### Rhodium(III)-Catalyzed Amidation of Aryl Ketone O-Methyl Oximes with Isocyanates by C-H Activation: Convergent Synthesis of **3-Methyleneisoindolin-1-ones**

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The 3-methyleneisoindolin-1-one structural motif is commonly present in a number of bioactive natural products and designed pharmaceutical molecules,<sup>[1]</sup> such as fumaridine (I),<sup>[1a]</sup> magallanesine (II),<sup>[1b]</sup> compound III showing local anesthetic activity superior to that of procaine, [1c] (E)-IV exhibiting anesthetic activity,<sup>[1d]</sup> and (Z)-IV and V showing sedative activity.<sup>[1e,f]</sup> In addition, 3-methyleneisoindolin-1-ones are useful intermediates in the synthesis of alkaloids, such as lennoxamine,<sup>[2a-c]</sup> fumaridine,<sup>[2d]</sup> fumaramidine,<sup>[2e]</sup> narceine imide,<sup>[2f]</sup> aristocularines,<sup>[2g]</sup> and aristolactams.<sup>[2h-j]</sup>



The synthetic utility of 3-methyleneisoindolin-1-ones, together with their biological activity, makes their synthesis an attractive task. The classical methods to 3-methyleneisoindolin-1-ones are Wittig reactions with phthalimides or addition of organometallic reagents to phthalimides, followed by dehydration.<sup>[3]</sup> However, these procedures typically suffer from poor regioselectivity in the case of unsymmetrical substrates. In addition, several synthetic protocols have been developed in the last few years,<sup>[4]</sup> such as heteroannulation

of o-(1-alkynyl)benzamides,<sup>[4a-g]</sup> annulation of 2-(2,2-dihalovinyl)benzonitriles,<sup>[4h]</sup> CuI/L-proline-catalyzed coupling of 2bromobenzamides and terminal alkynes,<sup>[4i-j]</sup> Heck-Suzuki-Miyaura domino reactions involving ynamides,<sup>[4k]</sup> Sonogashira coupling-carbonylation-hydroamination of 2-bromoiodobenzene,<sup>[41]</sup> a Sonogashira reaction of 2-iodobenzamides with terminal alkynes followed by NaOEt-mediated cyclization,<sup>[4m]</sup> and the one-pot regioselective elimination cyclization-Suzuki approach.<sup>[4n]</sup> However, in spite of their potential utility, these procedures typically suffer from intrinsic drawbacks, such as tedious and expensive substrate preparation, poor functional-group tolerance or harsh reaction conditions. In addition, stoichiometric amounts of environmentally hazardous byproducts cannot be avoided from the reagent and halide salts. Therefore, an efficient, simple, and environmentally friendly protocol under mild conditions is highly desirable.

Over the past several years, transition-metal-catalyzed aromatic C-H bond functionalization, one of the hot topics in current organic chemistry, represents a burgeoning field. While transition-metal-catalyzed addition of C-H bonds to alkene and alkyne derivatives has been extensively investigated,<sup>[5]</sup> analogous additions across polarized C-O<sup>[6]</sup> and C-N<sup>[7-8]</sup> multiple bonds have seen considerably less progress. Recently, several studies about Rh<sup>III</sup>-catalyzed oxidative coupling of N-aryl benzamides with activated olefins to give substituted 3-methyleneisoindolin-1-ones have been developed [Eq. (1)].<sup>[9]</sup> However, stoichiometric amounts of external oxidant are still required and the substitution on the methylene group is limited to electron-withdrawing groups. Very recently, Rh<sup>III</sup> and Ru<sup>II</sup>-catalyzed amidation of aryl and vinyl C-H bonds with isocyanates has been developed.<sup>[10]</sup> Herein, we report a new type of rhodium(III)-catalyzed annulation of aryl ketone O-methyl oximes with isocyanates in the absence of any additives under mild and neutral reaction conditions, wherein the directing group for C-H bond functionalization serves an auxiliary role of capturing the resulting amide group to afford synthetically and pharmaceutically important 3-methyleneisoindolin-1-ones [Eq. (2)]. It is noteworthy to mention that direct nucleophilic attack of the Rh-N moiety to the C-N bond is quite rare, although rhodium-catalyzed intramolecular nucleophilic cyclizations by C-H bond activation have been widely reported.<sup>[11]</sup>

We started our investigation by testing the Rh<sup>III</sup>-catalyzed addition of acetophenone (1a) to p-tolyl isocyanate 3a

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(Table 1). However, no product was observed, irrespective of the reaction conditions used (Table 1, entries 1–3), presumably due to the poor directing ability of the ketone group. Therefore, acetophenone *O*-methyl oxime (**2a**) with a more strongly metal coordinating functionality was investigated. Although the use of  $[RhCl_2(Cp^*)]_2$  ( $Cp^*=pentame$ thylcyclopentadienyl) proved unsuccessful in catalyzing this reaction (entry 4),  $[RhCl_2(Cp^*)]_2$  (5 mol %) in the presence of Ag[SbF<sub>6</sub>] (20 mol %) in THF at 100 °C provided the desired product **4a** in 84 % yield (entry 5). The prepared Rh<sup>III</sup> precursor [Rh(CH<sub>3</sub>CN)<sub>3</sub>(Cp<sup>\*</sup>)][SbF<sub>6</sub>]<sub>2</sub> led to a reactivity similar to that observed with [RhCl<sub>2</sub>(Cp<sup>\*</sup>)]<sub>2</sub> and Ag[SbF<sub>6</sub>] (entry 6), and [Rh(CH<sub>3</sub>CN)<sub>3</sub>(Cp<sup>\*</sup>)][SbF<sub>6</sub>]<sub>2</sub> was used for all subsequent optimization studies. A screen of solvents re-

Table 1. Reaction development.<sup>[a]</sup>



Entry	Substrate	Catalyst (5 mol %)	Solvent	Yield [%] <sup>[b]</sup>
1	1a	$[Rh(CH_3CN)_3(Cp^*)][SbF_6]_2$	THF	0
2	1a	$[RhCl_2(Cp^*)]_2, Ag[SbF_6]$	THF	0
3	1a	$[RhCl_2(Cp^*)]_2$	THF	0
4	2 a	$[RhCl_2(Cp^*)]_2$	THF	0
5	2 a	[RhCl <sub>2</sub> (Cp*)] <sub>2</sub> , Ag[SbF <sub>6</sub> ]	THF	84
6	2 a	$[Rh(CH_3CN)_3(Cp^*)][SbF_6]_2$	THF	87
7	2 a	$[Rh(CH_3CN)_3(Cp^*)][SbF_6]_2$	DCE	88
8	2 a	$[Rh(CH_3CN)_3(Cp^*)][SbF_6]_2$	PhMe	< 10
9	2 a	$[Rh(CH_3CN)_3(Cp^*)][SbF_6]_2$	DCM	43 (87)
10 <sup>[c]</sup>	2 a	$[Rh(CH_3CN)_3(Cp^*)][SbF_6]_2$	DCE	88
11 <sup>[d]</sup>	2 a	$[Rh(CH_3CN)_3(Cp^*)][SbF_6]_2$	DCE	82 (90)
12 <sup>[e]</sup>	2 a	$[Rh(CH_3CN)_3(Cp^*)][SbF_6]_2$	DCE	85
13 <sup>[f]</sup>	2 a	$[Rh(CH_3CN)_3(Cp^*)][SbF_6]_2$	DCE	85
14	2 a'	$[Rh(CH_3CN)_3(Cp^*)][SbF_6]_2$	DCE	62
15	2 a″	$[Rh(CH_3CN)_3(Cp^*)][SbF_6]_2$	DCE	65

[a] Reaction conditions: **1a** or **2a** (0.2 mmol), **3a** (0.3 mmol), Rh cat. (0.01 mmol), solvent (1 mL), 100 °C, 12 h. [b] Yield of isolated product; yield in parentheses is based on recovered starting material. [c] The reaction was carried out at 120 °C. [d] The reaction was carried out at 90 °C. [e] 2.5 mol% of catalyst was used. Reaction time is 24 h. [f] The reaction was scaled-up to a 2 mmol substrate level.

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vealed that using 1,2-dichloroethane (DCE) as the reaction solvent led to a reactivity similar to that observed with THF (entries 6–9). Raising the temperature did not result in any reduction in yield (entry 10) and lowering the temperature led to a slightly low conversion (entry 11). The present annulation reaction can also be carried out with good efficiency in the presence of 2.5 mol% of catalyst by simply lengthening the

reaction time to 24 h (entry 12). Finally, we were pleased to find that this reaction was successfully scaled-up to a 2 mmol substrate level without a decrease in yield (entry 13). More importantly, in this annulation reaction nothing is required except the catalyst and solvent to facilitate the addition as desired. In addition, N-phenyl and -benzyl ketimines were also readily converted to the desired product **4a** in moderate yields (entries 14 and 15).

Under the optimized conditions, the substrate scope with a range of acetophenone oximes (2) containing different substitution patterns was investigated (Table 2). It was found that the electronic nature of the substituents on the phenyl ring did not play a key role. With either electronwithdrawing or -donating groups, for example  $CF_3$  (4b), ester (4c), methoxy (4g), and methyl groups (4h), acetophenone oximes were readily converted to the corresponding products in good to excellent yields. Substitutions at the para (4b-h), meta (4i and 4j), and ortho (4k and 4l) positions were all well tolerated. Notably, the tolerance of the halides (4d and 4e) offers the opportunity for further functionalization. To scrutinize further the regioselectivity, the reaction of meta-substituted acetophenone oximes selectively occurred at the less sterically hindered position (4i and 4j). For example, *meta*-methyl-substituted oxime gave a single regioisomer (4i) and meta-chloro-substituted oxime produced a 10:1 ratio of regioisomers 4j. Steric bulkiness on the phenyl ring was also tested. To our delight, all the reactions with a methyl group at the ortho, meta, or para positions of the phenyl ring showed good to excellent reactivities (4h, 4i, and 4k), thus showing high tolerance for steric hindrance.

We next explored the possibility of changing the substituents at the methyl group of acetophenone oximes and were pleased to find that both alkyl and aryl substitutions were compatible with these conditions to give the corresponding products in excellent yields (4m-q). For the stereochemistry of the present transformation, it was found that alkyl-substituted acetophenone oximes gave inseparable *E* and *Z* isomers (4m and 4n) in a ratio of nearly 1.7:1. Gratifying, in case of aryl-substituted acetophenone oximes (4o-q) as substrates, *E* isomers were isolated as the major products in excellent yields and with good diastereoselectivities. Their geometry was established through NOE studies.



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[a] Reaction conditions: 2 (0.2 mmol), 3a (0.3 mmol), Rh cat. (0.01 mmol), DCE (1 mL), 100 °C, 12 h. The yield of isolated product is given. [b] A mixture of 4j and minor regioisomeric product was determined in a ratio of 10:1.

In addition to 3a, other isocyanates were also investigated for the reaction (Table 3). It was found that the reactivity of this reaction was to some degree sensitive to the substitution patterns (4a, 4r–u) and electronic properties of the phenyl ring, and benefited from electron-donating groups (4a and 4r). Notably, the tolerance of the bromo (4s) and ester groups (4u) offers the opportunity for further functionaliza-



[a] Reaction conditions: **2a** (0.2 mmol), **3** (0.3 mmol), Rh cat. (0.01 mmol), DCE (1 mL), 100 °C, 12 h. The yield of isolated product is given.

tion. In addition, 2-naphthyl isocyanate also gave the corresponding product 4v in 80% yield. Particularly remarkable is the participation of alkyl isocyanate in this reaction, providing the corresponding derivative 4w in 60% yield.

To probe the catalytic mechanism, we carried out a competition experiment between equimolar amounts of deuterio-**2a** and **2a** with *p*-tolyl isocyanate **3a** under our standard conditions for 1 h, which results in the intermolecular kinetic isotope effect  $(k_{\rm H}/k_{\rm D})$  of 3.5:1 (Scheme 1A). However,



Scheme 1. Mechanistic studies: a)  $[Rh(CH_3CN)_3(Cp^*)][SbF_6]_2$  (5 mol %), DCE, 100 °C, 1 h,  $k_H/k_D = 3.5:1$ ; b) *p*-tolyl isocyanate  $[Rh(CH_3CN)_3-(Cp^*)][SbF_6]_2$  (5 mol %), DCE, 100 °C, 2 h.

when  $[D_5]$ **2a** was subjected to the standard reaction conditions, only modest deuterium exchange was observed at the *ortho* positions of both the unreacted oxime (25 % H) and the product (13 % H) (Scheme 1B). Although elucidation of the rate law for the annulation reaction is necessary to interpret this result properly, a notable primary kinetic isotope effect (KIE,  $k_{\rm H}/k_{\rm D}$ =3.5) suggests that the C–H bond cleavage is likely involved in the rate-limiting step.<sup>[12]</sup>

Although the reaction mechanism remains to be elucidated, we tentatively propose the following reaction pathway (Scheme 2). The catalytic annulation reaction should involve initially the coordination of the oxime nitrogen to the rhodium center and subsequent ortho C-H bond activation forms a five-membered rhodacycle A and the release of one equivalent of proton (H<sup>+</sup>). After the ligand exchange from acetonitrile to isocyanate, the coordinating complex B forms. Selective insertion of isocyanate into the Rh-C bond of intermediate **B** gives the seven-membered rhodacycle **C**, which undergoes an intramolecular insertion of the oxime group into the nitrogen-Rh bond to form intermediate **D** (path a). This intermediate is protonated by the acid that is generated in situ at the initiating step, followed by elimination of one molecule of methoxyamine, thus producing the desired product 4. This final step is also accompanied by the regeneration of the active catalyst. On the other hand, protonation of C affords intermediate E (path b), in which rhodium could activate the oxime for intramolecular nucleophilic ad-

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Scheme 2. Proposed mechanism ( $L = CH_3CN$ ).

dition by coordination or serving as a Lewis acid. Finally, elimination of one molecule of methoxyamine affords product **4** and regenerates the catalyst.

We carried out several experiments to probe the reaction pathway. To our delight, when using 2n as the substrate, the intermediate 4n' was obtained in 15% yield by lowering the reaction temperature to 90°C and shortening the reaction time to 5 h (Scheme 3A). Subjecting intermediate 4n' to



Scheme 4. Conditions: a) NaH, dimethyl carbonate, toluene, reflux for 3 h, 88%; b) MeONH<sub>2</sub>·HCl, NaOAc, MeOH/H<sub>2</sub>O, 80°C for 2 h, 93%; c) isocyanate, [Rh(CH<sub>3</sub>CN)<sub>3</sub>(Cp\*)][SbF<sub>6</sub>]<sub>2</sub>, DCE, 140°C for 16 h, (*E*)-8 (73%), (*Z*)-8 (12%); d) Pd/H<sub>2</sub>, MeOH, 60°C for 4 h; e) 15% K<sub>2</sub>CO<sub>3</sub>, MeOH, 80°C for 10 h; f) 1-methylpiperazine, EDC, HOBt, THF, 25°C for 16 h.

Reaction of commercially available starting material **5** with dimethyl carbonate, followed by treatment with O-methyl-hydroxylamine hydrochloride in MeOH and H<sub>2</sub>O in the

presence of NaOAc, gave oxime **7** in 82% yield for the two steps. Rh-catalyzed annulation of oxime **7** and 4-fluorophenyl isocyanate provided the key intermediate **8** in 85%

yield as a mixture of E and Z

isomers (6:1). Hydrogenation and hydrolysis of the ester

group, followed by treatment of 1-methylpiperazine in the presence of *N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide

hydrochloride (EDC) and 1-hy-

(HOBt), afforded the bioactive

compound **V** in 83% yield for the three steps.<sup>[1f]</sup> On the other hand, direct hydrolysis of the

hydrate

droxybenzotriazole



Scheme 3. Probing the reaction mechanism: a)  $[Rh(CH_3CN)_3(Cp^*)][SbF_6]_2$  (5 mol%), DCE, 90°C, 5 h, 15%; b)  $[Rh(CH_3CN)_3(Cp^*)][SbF_6]_2$  (5 mol%), DCE, 100°C, 12 h, 95%; c) DCE, 100°C, 12 h, 24%.

standard reaction conditions gave **4n** in 95% yield, whereas only a 24% yield was observed in the absence of catalyst  $[Rh(CH_3CN)_3(Cp^*)][SbF_6]_2$  (Scheme 3B). These results indicate the existence of path b and suggest that the subsequent intramolecular nucleophilic addition is mainly promoted by the Rh catalyst.

To further illustrate the synthetic usage of the present method, we developed an efficient and concise synthesis of bioactive compounds (E)-**IV** and **V**, as depicted in Scheme 4.

ester group and subsequent treatment with 1-methylpiperazine provided compound (*E*)-**IV** in 89% yield over two steps.<sup>[1d]</sup>

In summary, we have developed a novel rhodium-catalyzed annulation of aryl ketone *O*-methyl oximes with isocyanates for the synthesis of 3-methyleneisoindolin-1-ones by C–H bond activation. The reaction can be carried out in the absence of any additives and environmentally hazardous waste production, without the requirement of special techniques. This reaction is potentially applicable in laboratory and industrial synthesis. Most importantly, this process gives a simple and straightforward access to 3-methyleneisoindolin-1-ones and may find applications in the synthesis of complex natural products or designed bioactive compounds.

#### **Experimental Section**

**General procedure:** An oven-dried reaction vessel was charged with  $[Rh(CH_3CN)_3(Cp^*)][SbF_6]_2$  (8.4 mg, 5 mol%, 0.01 mmol), DCE (1 mL), substrate 2 (0.2 mmol), and substrate 3 (0.3 mmol). The reaction mixture was stirred in the sealed tube at 100 °C under N<sub>2</sub> for 12 h. The resulting mixture was cooled to room temperature, filtered through a short silica gel pad, and transferred to a silica gel column directly to give product 4.

**Keywords:** annulation  $\cdot$  C–H activation  $\cdot$  isocyanates  $\cdot$  ketones  $\cdot$  rhodium

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# COMMUNICATION



**Going green!** The rhodium(III)-catalyzed annulation of aryl ketone *O*methyl oximes with isocyanates for the synthesis of 3-methyleneisoindolin-1ones is reported (see scheme). This



reaction exhibits high regioselectivity, functional-group tolerance, and broad substrate scope, without the use of additives or production of environmentally hazardous waste.

#### Annulation

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Rhodium(III)-Catalyzed Amidation of Aryl Ketone *O*-Methyl Oximes with Isocyanates by C-H Activation: Convergent Synthesis of 3-Methyleneisoindolin-1-ones



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