide **5k** was subjected to the reaction with **6a**, only *N*-alkenylated product **8d** was isolated in 42% yield. In this case, intramolecular oxidative Heck reaction did not occur probably because of poor C−H bond activation *ortho*- to amide group. Interestingly, reaction of **5a** and a disubstituted alkene **6c** did not give the desired isoindolin-1-one. However, the reaction gave isoindolin-1-one **7m** in 67% yield, which could occur by the loss of the olefinic methyl group. Identification of a reasonable explanation is a subject of further investigation.

To understand the origin of the formation of isoindolin-1-one **7a**, the two enamides were independently subjected to the optimized conditions (Scheme 3). A complete conversion of *E*-

Scheme 3. Intramolecular Cyclization of Enamides



enamide **8a** to isoindolin-1-one **7a** was observed. However, *Z*-enamide **9a** did not undergo intramolecular oxidative cyclization to give **7a**. Interestingly, primary benzamides did not react with alkenes that did not have carbonyl groups. These reactions even did not produce the corresponding *N*-alkenylated products. These experiments suggest that alkenes containing carbonyl groups are compatible for isoindolidinone synthesis. However, reaction of benzylamine and methyl acrylate also did not give the corresponding cyclized product under the standard condition. The two substrates, benzenesulfonamide and *N*-methoxybenzene sulfonamide, were also exposed to the optimized conditions independently in the presence of methyl acrylate. However, no significant reaction was observed in these cases. This experiment suggests that a carbonyl functionality is required for *ortho* C−H palladation. Importantly, isomerization of one enamide to the other was not observed under the optimized conditions. Pivotal feature to this study was the observation that only *E*-enamide **8a** could undergo cyclization to give isoindolin-1-one **7a** and both carbonyl functionalities are required on both substrates.

To rationalize the experimental observation, quantum chemical analysis was performed, based on the rich experience in our lab on several similar studies.[12] Density functional analysis (DFT) using B3LYP/6-311+G(d,p) level was performed to verify the hypothesis that only *E*-enamides undergo cyclization (and not *Z*-enamides) to give isoindolin-1-ones. The optimized 3D structures of the important intermediates are given in Figure 2. The energy difference between *E* (**8a**) and *Z*-enamides (**9a**) is 5.24 kcal/mol (in favor of *Z*-isomer). The extra stability of *Z*-isomer **9a** can be rationalized from the observed intramolecular hydrogen bond.[7]

The *E* and *Z*-enamides can be further activated by $Pd(OAc)_2$ to form **8a-Pd-1**, **8a-Pd-2**, and **9a-Pd-1**. The geometrical features of these activated species **8a**-Pd (**8a-Pd-1** and **8a-Pd-2**) and **9a**-Pd (**9a-Pd-1**) are quite different, and they strongly influence the next course of the reaction, i.e., intramolecular cyclization. The *E*-enamide can form two different palladium coordinated species between C4−O7 (**8a-Pd-1**) and C4−O1 (**8a-Pd-2**), whereas the *Z*-enamide can form only one complex between C4−O7 (**9a-Pd-1**) (Figure 2). For the formation of isoindolinones by intramolecular cyclization, there must be a possibility of rotation across C6−N5 bond (by 180°) so that the Ar−H can be in close proximity to Pd for activation. The rotation across C6−N5 in **8a-Pd-2** can lead to conformer **8a-**

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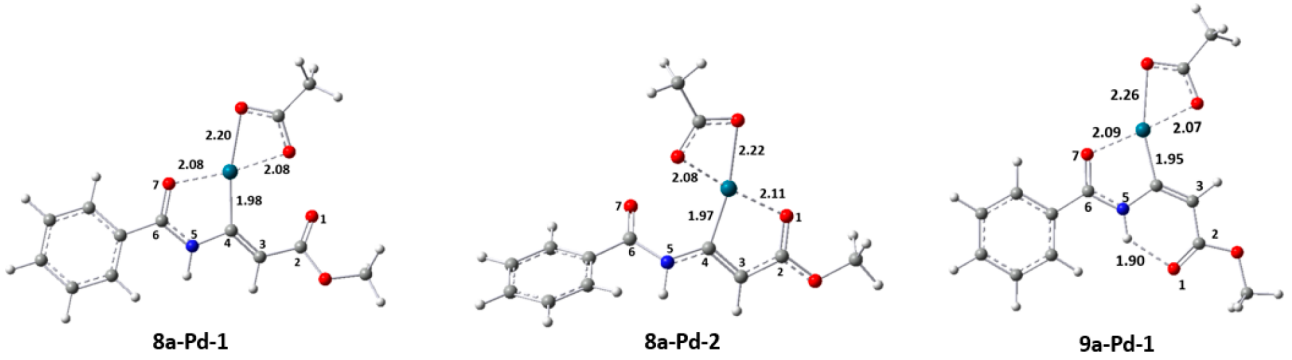
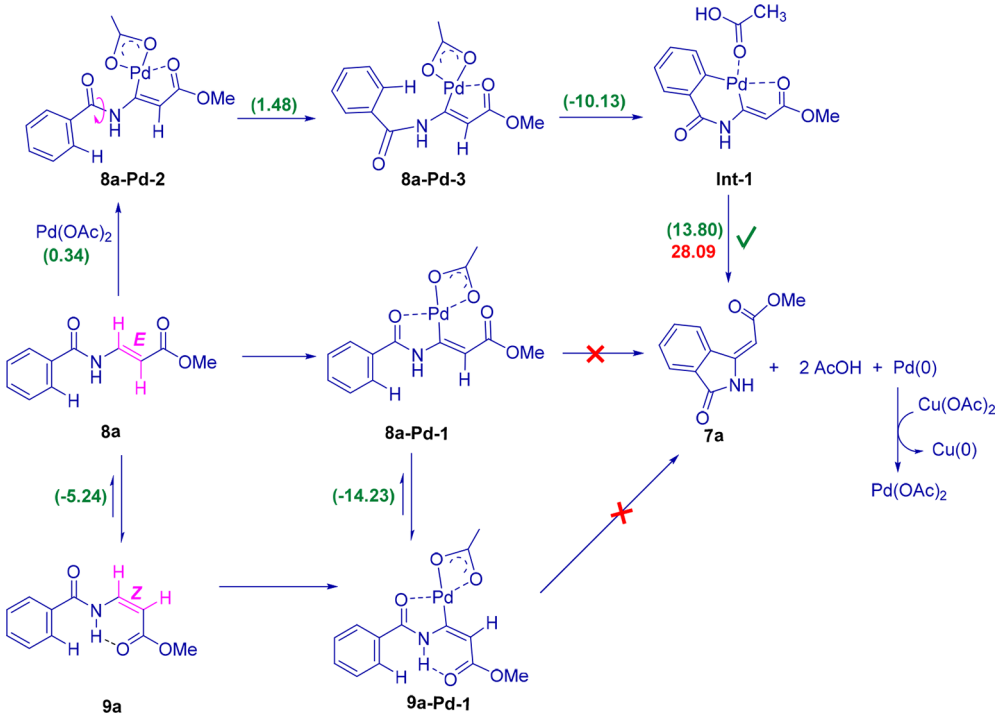


Figure 2. 3D Structures of palladium complexes **8a-Pd-1**, **8a-Pd-2**, and **9a-Pd-1** (bond lengths in Angstrom (Å)).

Scheme 4. Proposed Pathway[a]



[a]The numerical value in red color represents the activation barrier and the given energy values are in kcal/mol.

Pd-3 (Scheme 4). However, such rotation is hindered in the case of **8a-Pd-1** and **9a-Pd-1**. Though the **9a-Pd-1** is energetically more favored than **8a-Pd-2** (14.23 kcal/mol), it cannot lead to intramolecular cyclization due to hindered rotation across C6–N5 (Scheme 4). The 3D structure of **8a-Pd-3** clearly suggests that the palladium and ArH are in close proximity and hence the activation of ArH is easy. Thus, **8a-Pd-3** is a reactive intermediate that can lead to cyclization via **Int-1**, but not **9a-Pd-1**. Finally, **Int-1** will undergo cyclization to give rise to desired product **7a** via **TS1** with barrier of 28.08 kcal/mol and an overall energy barrier is 19.79 kcal/mol. This hypothesis is further supported by the experimental fact that acrylates are the only viable alkenes that could participate in the reaction. This could explain the observed differences in the geometry driven selectivity toward the formation of 3-methyleneisoindolin-1-ones. However, a detailed study is required to establish the geometry driven cyclization of enamides.

In conclusion, a palladium-catalyzed tandem oxidative *N*-alkenylation of primary benzamides with acrylates gave *E*-enamides regioselectively, which upon subsequent intramolecular oxidative cyclization gave 3-methyleneisoindolin-1-ones. Our investigation reveals, for the first time, that intramolecular oxidative cyclization of enamides depends upon the geometry of the enamides. Only *E*-enamides undergo intramolecular oxidative cyclization to yield 3-methyleneisoindolin-1-ones. Distinct from the current literature, our protocol does not require a directing group in benzamides and is an umpolung strategy to the literature approaches. The current study should prompt further investigations on geometry-driven intramolecular oxidative cyclization of other systems.

EXPERIMENTAL SECTION

General Methods. Unless noted otherwise, all reagents and solvents were purchased from commercial sources and used as received. All palladium-catalyzed reactions were performed in a screw-cap vial. The (^{1}H) and (^{13}C) NMR spectra were obtained using a 400 and 100 MHz spectrometer, respectively, with Me_4Si as an internal standard. Coupling constants (J values) are reported in hertz (Hz). The chemical shifts (δ) values are reported in parts per million (ppm).

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Column chromatography was performed using silica gel (100−200 mesh). High-resolution mass spectra (HRMS) were obtained using electron spray ionization (ESI) technique and as TOF mass analyzer. All melting points were taken using a melting point apparatus equipped with a calibrated thermometer and are uncorrected. New compounds were characterized by melting point, ^{1}H NMR, ^{13}C NMR, IR, and HRMS data.

General Procedure for the Synthesis of Isoindolinone and N-Alkenylated derivatives. In an oven-dried screw cap vial equipped with a magnetic stir bar, benzamides (0.25 mmol), $Pd(OAc)_2$ (10 mol %), $Cu(OAc)_2.H_2O$ (0.5 mmol), pyridine (20 mol%), alkene (0.5 mL) and 1,4 dioxane (1 mL) was added and reaction mixture was heated at 110 °C for 48 h. The reaction mixture was allowed to cool to room temperature and then it was diluted with ethyl acetate (10 mL) and water (5 mL) was added, the layers were separated. The organic layer was dried (Na_2SO_4), concentrated under reduced pressure, and purified by column chromatography on silica using (ethyl acetate/hexane = 1:9−2:8) as an eluent to give the desired product.

*Methyl (E)-2-(3-Oxoisoindolin-1-ylidene)acetate (**7a**).* White solid; Yield 87% (49 mg); mp 123−125 °C; ^{1}H NMR ($CDCl_3$): δ 9.63 (s, 1H), 7.92−7.91 (d, J = 8.4 Hz, 1H), 7.89−7.71 (d, J = 8.1 Hz, 1H), 7.67−7.63 (m, 2H), 5.80 (s, 1H), 3.84 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 168.0, 167.9, 147.5, 136.4, 132.4, 131.8, 129.6, 124.1, 121.0, 91.2, 51.8; HRMS(ESI) m/z calcd for $C_{11}H_{10}NO_3$ $[M+H]^+$ 204.0661, found 204.0659; IR (KBr): 3774, 2924, 1729, 1464, 1247, 710 cm^{-1}.

*Ethyl (E)-2-(3-Oxoisoindolin-1-ylidene)acetate (**7b**).*[7] White solid; Yield 67% (36 mg); ^{1}H NMR ($CDCl_3$): δ 9.64 (s, 1H), 7.91 (dd, J = 6.6, 1.6 Hz,1H), 7.72 (dt, J = 6.3, 1.1 Hz, 1H), 7.66−7.61 (m, 2H), 5.80 (s, 1H), 4.32 (q, J = 7.2 Hz, 2H), 1.38 (t, J = 7.2 Hz, 3H); HRMS(ESI) m/z calcd for $C_{12}H_{12}NO_3$ $[M+H]^+$ 218.0817, found 218.0809.

*Methyl (E)-2-(4-Methyl-3-oxoisoindolin-1-ylidene)acetate (**7c**).* Yellow solid; Yield 64% (35 mg); mp 133−139 °C; ^{1}H NMR ($CDCl_3$): δ 9.54 (s, 1H), 7.53−7.48 (m, 2H), 7.37 (d, J = 7.6 Hz, 1H), 5.74 (s, 1H), 3.83 (s, 3H), 2.72 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 168.9, 168.1, 147.6, 138.5, 136.9, 133.8, 132.3, 126.5, 118.5, 90.1, 51.6, 17.2; HRMS (ESI) m/z calcd for $C_{12}H_{12}NO_3$ $[M+H]^+$218.0817, found 218.0811; IR (KBr): 3386, 2925, 1734, 1693, 1651, 1194, 793 cm^{-1}.

*Methyl (E)-2-(5-Methyl-3-oxoisoindolin-1-ylidene)acetate (**7d**).* White semisolid; Yield 68% (37 mg); ^{1}H NMR ($CDCl_3$): δ 9.55 (s, 1H), 7.67 (s, 1H), 7.58 (d, J = 7.8 Hz, 1H), 7.45 (d, J = 7.9 Hz, 1H), 5.72 (s, 1H), 3.81 (s, 3H), 2.49 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 168.2, 168.0, 147.7, 133.8, 133.7, 129.9, 124.4, 120.8, 90.6, 51.7, 21.8; HRMS(ESI) m/z calcd for $C_{12}H_{12}NO_3$ $[M+H]^+$ 218.0817, found 218.0815; IR (KBr): 3329, 1747, 1697 1488,1126, 786 cm^{-1}.

*Methyl (E)-2-(6-Isopropyl-3-oxoisoindolin-1-ylidene)acetate (**7e**).* White solid; Yield 58% (35 mg); mp 150−159 °C; ^{1}H NMR ($CDCl_3$): δ 9.54 (s, 1H), 7.79 (d, J = 7.5 Hz, 1H), 7.53 (s, 1H), 7.48 (d, J = 7.5 Hz, 1H), 5.78 (s, 1H), 3.81 (s, 3H), 3.06−3.03 (m, 1H), 1.31 (d, J = 6.4 Hz, 6H); ^{13}C NMR ($CDCl_3$):δ 168.1, 168.0, 154.8, 147.9, 136.8, 130.3, 127.4, 124.0, 118.8, 90.7, 51.7, 34.6, 23.8; HRMS (ESI) m/z calcd for $C_{14}H_{16}NO_3$ $[M+H]^+$ 246.1130 found 246.1129; IR (KBr): 3263, 2954, 2343, 1694, 1385, 1272, 790 cm^{-1}.

*Methyl (E)-2-(6-Methoxy-3-oxoisoindolin-1-ylidene)acetate (**7g**).* White solid; Yield 60% (35 mg); mp 142−144 °C; ^{1}H NMR ($CDCl_3$): δ 9.48 (s, 1H), 7.89 (d, J = 8.3 Hz,1H), 7.16 (d, J = 1.9 Hz, 1H), 7.13 (dd, J = 8.3, 2.0 Hz, 1H), 5.74 (s, 1H), 3.97 (s, 1H), 3.85 (s, 3H); ^{13}C NMR ($CDCl_3$): δ167.9, 163.8, 147.6, 138.7, 125.5, 122.0, 117.8, 114.4, 105.9, 90.8, 55.9, 51.7; HRMS(ESI) m/z calcd for $C_{12}H_{12}NO_4$ $[M+H]^+$ 234.0766, found 234.0759; IR (KBr): 3256, 1734, 1685, 1267, 1014, 836 cm^{-1}.

*Methyl (E)-2-(5,6-Dimethyl-3-oxoisoindolin-1-ylidene)acetate (**7h**).* White solid; Yield 68% (43 mg); mp 170−175 °C; ^{1}H NMR ($CDCl_3$): δ 9.49 (s, 1H), 7.62 (s,1H), 7.44 (s, 1H), 5.70 (s, 1H), 3.81 (s, 3H), 2.39 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 168.4, 168.1, 148.0, 142.5, 141.2, 134.5, 127.5, 124.7, 121.9, 94.8, 90.3, 51.6, 20.6, 20.4; HRMS(ESI) m/z calcd for $C_{13}H_{14}NO_3$$[M+H]^+$ 232.0974, found 232.0977; IR (KBr): 2925, 1718, 1433, 1258 cm^{-1}.

*Ethyl (E)-2-(5,6-Dimethyl-3-oxoisoindolin-1-ylidene)acetate (**7i**).* Cream solid; Yield 61% (37 mg); mp 168−170 °C; ^{1}H NMR ($CDCl_3$): δ 9.49 (s, 1H), 7.62 (s,1H), 7.43 (s, 1H), 5.70 (s, 1H), 4.28−4.26 (q, 2H), 2.39 (s, 6H), 1.37 (t, 3H); ^{13}C NMR δ = 168.46, 167.73, 147.81, 142.46, 141.17, 134.57, 127.57, 124.73, 121.87, 90.79, 60.50, 29.69, 28.46, 20.63, 20.39, 14.34; HRMS (ESI) m/z calcd for $C_{14}H_{16}NO_3$ $[M+H]^+$ 246.1130, found 246.1125; IR (KBr): 3327, 1721, 1467, 845 cm^{-1}.

*Methyl (E)-2-(5,6-Diethoxy-3-oxoisoindolin-1-ylidene)acetate (**7j**).* Yellowish solid; Yield 76% (60 mg); mp 112−113 °C; ^{1}H NMR ($CDCl_3$): δ9.40 (s, 1H), 7.3 (s,1H), 7.16 (s, 1H), 5.67 (s, 1H), 4.23−4.17 (q, 4H), 1.6−1.5 (t, 6H);^{13}C NMR ($CDCl_3$): δ 168.5, 168.0, 152.9, 152.1, 148.0, 129.6, 122.6, 106.6, 104.2, 90.1, 65.0, 64.9, 51.6, 14.6, 14.5; HRMS (ESI) m/z calcd for $C_{15}H_{17}NO_5Na$ $[M + Na]^+$ 314.1004, found 314.1011; IR (KBr): 3298, 3079, 2924, 1687, 1052 cm^{-1}.

*Methyl (E)-2-(6,7-Dimethoxy-3-oxoisoindolin-1-ylidene)acetate (**7k**).*[6e] White semisolid; Yield 40% (26 mg); ^{1}H NMR ($CDCl_3$): δ 9.65 (s, 1H), 7.62 (d, J = 8.1 Hz, 1H), 7.12 (d, J = 8.2 Hz, 1H), 6.23 (s, 1H), 4.01 (6H), 3.83 (s, 3H).

*Methyl (E)-3-Benzamidoacrylate (**8a**).*[8] White solid; Yield 87% (44 mg); ^{1}H NMR ($CDCl_3$): δ 8.45 (s, 1H), 8.30−8.23 (m, 1H), 7.88 (d, J = 7.1 Hz, 2H), 7.62 (dt, J = 5.6, 1.2 Hz, 1H), 7.52 (t, J = 7.84 Hz, 2H), 5.68 (d, J = 14.2 Hz, 1H), 3.77 (s, 3H); HRMS(ESI) m/z calcd for $C_{11}H_{12}NO_3$ $[M+H]^+$ 206.0817, found 206.0811.

*Methyl (E)-3-(2,6-Difluorobenzamido)acrylate (**8b**).* Yellowish semisolid; Yield 43% (25 mg); ^{1}H NMR ($CDCl_3$): δ8.24−8.17 (m, 1H), 7.96 (s, 1H), 7.54−7.46 (m, 1H), 7.06−7.02 (m, 2H), 5.67 (d, J = 14 Hz, 1H), 3.78 (s, 3H);^{13}C NMR($CDCl_3$): δ 166.5, 137.3, 124.3, 112.6, 112.3, 107.0, 97.9, 51.5; HRMS(ESI) m/z calcd for $C_{11}H_{10}F_2NO_3$ $[M+H]^+$ 242.0629, found 242.0622;IR (KBr): 3274, 1731, 1465, 1273, 680 cm^{-1}.

*Methyl (E)-3-(2-Ethoxybenzamido)acrylate (**8c**).* Yellow semisolid; Yield 59% (37 mg); ^{1}H NMR ($CDCl_3$): δ 10.25 (s, 1H), 8.36−8.25 (m, 2H), 7.55 (dt, J = 8.5, 4.6 Hz, 1H), 7.15 (t, J = 7.9 Hz, 1H), 7.02 (d, J = 8.2 Hz, 1H), 5.55 (d, J = 14.2 Hz, 1H), 4.30 (d, J = 6.9 Hz, 2H), 3.78 (s, 3H), 1.62 (t, J = 4.9 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 167.8, 157.2, 138.3, 134.4, 132.9, 121.7, 119.4, 112.5, 101.4, 65.1, 51.4, 14.7; HRMS (ESI) m/z calcd for $C_{13}H_{16}NO_4$ $[M+H]^+$ 250.1079 found 250.0177; IR (KBr): 3299, 1732, 744 cm^{-1}.

*Methyl (E)-3-(2,4-Difluorobenzamido)acrylate (**8d**).* Yellowish semisolid; Yield 42% (27 mg);^{1}H NMR ($CDCl_3$): δ 8.19−8.14 (m, 1H), 7.81 (d, J = 16.4 Hz, 1H), 7.13 (t, J = 8.7 Hz, 1H), 6.80 (d, J = 16.4 Hz, 1H), 6.60 (s, 1H), 5.90 (s, 1H), 3.86 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 165.4, 164.3, 136.5, 136.1, 134.6, 131.8, 131.2, 120.6, 114.0, 52.6; HRMS (ESI) m/z calcd for $C_{11}H_{10}F_2NO_3$ $[M+H]^+$ 242.0629, found 242.0630.

*Methyl (Z)-3-Benzamidoacrylate (**9a**).*[7] Creame solid;Yield60% (31 mg); ^{1}H NMR ($CDCl_3$): δ11.5 (s, 1H), 7.98 (d, J = 8.3 Hz, 2H), 7.80 (m, 1H), 7.61 (m, 1H), 7.53 (m, 2H), 5.31 (d, J = 8.8 Hz, 1H), 3.81 (s, 3H); HRMS(ESI) m/z calcd for $C_{11}H_{12}NO_3$ $[M+H]^+$ 206.0817, found 206.0818.

Computational Methods. The quantum chemical calculations were employed with Gaussian09 suite of programs.[13] The density functional theory (DFT)[14] was used for the geometry optimizations and frequency calculations for all the structures using B3LYP[15] functional and 6-311+G(d,p) basis set. To model the palladium complexes, the effective core potentials with standard double-ζ valence basis set (LanL2DZ)[16] were applied on palladium atom. The transition states were confirmed to have only one imaginary frequency. The energy values discussed in the manuscript are based on the free energy (ΔG) changes.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b00966.

Copies of ^{1}H and ^{13}C NMR spectra for all new compounds and Cartesian coordinates and absolute

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energies of the optimized geometries and transition state (PDF)

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Notes

The authors declare no competing financial interest.

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