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COMMUNICATION

Rhodium(III)-catalyzed oxidative mono- and di-olefination of isonicotinamides†

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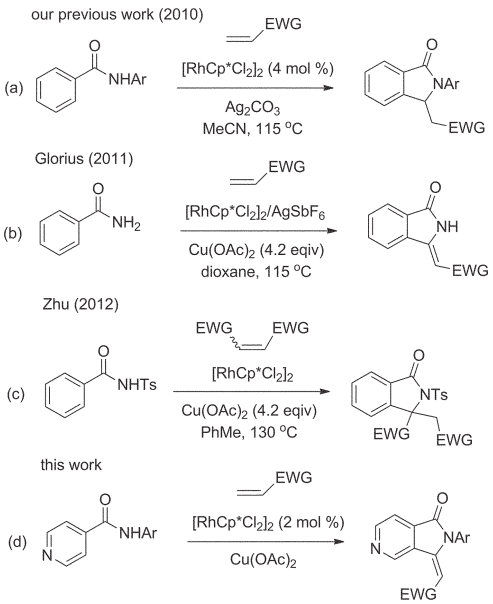
$[RhCp^*Cl_2]_2$ can catalyze the oxidative coupling of secondary isonicotinamides with activated olefins using $Cu(OAc)_2$ as an oxidant. The selectivity can be controlled by the solvent. In MeCN, the mono-olefination and two-fold oxidation reaction is the major pathway, while in THF this reaction gave mostly diolefination products. In both cases, the coupled products contain an exocyclic C═C bond.

The oxidative olefination of arenes, pioneered by Fujiwara and Moritani,[1] has been increasingly explored because this reaction allows direct functionalization of a C–H bond with an olefin, leading to the construction of a C–C bond and molecular complexity under simple conditions.[2] This protocol is advantageous in that no prior functionalization of the C–H bond is necessary, thus representing a step-economic and waste-reducing process. While palladium complexes have been well-known for decades in catalyzing oxidative olefination of arenes, rhodium(III)-catalyzed reactions have been increasingly explored, which has allowed the olefination of simple arenes[3] as well as arenes bearing various directing groups such as amide,[4] pyridyl,[5] carbamate,[6] sulfonamide,[7] imine,[8] ketone and aldehydes,[9] ester,[9b,10] and carboxylic groups.[11] In addition, inexpensive ruthenium catalysts have also been recently used for related oxidative coupling sequences, which could offer complementary reactivity and efficiency.[12]

We have recently studied Rh(III)-catalyzed oxidative coupling of *N*-aryl benzamides with activated olefins,[4a] in which process the olefination product is followed by aza-Michael cyclization to give γ-lactams (Scheme 1). To expand the synthetic utility of rhodium(III)-catalyzed oxidative coupling reactions, it is necessary to explore other electronically complementary carboxamide substrates. Isonicotinamides are interesting substrates, and we reasoned that the inclusion of the pyridine ring should significantly change the properties such that different reactivity and selectivity can be attained.[4f] In fact, achieving complementary reaction selectivity should be an important task in synthesis. We



Scheme 1 Rhodium-catalyzed olefination–cyclization of amides.

now report the olefination of isonicotinamides to give isoindolin-1-one rings, which represents a key structural motif in various natural and synthetic products that exhibit a wide range of biological activities as immunostimulants and anticancer agents.[13]

We embarked on our studies with the screening of the conditions for the coupling of isonicotinamide **1a** with *tert*-butyl acrylate. Using $[RhCp^*Cl_2]_2$ (2 mol%) as a catalyst and $Cu(OAc)_2$ as an oxidant (110 °C, sealed tube), both the mono- (**2aa**) and di-olefination products (**3aa**) were generated in all the solvents examined. These two products were characterized by NMR spectroscopy and mass spectrometry. Moreover, the (*E*) configuration of the exocyclic double bond in **2aa** was confirmed by NOESY, and this observed geometry is in line with that in the oxidative coupling of benzoic acids with acrylates.[11a] When acetone was used as a solvent, **2aa** and **3aa** were isolated in comparably low yields (Table 1, entry 3). Switching to DMF as a solvent gave no improvement of the coupling efficiency and selectivity (entry 4). Gratifyingly, the selectivity of mono-olefination was significantly improved when MeCN was used as a solvent, under which conditions (Conditions A) **2aa** was isolated

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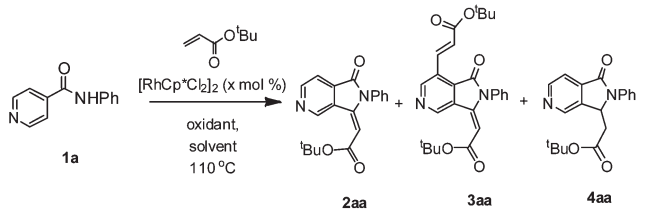
Table 1 Screening of reaction conditions[a]

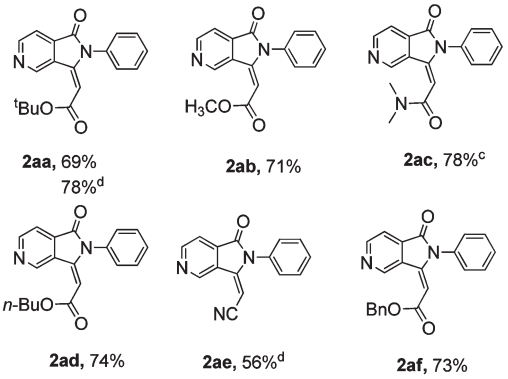


Entry	Oxidant	*x*	Solvent	Yield[b] (%) 2aa	3aa	4aa
1	$Cu(OAc)_2$	2	THF	12	40	<3
2[c]	$Cu(OAc)_2$	2	THF	8	72	<3
3	$Cu(OAc)_2$	2	Acetone	30	26	<3
4	$Cu(OAc)_2$	2	DMF	17	15	<3
5	$Cu(OAc)_2$	2	CH_3CN	69	6	<3
6[d]	$Cu(OAc)_2$	2	CH_3CN	61	9	<3
7	$Cu(OAc)_2$	4	CH_3CN	78	<3	12
8	Ag_2CO_3	4	CH_3CN	<3	<3	23

[a] Conditions: **1a** (0.5 mmol), *tert*-butyl acrylate (1.5 equiv), oxidant (4.2 equiv for $Cu(OAc)_2$ and 2.1 equiv for Ag_2CO_3), $[RhCp^*Cl_2]_2$ (2 or 4 mol%), solvent (5 mL), 12 h, sealed tube under N_2. [b] Isolated yield. [c] **1a** (0.5 mmol), *tert*-butyl acrylate (2.5 equiv), $Cu(OAc)_2$ (4.2 equiv), $[RhCp^*Cl_2]_2$ (2 mol%), solvent (5 mL), 12 h, sealed tube under N_2. [d] **1a** (0.3 mmol), *tert*-butyl acrylate (1.1 equiv), $Cu(OAc)_2$ (4.2 equiv), $[RhCp^*Cl_2]_2$ (2 mol%), solvent (3 mL), 12 h, sealed tube under N_2.

in 69% yield and **3aa** in only 6% yield. However, we failed to further suppress the di-olefination product by lowering the molar ratio of *tert*-butyl acrylate to isonicotinamide (entry 7). Furthermore, by increasing the loading of the catalyst to 4 mol%, while the efficiency of the synthesis of **2aa** was expectedly improved (78%), the yield of the minor product **4aa** was also increased (entry 6). In contrast, by following the conditions of choice in the oxidative olefination of *N*-aryl benzamides (Scheme 1a),[4b] the expected lactam **4aa** was isolated in only 23% (entry 8), indicating that replacing the phenyl group with a pyridine ring has caused significant changes in selectivity and reactivity.[4f] Interestingly, when THF was used as a solvent, the diolefination product **3aa** was isolated as the major product (40%). Further optimization by providing an excess of the olefin (2.5 equiv, Conditions B) afforded **3aa** in 72% yield. It is noteworthy that Glorius and coworkers have recently reported an example of Rh(III)-catalyzed two-fold oxidative olefination of a primary benzamide leading to exocyclized NH γ-lactams.[9a] However, the exocyclic C═C bond in those products are exclusively (*Z*)-configured (Scheme 1b). We also noted that the related benzene ring analogues of γ-lactam **2aa** with an exocyclic C═C bond have been synthesized *via* cyclization of *ortho*-alkynylbenzamides when mediated by a base or silver salts[14] and by a stoichiometric amount of iodine.[15] In addition, Yu and coworkers have achieved a Pd(0)-catalyzed arylation of related nicotinamides and isonicotinamides.[16]

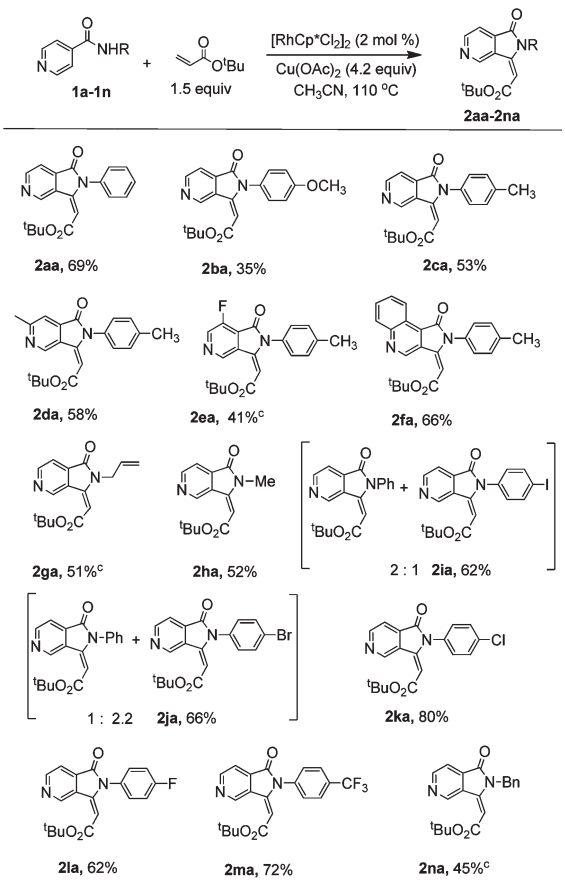
With the mono-olefination conditions in hand, we next explored the coupling of **1a** with a series of activated olefins (Scheme 2). Acrylates readily coupled with **1a** in comparably high yields. The activated alkene substrate is not limited to acrylates; acrylamide and acrylonitrile also coupled with **1a** (**2ac** and **2ae**) although lower efficiency was observed for acrylonitrile.



[a] Reaction conditions: **1a** (0.5 mmol), alkene (1.5 equiv), $Cu(OAc)_2$ (4.2 equiv), $[RhCp^*Cl_2]_2$ (2 mol %), CH_3CN (5 mL), 110 °C, 12 h, sealed tube under N_2. [b] Isolated yield. [c] 24 h. [d] Reaction conditions: **1a** (0.5 mmol), alkene (1.5 equiv), $Cu(OAc)_2$ (4.2 equiv), $[RhCp^*Cl_2]_2$ (4 mol %), CH_3CN (5 mL), 110 °C, 12 h, sealed tube under N_2.

Scheme 2 Mono-olefination of **1a** using activated olefins.[a,b]

The scope of the isonicotinamide substrate was defined in the coupling with *tert*-butyl acrylate under the mono-olefination conditions (Scheme 3). While isonicotinamides bearing both

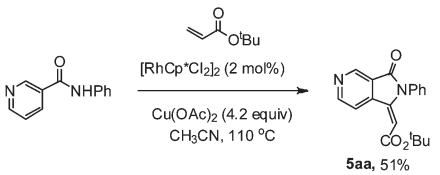


[a] Reaction conditions: amide (0.5 mmol), acrylate (1.5 equiv), $Cu(OAc)_2$ (4.2 equiv), $[RhCp^*Cl_2]_2$ (2 mol %), CH_3CN (5 mL), 110 °C, 12 h, sealed tube under N_2. [b] isolated yield. [c] 4 mol % of $[RhCp^*Cl_2]_2$ was used.

Scheme 3 Coupling of isonicotinamides with *tert*-butyl acrylate.[a,b]

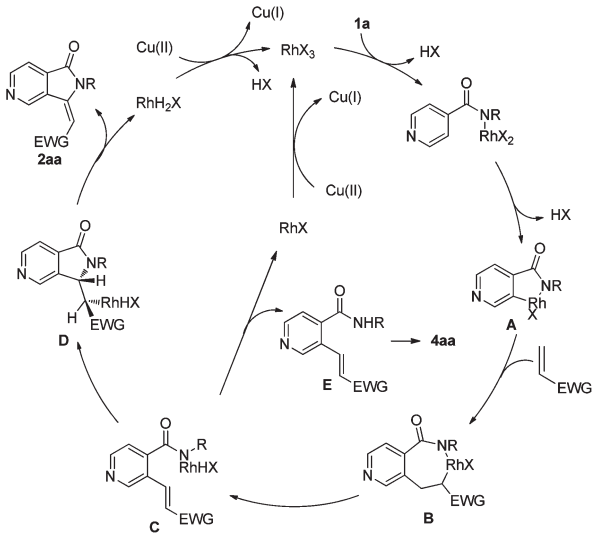
electron-rich and -poor *N*-aryl groups reacted to afford the desired product (35–80%), those with an electron-rich *N*-aryl ring tend to react slowly (**2ba** and **2ca**). In most cases, only a small amount of the diolefination product was isolated (3–8%), which corresponds to a typical selectivity of 10 : 1 in favor of mono-olefination. *para*-Halogen substitution in the *N*-aryl group is tolerated to some extent. While *para*-fluoro and -chloro substituted substrates reacted smoothly (**2ka** and **2la**), a mixture of both halogen-retentive and hydrodehalogenative coupled products (**2ia** and **2ja**) was isolated for *para*-Br and *para*-I substituted isonicotinamides. We further demonstrated that this coupling reaction is applicable to substrates bearing different substituents in the pyridine ring. Introduction of a fluoro group *ortho* to the amide functionality lowered the efficacy of this reaction (**2ea**, 26%). However, the yield was improvable to 41% when the loading of $[RhCp^*Cl_2]_2$ was increased to 4 mol%. When a 2-methylisonicotinamide was used as a substrate, product **2da** was generated as the single isomeric product, indicating that olefination occurred selectively at the less hindered position. In addition, by fusing a benzene ring to the pyridine unit, selective olefination of this quinoline-functionalized amide occurred at the *ortho* position (**2fa**), instead of at the possible *peri* position.[4b] The *N*-substituents are not limited to aryl groups; *N*-Me, -allyl, and -benzyl substrates all coupled with *tert*-butyl acrylate albeit in somewhat lower yield. Mono-olefination of *N*-methyl isonicotinamide suffered from lower selectivity; in addition to the mono-olefination product **2ha** (52%), the di-olefination product was isolated as a minor product (21%).

For comparison purposes, *N*-phenylnicotinamide was allowed to react with *tert*-butyl acrylate under the mono-olefination conditions (eqn (1)), and the 4-position olefination product **5aa** was isolated as the major product (51% yield) in addition to an unidentifiable mixture, while the 2-position olefination product was not detected.



5aa, 51% (1)

Several experiments have been carried out to probe the reaction mechanism. Subjection of **4aa** to the mono-olefination conditions afforded no **2aa**, suggesting that product **4aa** is not a possible intermediate. Similarly, we confirmed that **2aa** is not an intermediate leading to **3aa**. Thus a plausible catalytic cycle is given in Scheme 4. *N*-Ligation of the isonicotinamide is followed by cyclometallation to give a five-membered metallacycle **A**. Insertion of an olefin to the Rh–C bond of **A** generates a seven-membered metallacycle **B**, which is proposed to undergo β-hydride elimination to afford a rhodium amidate C. *cis* Amidorhodation of the C═C bond *via* a four-membered ring transition affords a rhodium(III) alkyl species **D**, which further undergoes β-hydride elimination to release the final product **2aa**. The resulting rhodium hydride species is then converted to the active rhodium(III) catalyst in the presence of a Cu(II) oxidant. It should be noted that four equivalents of $Cu(OAc)_2$ oxidant is necessary in this step. Indeed, a slight excess was provided in our experiment. Alternatively, intermediate **C** can undergo

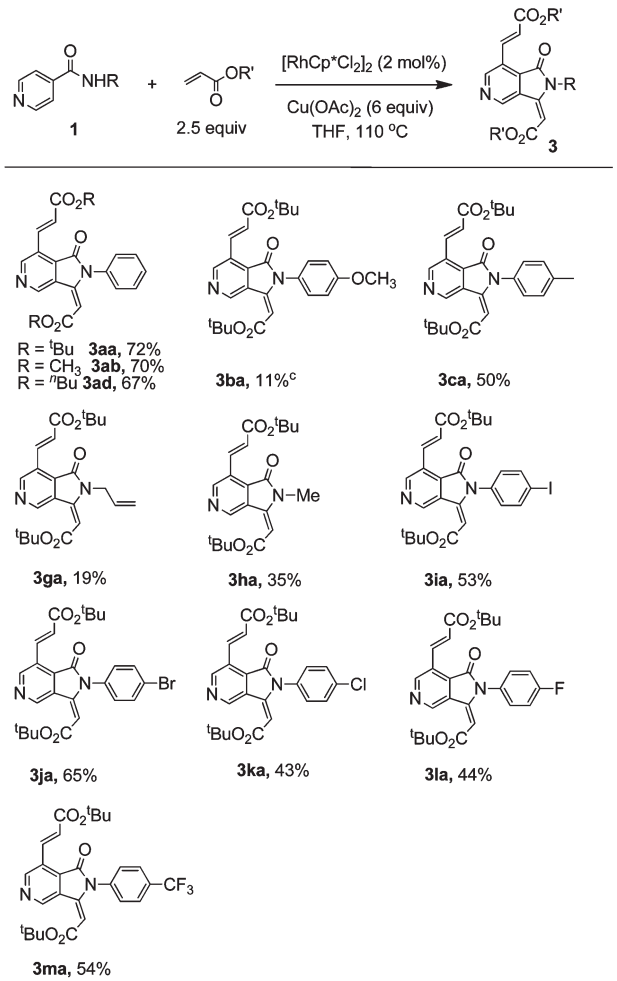


Scheme 4 Proposed catalytic cycle for mono-olefination.

reductive elimination to give the olefination intermediate **E**, and a subsequent rhodium-catalyzed intramolecular aza-Michael addition furnishes **4aa**.

The scope of diolefination of isonicotinamides was next explored (Conditions B, Scheme 5). Diolefination of *N*-phenyl isonicotinamide with acrylates afforded products **3aa–3ad** in good yields.[17] However, the efficiency of this reaction dropped significantly when a *para*-OMe group was introduced to the *N*-phenyl ring (**3ba**). Moderate to good yields of the diolefination products were obtained when *para*-substituents such as Me, halogens, and CF_3 were introduced to the *N*-aryl ring. In contrast to the hydrodehalogenative coupling products (**2ia** and **2ja**) observed in mono-olefination reactions, all halogen substituents are retained. Extension of the *N*-substituent to allyl and Me groups met with some difficulty and the expected products were isolated in rather low yield. Thus the efficiency of this coupling reaction is strongly dependent on the *N*-substituent, and substrates with an *N*-alkyl or an electron-rich *N*-aryl tend to give a sluggish reaction. When mono-olefination product **2aa** was allowed to react with *tert*-butyl acrylate under the same conditions, no diolefination product was detected, suggesting that the 2nd olefination should occur prior to the cyclization step. Thus it is likely that intermediate **C** (Scheme 4) undergoes a competitive *ortho* C–H activation, leading to a diolefination intermediate, the C═C bond in which was oxidatively amidated to give product **3aa**.

In summary, we have achieved Rh(III)-catalyzed mono- and di-olefination of secondary isonicotinamides using activated olefins. Although both mono- and di-olefination products were generated under conditions examined, mono-olefination occurred as the major reaction pathway when carried out in MeCN using $Cu(OAc)_2$ as an oxidant. This reaction likely follows a sequence of oxidative olefination-oxidative amidation. In contrast, when conducted in THF as a solvent, the selectivity is shifted such that the diolefination product becomes the major product. Under these conditions, the reaction occurred with moderate selectivity and efficiency. The contrast between the current isonicotinamides and the previously reported benzamides in olefination reactions highlighted the differences in reaction selectivity and efficiency



[a] Conditions: *N*-phenylisonicotinamide (0.5 mmo l), *tert*-butyl acrylate (2.5 equiv), $Cu(OAc)_2$ (6 equiv), $[RhCp^*Cl_2]_2$ (2 mol %), THF (5 mL), 110 °C, 12 h, sealed tube under N_2. [b] Isolated yield. [c] **3b** (0.5 mmol), *tert*-butyl acrylate (2.5 equiv), $Cu(OAc)_2$ (6 equiv), $[RhCp^*Cl_2]_2$ (2 mol %), $AgSbF_6$ (8 mol %), tetrahydropyran (5 mL), 110 °C, 12 h, sealed tube under N_2.

Scheme 5 Coupling of *N*-phenylisonicotinamide with *tert*-butyl acrylate.[a,b]

caused by electronic effects. The inclusion of a pyridine ring has engendered rich and diversified reactivity.

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17 In most cases, only a small amount of the mono-olefination product was obtained

