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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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Enzymatic prenyl transfers are heavily trafficked biosynthetic pathways,¹ yet synthetic catalysts for direct 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 insertions 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 complications potentially arising from over-prenylation, initial studies focused on amides derived from *ortho*-methoxybenzoic acid. To our delight, it was found that the cationic iridium complex assembled from [Ir(cod)₂]BAR^F and *rac*-BINAP catalyzes the coupling of *N*-benzyl amide **1a** and 1,1-dimethylallene in THF solvent at 120 °C in 78% isolated yield. Cationic iridium complexes were required for coupling. One complication, however, is that prenylation of *N*-benzyl amide **1a** delivers a 3:1 mixture of olefin regioisomers **2a** and **3a**, respectively (Table 1, entry 1). Based on 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, it was found that primary amides consistently 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 evident in advance of prenylation are sufficiently strong to 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).

To evaluate the scope of this process, these conditions were applied to a diverse set of aromatic carboxamides **1e-1m**. In each case, good to excellent yields of the desired aryl C-H

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Supporting information available: Experimental procedures and spectral data for new compounds. This material is available free of charge *via* the internet at <http://pubs.acs.org>.

prenylation product were obtained. Remarkably, *ortho*-substituted aryl carboxamides are not required to suppress isomerization or over-prenylation (Table 2, adducts **2g**, **2i**, **2j-m**). Indeed, the parent benzamide **1m** is prenylated under these conditions in 84% isolated yield using only 2 mol% of the iridium catalyst. 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 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 (Table 3).¹¹ α,β -Unsaturated carboxamides **1q-1s** also were examined.¹² The desired adducts **2q-2s** were generated in good isolated yields as single isomers (Table 4).

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* (eqn. 1). This result is consistent with a catalytic mechanism involving *ortho*-C-H oxidative addition followed by allene hydrometallation 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.

eqn. 1

In summary, we report the first catalytic C-H activation initiated C-C coupling of allenes, as demonstrated by the direct prenylation of aromatic, heteroaromatic and α,β -unsaturated carboxamides. Future studies will focus on the development of related transformations where redistribution of hydrogen serves to promote byproduct-free C-C bond formation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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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)

^aIn all cases, cited yields are of isolated material. See Supporting Information for detailed experimental procedures.

Table 2

Iridium catalyzed C-H prenylation of aryl carboxamides **1e-1m**.^a

^aIn all cases, cited yields are of isolated material and represent the average of two or more runs. See Supporting Information for detailed experimental procedures.

^bA 5:1 ratio of **2f** to *iso*-**2f** was obtained. For *iso*-**2f**, prenylation occurs at the alternate *ortho*-position.

Table 3Iridium catalyzed C-H prenylation of heterocyclic aromatic carboxamides **1n-1p**.^a

2n 74% Yield, 14 h 5 mol% Ir-cat	2o 68% Yield, 16 h 5 mol% Ir-cat ^b	2p 71% Yield, 24 h 2 mol% Ir-cat
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^a As described in Table 2 footnotes.^b Two equivalents of 1,4-cyclooctadiene were added to suppress olefin isomerization.

Table 4Iridium catalyzed C-H prenylation of α,β -unsaturated carboxamides **1q-1s**.^a

2q	2r	2s
77% Yield, 15 h 5 mol% Ir-cat	72% Yield, 15 h 5 mol% Ir-cat	73% Yield, 14 h 2 mol% Ir-cat

^a As described in Table 2 footnotes.