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# Direct Prenylation of Aromatic and α,β-Unsaturated Carboxamides via Iridium-Catalyzed C−H Oxidative Addition−Allene Insertion

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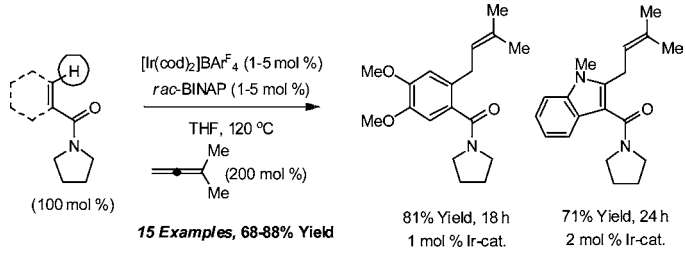
## ABSTRACT




**Exposure of aromatic carboxamides 1e−1m, heteroaromatic carboxamides 1n−1p, and α,β-unsaturated carboxamides 1q−1s to 1,1-dimethylallene in the presence of the a cationic iridium complex derived from $[Ir(cod)_2]BAr^F_4$ and *rac*-BINAP results in direct C−H prenylation to furnish adducts 2e−2m, 2n−2p, and 2q−2s, respectively, in good isolated yields as single isomers.**

Enzymatic prenyl transfers are heavily trafficked biosynthetic pathways,[1] yet synthetic catalysts for C−H prenylation are unknown.[2−4] Having recently developed protocols for catalytic carbonyl prenylation employing 1,1-dimethylallene as the prenyl donor,[5] catalytic *ortho*-C−H insertion of 1,1-dimethylallene was viewed as a potential strategy for the direct prenylation of aryl C−H bonds. Due largely to the pioneering efforts of Murai,[6] Lewis base-directed catalytic C−H activation initiated olefin insertions, and alkyne inser-

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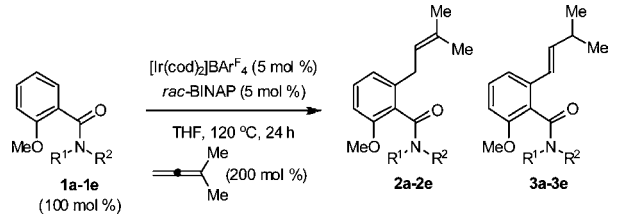
tions are well developed. *To our knowledge, analogous C−H activation-initiated insertions of allenes remain unexplored.*[2−4,6,7] Here, we report that cationic iridium complexes catalyze the coupling of 1,1-dimethylallene to aromatic carboxamides, heteroaromatic carboxamides, and α,β-unsaturated carboxamides to furnish the products of C−H prenylation in good isolated yield as single isomers.[8]

To avoid potential overprenylation, initial studies focused on amides derived from *ortho*-methoxybenzoic acid. To our delight, the cationic iridium complex assembled from $[Ir(cod)_2]BAr^F{}_4$ and *rac*-BINAP[8f] was found to catalyze the coupling of *N*-benzyl amide **1a** and 1,1-dimethylallene in THF solvent at 120 °C in 78% isolated yield. Neutral iridium complexes did not promote coupling. One complication, however, is that *N*-benzyl amide **1a** delivers a 3:1 mixture of olefin regioisomers **2a** and **3a**, respectively (Table 1, entry 1). On the basis of the notion that isomerization occurs by way of amide-directed allylic C−H insertion of **2a**, it was reasoned that tertiary amides may suppress isomerization by twisting out of plane upon introduction of the prenyl moiety, which should attenuate the amides directing influence. Consistent with this hypothesis, primary amides provide good yields of prenylation product, but as mixtures of olefin regioisomers **2a** and **3a**, whereas tertiary amides, such the dibenzyl amide **1b** and amide **1d** derived from morpholine, do not participate in the coupling (Table 1, entries 2 and 3). Presumably, amides **1b** and **1d** are too large, and nonbonded interactions twist the amide out of plane and prohibit coupling. It was postulated that amide **1e** derived from pyrrolidine should be smaller and more Lewis basic, potentially providing an ideal combination of steric and electronic features. Indeed, upon exposure of amide **1e** to 1,1-dimethylallene under the aforementioned conditions, the desired product of C−H prenylation **2a** was obtained in 70% isolated yield as a single isomer (Table 1, entry 5).

**Table 1.** Selected Examples Revealing the Influence of the Amide Directing Group in Iridium-Catalyzed Aryl C−H Prenylation[a]




| entry | **1a**−**1e** | $R^1$ | $R^2$ | yield **2a**:**3a** |
|---|---|---|---|---|
| 1 | **1a** | benzyl | H | 78% (3:1) |
| 2 | **1b** | benzyl | benzyl | recovered **1a** |
| 3 | **1c** | cyclohexyl | H | 80% (2.4:1) |
| 4 | **1d** | morpholinyl | --- | recovered **1a** |
| 5 | **1e** | pyrrolidinyl | --- | 70% (>20:1) |

[a] In all cases, cited yields are of isolated material. See Supporting Information for detailed experimental procedures.

To evaluate the scope of this process, these conditions were applied to aromatic carboxamides **1e**−**1m**. In each case, good to excellent yields of the desired aryl C−H prenylation products were obtained. Remarkably, *ortho*-substituted aryl carboxamides are not required to suppress isomerization or overprenylation (Figure 1, adducts **2g**, **2i**, **2j**−**m**). Indeed,

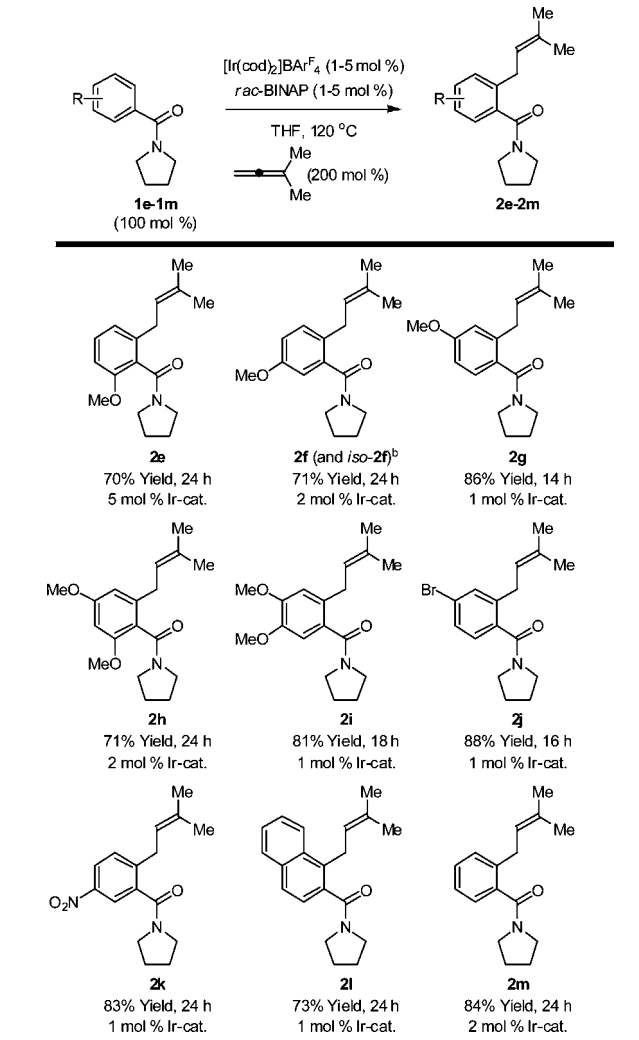



**Figure 1.** Iridium-catalyzed C−H prenylation of aryl carboxamides **1e**−**1m**. In all cases, cited yields are of isolated material and represent the average of two or more runs. See Supporting Information for detailed experimental procedures. [b]A 5:1 ratio of **2f** to *iso*-**2f** was obtained. For *iso*-**2f**, prenylation occurs at the alternate *ortho*-position.

the parent benzamide **1m** is monoprenylated under these conditions in 84% isolated yield. Only in the case of the *meta*-methoxy derivative **1f** was a mixture of isomeric adducts obtained, yet the corresponding *meta*-nitro derivative **1k** undergoes prenylation to furnish a single isomeric product **2k**.[9] Additionally, the naphthoic amide **1l** prenylates at the

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more hindered position. These data suggest electronic features of the substrate strongly influence regioselectivity.

To further evaluate the scope of this process, catalytic aryl C−H prenylation of heterocyclic aromatic carboxamides **1n**−**1p** was attempted.[10] In each case, the prenylated adducts **2n**−**2p** are obtained in good isolated yields as single isomers. The conversion of indole 3-carboxamide **1p** to the 2-prenyl derivative **2p** is significant given the abundance of prenylated indoles in Nature (Figure 2).[11] α,β-Unsaturated carboxamides

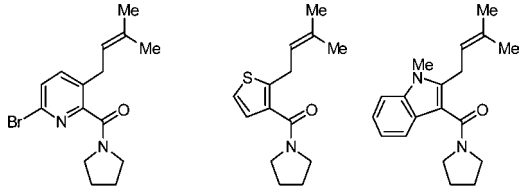



**Figure 2.** Iridium-catalyzed C−H prenylation of heterocyclic aromatic carboxamides **1n**−**1p**. As described in Figure 1 footnotes. [b]Two equivalents of 1,4-cyclooctadiene was added to suppress olefin isomerization.

**1q**−**1s** also were examined.[12] The desired adducts **2q**−**2s** were generated in good isolated yields as single isomers (Figure 3).

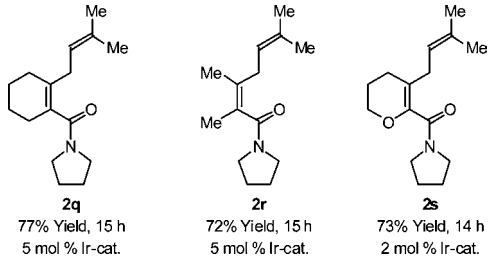
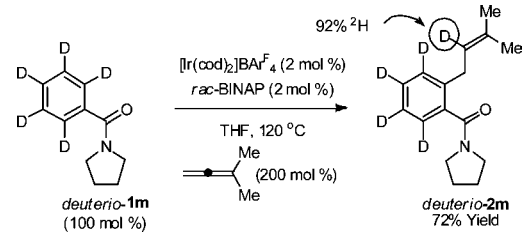



**Figure 3.** Iridium-catalyzed C−H prenylation of α,β-unsaturated carboxamides **1q**−**1s**. As described in Figure 1 footnotes.

To corroborate the catalytic mechanism, *deuterio*-**1m** was subjected to standard conditions for C−H prenylation. As anticipated, deuterium was transferred to the vinylic position of the adduct *deuterio*-**2m** (Scheme 1). This result is consistent with a catalytic mechanism involving *ortho*−C-H

**Scheme 1.** Iridium-Catalyzed C−H Prenylation of *deuterio*-**2m**a




[a] As described in Figure 1 footnotes.

oxidative addition followed by allene hydrometalation to furnish an aryl-allyl iridium complex, which upon C−C reductive elimination from the primary σ-allyliridium haptomer delivers the product of prenylation with regeneration of cationic iridium(I). Incomplete levels of deuterium incorporation may arise *via* β-hydride elimination from the tertiary σ-allyliridium haptomer of the aryl-allyl iridium intermediate (Scheme 1).

In summary, we report the first catalytic C−H activation initiated C−C coupling of allenes, as demonstrated by the direct C−H prenylation of aromatic, heteroaromatic, and α,β-unsaturated carboxamides. Future studies will focus on the development of related transformations that promote C−C bond formation in the absence of premetalated reagents and, consequently, in the absence of stoichiometric metallic byproducts.

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**Supporting Information Available:** Spectral data for all new compounds ($^1$H NMR, $^{13}$C NMR, IR, HRMS). This material is available free of charge via the Internet at http://pubs.acs.org.

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