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New Heteroannulation Reactions of *N*-Alkoxybenzamides by Pd(II) Catalyzed C−H Activation

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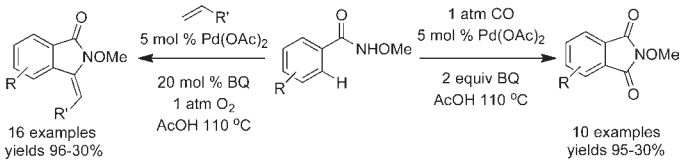
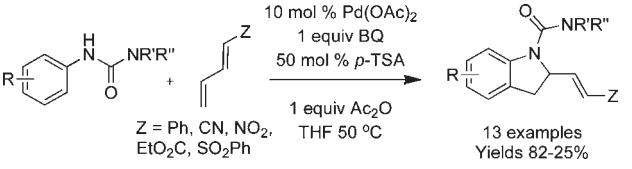
ABSTRACT



A new palladium(II) catalyzed methodology for the direct synthesis of alkylidene isoindolinones from *N*-alkoxybenzamides is presented. Isoindolinone formation proceeds through a highly efficient and *E*-selective C−H activation/Heck/Aza-Wacker sequence. Substoichiometric amounts of benzoquinone can be employed in a cooperative oxidation system with O_2, leading to facile purification of products. Modification of the reaction conditions provides a general route to substituted phthalimides by carbonylation with CO. Both systems were found to tolerate a wide range of functionality.

New efficient methods for the synthesis of highly substituted heterocycles continue to be an area of intense activity, especially in the context of natural product related substructures and medicinal chemistry.[1] Recently, transition metal catalyzed C−H activation has become a dominant theme for the synthesis of heterocyclic systems as it avoids the requirement of (pseudo)halide heteroaryl substrates in conventional Pd(0) catalyzed sequences.[2] We recently reported the development of a palladium(II)-catalyzed indoline synthesis proceeding via a urea directed C−H activation/1,2 carboamination sequence (Scheme 1) .[3]

Scheme 1. Urea Directed C−H Carboamination of 1,3-Dienes



We have now elaborated this concept so as to generate isoquinolones from dienes and benzamides. Initial tests with simple benzamides resulted in no diene addition products, even at elevated temperatures and with high catalyst loadings. The ability of *N*-methoxyamides to facilitate C−H activation on sp^3 and sp^2 centers has been amply

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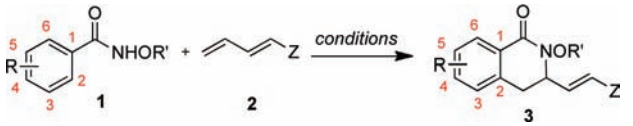
demonstrated, most notably through studies by Yu.[4] More recently, the work of Fagnou,[5] Glorius,[6] and Li[7] has proven the generality of this moiety as a C−H activating group.

Switching from simple benzamides to *N*-alkoxy benzamides **1** led to the desired reactivity, and a number of isoquinolinones **3** were generated, albeit in low to moderate yields. The best results were obtained by exploiting a cooperative oxidation system,[8] whereby only 20 mol % of benzoquinone (BQ) was required when the reactions were carried out under an atmosphere (balloon) of O_2 (Table 1).

Table 1. Methoxybenzamide Directed Carboamination of 1,3-Dienes



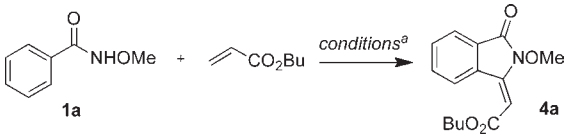
entry	R	R′	Z	yield of **3** (%)
1[a]	H	Me	Ph	10
2[a]	H	Et	Ph	7
3[a]	H	*i*Pr	Ph	6
4[a]	H	Me	CO_2Et	3
5[b]	H	Me	CO_2Et	64
6[b]	6-Me	Me	CO_2Et	35
7[b]	5-Me[c]	Me	CO_2Et	49
8[b]	4-Me	Me	CO_2Et	50
9[b]	5-OMe[d]	Me	CO_2Et	52

[a] $(MeCN)_2PdCl_2$ 10 mol %, Oxone 0.7 equiv, 1,2-DCE, 80 °C, 24 h. [b] $Pd(OAc)_2$ 10 mol %, BQ 20 mol %, O_2, AcOH, 110 °C, 24−48 h. [c] 17:3 ratio of 5- vs 3-Me isomers. [d] 5:4 ratio of 5- vs 3-OMe isomers.

Despite extensive studies, we were unable to expand the scope or increase the yields outside of those described in Table 1. To probe the C−H activation step, we tested an oxidative Heck type coupling[9] of *N*-methoxybenzamide **1a** with butyl acrylate instead of 1,3-diene **2**. Surprisingly, this led to generation of the annulated ring system **4a**. We recently described the formation of heterocyclic systems via an efficient aza-Wacker reaction,[10] and Zhu and Falck[11] have disclosed related findings concerning the formation of *saturated* isoindolinones via efficient C−H activation/Heck reactions of NTs benzamides. The formation of *alkylidene* isoindolinone **4a** is likely the result of a sequential C−H activation/Heck/intramolecular aza-Wacker sequence, proceeding with exceptional *E*-selectivity.

After some optimization (Table 2), the isoindolinone **4a** was obtained in excellent yield. In the absence of O_2, at least 2 equiv of BQ were required (entries 1−6) indicating that two distinct Pd(0)→Pd(II) redox steps are involved in the sequence. The use of the 20 mol % BQ/O_2 system gave

Table 2. Methoxybenzamide Directed *E*-Selective Carboamination of Butyl Acrylate: Optimization Study



entry	temp (°C)	oxidant	yield (%)[b]
1	120	BQ 1 equiv, N_2	32
2	120	BQ 2.5 equiv, N_2	67
3	110	BQ 2.5 equiv, N_2	76
4	90	BQ 2.5 equiv, N_2	55
5	110	BQ 1 equiv, air	63
6	110	BQ 3 equiv, N_2	79
7	110	O_2	21
8	110	BQ 3 equiv, O_2	85
9	110	BQ 0.5 equiv, O_2	90
10	**110**	**BQ 0.2 equiv, O_2**	**95**
11	110	BQ 0.1 equiv, O_2	74
12	110	HQ 0.2 equiv, O_2	9

[a] $Pd(OAc)_2$ 5 mol %, *N*-methoxybenzamide (0.5 mmol), butyl acrylate (1 mmol), AcOH (4 mL), 24 h. [b] Isolated yields

the best results (entry 10). Not only was the yield of **4a** highest with this procedure, but the product was also significantly easier to purify. The reaction was highly tolerant of solvent/reagent quality; indeed, laboratory grade reagents can be used without further purification, while addition of external desiccants[3] (Ac_2O or 4 Å sieves) decreased catalyst turnover.

With these optimized conditions in hand we explored the scope of the reaction with a variety of substituted *N*-alkoxybenzamides and alkenes (Scheme 2). With the parent system **1a** it was found that electron-deficient alkenes made the best coupling partners, although even styrene was found to give moderate yields of cyclized product **4g**. For example, **4u** and **4v** proved interesting cases as saturated products, similar to Zhu and Falck, were obtained. In these cases we suspect that ring closure proceeds via a Michael addition, rather than via Pd(II) catalysis (*vide infra*). With

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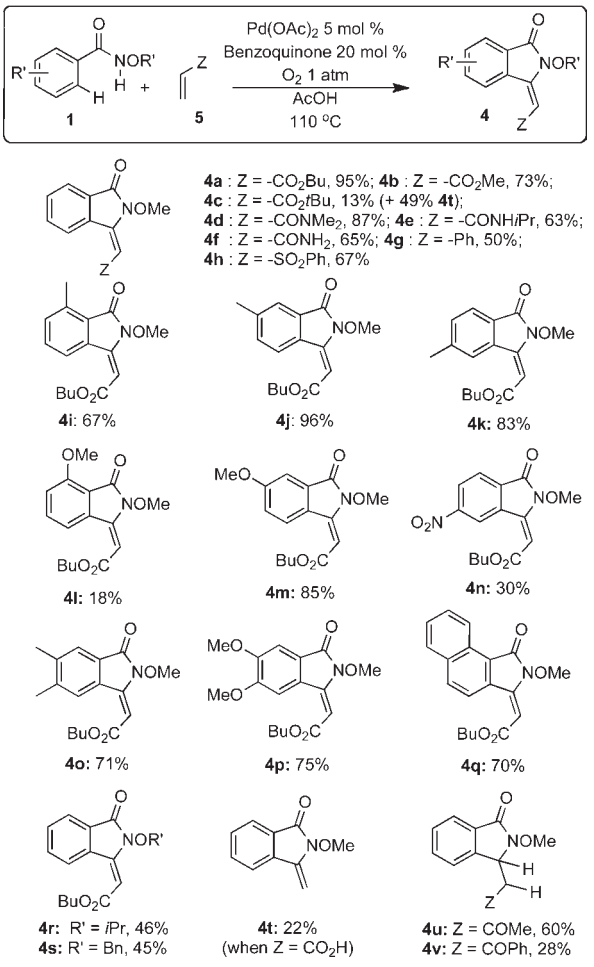
Scheme 2. Scope of *N*-Alkoxybenzamide Directed Synthesis of *E*-Alkylidene Isoindolinones

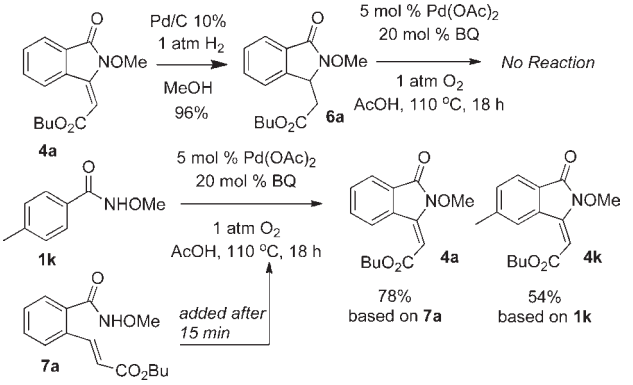


t-Bu acrylate the major product was the decarboxylated alkene **4t**. This was also the only product isolated when acrylic acid was used, suggesting that in the former case the initial product **4c** undergoes acid catalyzed *t*-Bu elimination followed by decarboxylation.[12] The aryl ring proved tolerant to substitution, and in most cases moderate to excellent yields of heteroannulated product were formed. In all examples only the *E*-alkene was observed.[13] The reactions also proceeded with complete regioselectivity as evidenced by examples **4j** and **4m**.

In the cases of **4l** and **4n** consistently low yields were obtained, despite several repeat reactions. With **4n**, as we have previously found, aryl nitro substitution has a detrimental effect on C−H activation.[3,14] We have also found that substitution *ortho*- to a urea C−H activating group impairs the directing ability of that group;[14] a similar situation likely exists in the case of **4l**. Finally, the use of other *N*-alkoxybenzamides was much less successful (**4r** and **4s**), suggesting that the smaller, less sterically demanding −OMe group plays a key role in directing the C−H insertion of Pd(II).

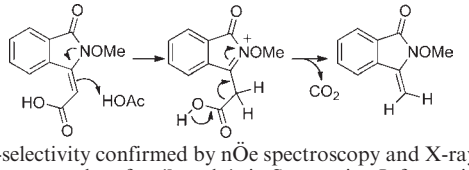
Attention was then turned to the likely sequence of events involved in the reaction (**1**→**4**). Hydrogenation of **4a** gave **6a**, which was inert when tested under the standard heteroarylation conditions (Scheme 3) ruling out the intermediacy of alkyl isoindolinones (**6**) during the catalytic cycle. The putative C−H activation Heck product **7a** was prepared[15] in order to assess its potential intermediacy in the reaction sequence. *N*-Methoxybenzamide **1k** was reacted with butyl acrylate for 15 min under the standard conditions, to ensure that turnover had ensued, and then **7a** was added (Scheme 3). This yielded both isoindolinones **4a** and **4k**, confirming the potential viability of **7a** as an intermediate in the sequence.

Scheme 3. Investigation of Possible Reaction Intermediates



On the basis of these preliminary experiments, a plausible mechanism can be proposed (Figure 1) in which MeO directed C−H insertion of Pd(II) leads to the palladacycle ***I***. This can then undergo a Heck type addition to ***II*** and then a β-hydride elimination to generate **7**. A second Pd(II)-catalytic cycle effects an aza-Wacker sequence, in which **7** is cyclized to ***III***, followed by C−C rotation and then β-hydride elimination to generate alkylidene isoindolinone **4**. The overall *E*-selectivity of the reaction is consistent with a stereospecific aza-Wacker reaction involving the *E*-alkene intermediate **7** and proceeding via the *syn*-amino palladation mechanism described by Stahl.[16] In the case of **4u** and **4v** (Scheme 2), intermediates **7u** and **7v** (Z = COMe

(12) A plausible decarboxylation mechanism is decribed below:



(13) *E*-selectivity confirmed by nÖe spectroscopy and X-ray crystallography; e.g., see data for **4b** and **4e** in Supporting Information.

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(15) See Supporting Information.

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and COPh, respectively) would be α,β-unsaturated ketones, rather than esters, and more susceptible to a non-Pd catalyzed Michael addition, thus generating alkyl rather than alkenylidene isoindolinones.

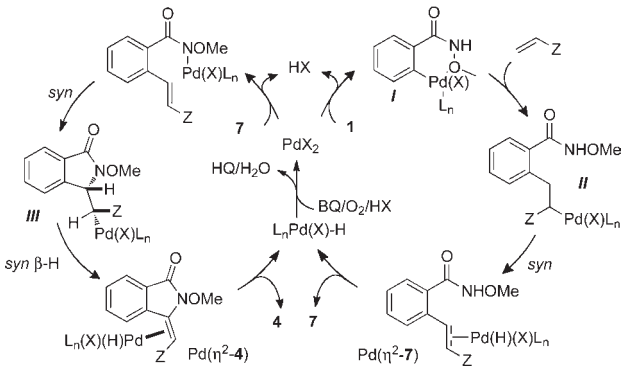


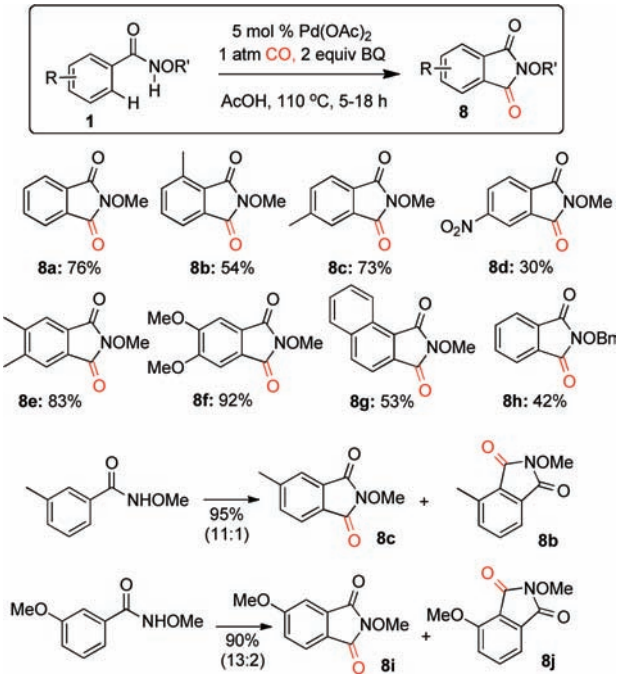
Figure 1. C−H activation/Heck/aza-Wacker mechanism.

Previously we[14] and others[17] have demonstrated the viability of carbonylation sequences for the synthesis of heterocycles and functionalization of arenes via C−H activation. We thus explored whether an analogous procedure using *N*-methoxybenzamides would provide a direct route to substituted phthalimides.

Initial tests using **1a** and catalytic BQ under O_2/CO gave low conversions (18% by NMR), whereas using 2 equiv of BQ under 1 atm of CO allowed the isolation of *N*-methoxyphthalimide **8a** in good yield (Scheme 4). Interestingly, the reaction proved to be very sensitive to the solution-phase CO concentration; increasing the CO pressure (2−4 atm) or diluting with N_2 (1:1) resulted in reduced yields. Even the mass-transfer rate had an impact, with lower solution phase surface area giving better results; the "Reduced volume" Radleys tubes were found to be optimal, whereas reactions in a standard round-bottom flask under identical conditions resulted in consistently poor yields of **8a**.

These optimized conditions were then applied to a variety of substituted *N*-methoxybenzamides (Scheme 4). Once again the general trend was that electron-donating groups afford the products in highest yields, whereas aryl NO_2 substitution or steric hindrance at the N-center decrease the yield. Compared to the isoindolinones in Scheme 2, both the *m*-methyl- and *m*-methoxy-*N*-methoxybenzamide examples displayed a slight loss of regioselectivity. Although the yields of the corresponding phthalimides were excellent, small amounts of the regioisomers **8b** and **8j** could be isolated. This result would appear to indicate that different active Pd species are involved in the C−H insertion step, as compared to the reactions generating isoindolinones (Scheme 2).

Scheme 4. Carbonylation of *N*-Alkoxybenzamides



In summary, we have demonstrated the efficacy of the *N*-methoxyamide moiety as a C−H activating group in a new synthesis of isoindolinones. The reaction is notable for using low BQ loadings (20 mol %) and is *E*-selective. The reaction conditions can also be modified to provide a general route to substituted phthalimides by carbonylation with CO.

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Supporting Information Available. Detailed experimental procedures and spectral characterization of all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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