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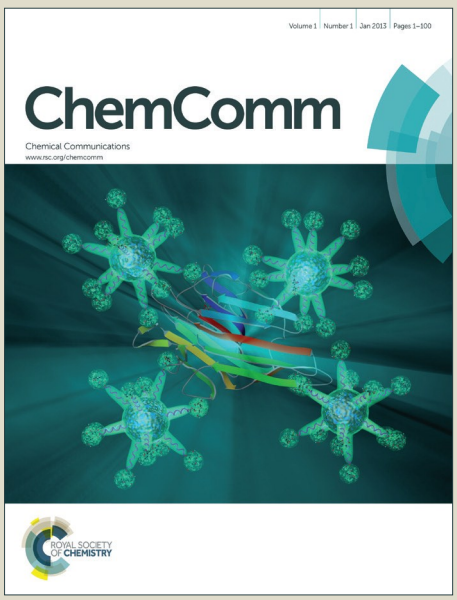

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Journal Name

COMMUNICATION

Rh(III)-catalyzed C-H activation reaction forming 1*H*-isoindoles containing a quaternary carbon center from aryl ketones or benzylamines

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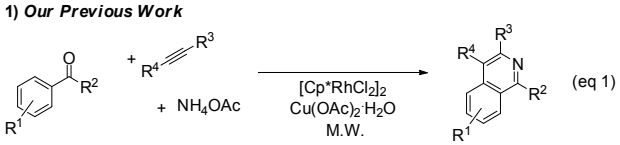
Rh(III)/Cu(OAc)$_2$ catalyzed, one-pot reactions of aryl ketones, acrylate esters and ammonium acetate or α-substituted benzylamines under microwave irradiation conditions produce 1*H*-isoindoles bearing a quarternary carbon center.

Several transition metal-catalyzed reactions that produce isoquinolines and pyridines have been developed recently.[1] In comparison to conventional methods, these processes have advantageous features associated with convenience and atom economy. In a recent effort, we uncovered a novel one-pot multi-component process promoted by a Rh(III) catalyst that generates substituted isoquinolines (eq. 1).[2] An advantage of this protocol is that it does not require pre-preparation of imine functionalized substrates.

Isoindoles are members of the broad *N*-heterocycle family that hold special interest and importance because they serve as precursors of alkaloids,[3] antitumor agents[4] and laser dyes.[5] In this group, 1*H*-isoindoles are particularly difficult to prepare because of their intrinsic ability to isomerize to form aromatic isoindoles.[6] Recently Li and co-workers reported a method for synthesis of 1*H*-isoindole starting with specially designed *N*-sulfinyl ketoimines and alkene.[7] In the study described below, we developed a new Rh(III)-catalyzed, C-H bond activation reaction between aryl ketone, acrylate ester, and NH_4OAc or α-substituted benzylamine that produces 1*H*-isoindole (eq. 2). The presence of quaternary carbon centers in the 1*H*-isoindole produced in this manner prevents the prototropic shift process that leads to aromatization. In this reaction, microwave irradiation was utilized for the facile *N*-annulation reaction compared with conventional heating.[8]

1) ***Our Previous Work***



2) ***This Work***

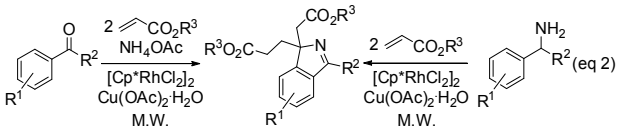
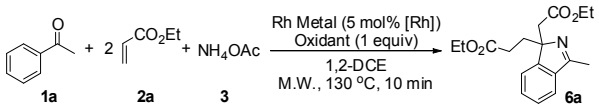


TABLE 1. Optimization of the Rh(III) Catalyzed 1*H*-Isoindole Synthesis Method[a]



Entry	Metal	Oxidant	Temp (°C)	Yield (%)[b]
1	$[Cp^*RhCl_2]_2$ (**4**)	$Cu(OAc)_2{\cdot}H_2O$ (**5**)	130	95
2	$Cp^*Rh(MeCN)_3(SbF_6)_2$	**5**	130	73
3	$(Ph_3P)_3RhCl$	**5**	130	0
4	**4**	$Pd(OAc)_2$	130	32
5	**4**	AgOAc	130	0
6	**4**	**5**	110	62
7	**4**	**5**	150	70
8[c]	**4**	**5**	130	37

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (2 equiv), **3** (2 equiv), Rh metal (5 mol%), Oxidant (1 equiv), 1,2-dichloroethane (200 mg), M.W. (microwave) at 130 °C for 10 min. [b]GC yields. [c]Conventional heating at 130 °C for 24 h.

In an initial phase of the study aimed at exploring conditions required to promote the 1*H*-isoindole forming Rh(III)-catalyzed reaction, acetophenone (**1a**) was chosen as a model aryl ketone substrate (Table 1). Reaction of **1a** with ethyl acrylate (**2a**) and NH_4OAc **3** was carried out in the presence of $[Cp^*RhCl_2]_2$ (**4**, 5 mol%) and $Cu(OAc)_2{\cdot}H_2O$ (**5**, 1 equiv) at 130 °C for 10 min under microwave irradiation conditions. This

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† Footnotes relating to the title and/or authors should appear here.
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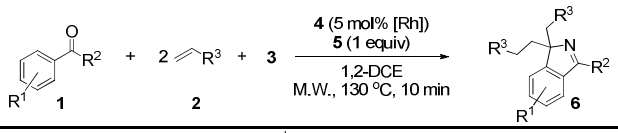
process formed 1*H*-isoindole **6a** in a 95% GC yield (entry 1). While employing $[Cp^*Rh(MeCN)_3(SbF_6)_2]$ as the catalyst did not improve the yield of this reaction (entry 2), using Rh(I) complexes like $[(Ph_3P)_3RhCl]$ did not promote the reaction (entry 3). Likewise, the use of other oxidants such as $Pd(OAc)_2$ and AgOAc instead of **5** did not improve the yield of **6a** (entries 4 and 5). Decrease in reaction temperature from 130 to 110 °C lead to a decrease in the product yield (entry 6). Even in high temperature of 150 °C, only 70% yield of **6a** was obtained (entry 7). Finally, when the reaction was carried out at 130 °C for 24 h using conventional heating, **6a** was generated in only a 37% GC yield, implying that the microwave irradiation is required to promote a highly efficient reaction (entry 8).

Table 2. Rh(III)-catalyzed synthesis of 1*H*-isoindoles from aryl ketones[a]



1 2 6

Entry	Aryl ketone **1**	Acrylate **2**	Isolated yield of **6** (%)
1	**1a**	**2a**	**6a**; $R^3 = CO_2Et$, 88%
2		**2b**	**6b**; $R^3 = CO_2Me$, 75%
3		**2c**	**6c**; $R^3 = CO_2n$-Bu, 79%
4	**1b**; R^2 = Ph	**2a**	**6d**; R^2 = Ph, 96%
5	**1c**; R^2 = *n*-Hex[b]		**6e**; R^2 = *n*-Hex, 60%
6	**1d**; R^2 = Cy[c]		**6f**; R^2 = Cy, 56%
7	**1e**	**2a**	**6g**, 81%
8	**1f**; R^1 = *p*-COMe	**2a**	**6h**; R^1 = *p*-COMe, 64%
9	**1g**; R^1 = *p*-Cl		**6i**; R^1 = *p*-Cl, 88%
10	**1h**; R^1 = *p*-Br		**6j**; R^1 = *p*-Br, 91%
11	**1i**; R^1 = *p*-OMe		**6k**; R^1 = *p*-OMe, 85%
12	**1j**; R^1 = *o*-OMe		**6l**; R^1 = *o*-OMe, 95%
13	**1k**; R^1 = OMe	**2a**	**6m**; R^1 = OMe, 45% **6n**; R^1 = OMe, 31%
14	**1l**; R^1 = OH		**6o**; R^1 = OH, 48% **6p**; R^1 = OH, 25%
15	**1m**; R^1 = NHCOMe		**6q**; R^1 = NHCOMe, 3% **6r**; R^1 = NHCOMe, 67%
16	**1n**	**2a**	**6s**, 56%

[a]Reaction conditions: **1** (0.2 mmol), **2a** (2 equiv), **3** (2 equiv), **4** (5 mol%), **5** (1 equiv), 1,2-dichloroethane (200 mg), M.W. (microwave) at 130 °C for 10 min. [b]Hex = hexyl. [c]Cy = cyclohexyl.

The acrylate ester scope of the 1*H*-isoindole forming process was explored. The results (Table 2) show that under the optimized conditions reactions of acetophenone (**1a**) with ethyl (**2a**), methyl (**2b**) and n-butyl acrylate (**2c**) produce the respective 1*H*-isoindoles **6a**-**6c** in good yields (entries 1-3).

The scope of the process was further probed in studies of the reactions of ethyl acrylate **2a** with acetophenone analogs possessing a phenyl (benzophenone, **1b**), alkyl (heptanophenone, **1c**) and cyclohexyl (cyclohexyl phenyl ketone, **1d**) groups. These processes generate the respective 1*H*-isoindoles in moderate to high yields (entries 4-6). In addition, reaction of the cyclic arylketone α-tetralone (**1e**) formed 1*H*-isoindole **6g** in 81% yield (entry 7). In addition, the electron-withdrawing group-substituted acetophenones **1f-h** react with **2a** to produce 1*H*-isoindole **6h-j** in 64%, 88% and 91% yield, respectively (entries 8-10). The reactions of the electron-donating methoxy group-substituted analog **1i** and **1j** produced **6k** (85%) and **6l** (95%) (entries 11 and 12).

An investigation was carried out to gain information about the regioselectivities of *N*-annulation reactions of *m*-substituted aryl ketones. The results show that reaction of 3-methoxyacetophenone (**1k**) with **2a** produces a mixture of **6m** and **6n** in respective 45% and 31% yields (entry 13). In an analogous manner, **1l** bearing *meta*-hydroxyl group reacts to form a mixture of **6o** and **6p** in respective 48% and 25% yields (entry 14). In contrast reaction of *m*-acetamidoacetophenone (**1m**) formed a mixture of the respective 1*H*-isoindole **6q** and **6r** in 3% and 67% yields, suggesting that the acetamido group has a pronounced steric effect on the regiochemistry of the process (entry 15). A similar strong directing effect is at work in governing the high degree of regioselctivity that attends reaction of the *m*-methylacetophenone (**1n**), which produced 1*H*-isoindole **6s** exclusively (56%, entry 16).

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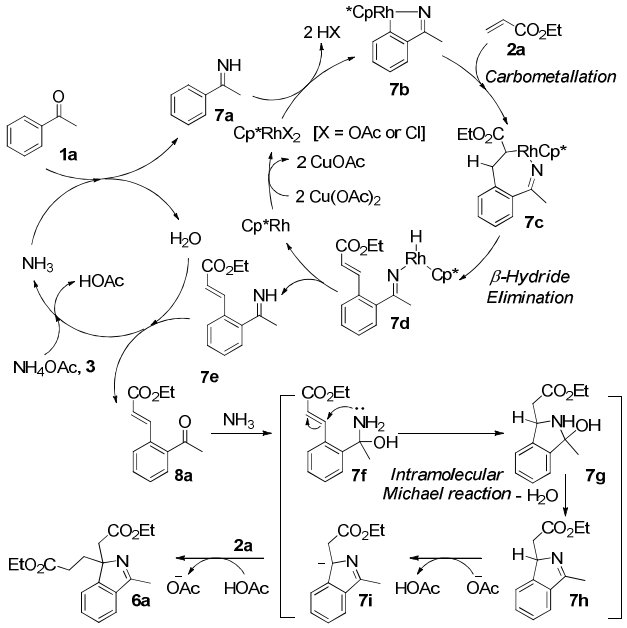
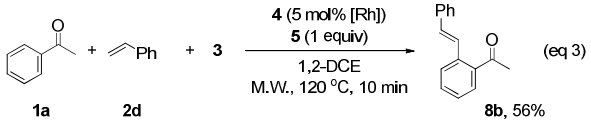


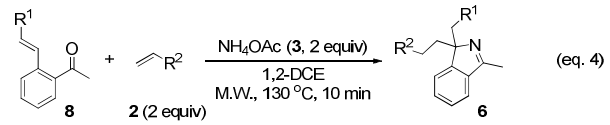
SCHEME 1. Proposed mechanism for the synthesis of 1*H*-isoindole.

A plausible mechanism for the 1*H*-isoindole **6a** forming Rh(III)-catalyzed reaction of aromatic ketones **1a** and acrylate esters **2a** is given in Scheme 1. The overall process takes place in two stages involving *ortho*-vinylation of **1a** and followed by *N*-annulation. Condensation of acetophenone **1a** with ammonia acetate (**3**) occurs first to generate imine **7a**, which reacts with $Cp^*Rh(OAc)_2$ to give the five-membered rhodacycle complex **7b**.[9] Carbometallation of ethyl acrylate **2a** with **7b** then occurs to form the seven-membered rhodacycle **7c**, which undergoes β-hydride elimination to give the imino-Rh complex **7d**. Reductive elimination of **7d** produces imine **7e** and a Rh(I) species, which is oxidized by $Cu(OAc)_2$ to regenerate the active $Cp^*Rh(OAc)_2$ catalyst. *Ortho*-vinylated ketone **8a** then forms by hydrolysis of **7e** with H_2O generated in the initial condensation step. Next, 1,2-addition of NH_3 to ketone **8a** occurs to form α-hydroxyl amine **7f**, which undergoes intramolecular 1,4-addition and dehydration to generate **7h**. Finally, deprotonation of modestly acidic **7h** gives anion **7i**, which participates in conjugate addition[10] to the acrylate **2a** to produce 1*H*-isoindole **6a**.



(eq 3)

To confirm the involvement of the aryl-acrylate intermediate **8a** in this process, reaction of **1a** with styrene (**2d**) was carried out using identical conditions. The observation that this process produces aryl-styrene **8b** exclusively (eq 3) shows that an *ortho*-vinylation step forming **8a** is likely involved in the mechanistic pathway for 1*H*-isoindole formation.

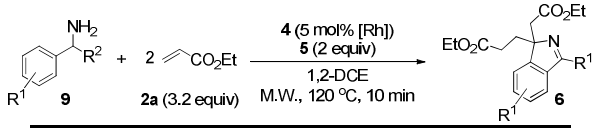


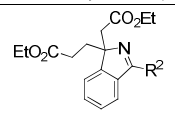
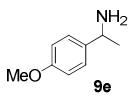
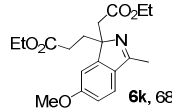
(eq. 4)

8a; $R^1 = CO_2Et$ **2a**; $R^2 = CO_2Et$ **6a**; $R^1 = CO_2Et$, $R^2 = CO_2Et$, 78%
2b; $R^2 = CO_2Me$ **6t**; $R^1 = CO_2Et$, $R^2 = CO_2Me$, 68%
8c; $R^1 = CO_2Me$ **2a** **6u**; $R^1 = CO_2Me$, $R^2 = CO_2Et$, 72%

Furthermore, we found that *N*-annulation reaction of aryl-acrylate **8a** with acrylic ester to form 1*H*-isoindole **6a** did not require transition metal catalyst (eq. 4). Specifically, reactions of esters **8a** and **8c**, prepared by using known methods,[11] with acrylate ester **2a** and **2b** and ammonium acetate (**3**) took place in the absence of transition metal catalysts **4** and **5** to form the corresponding 1*H*-isoindoles **6a, 6t** and **6u** in 68-78% isolated yields.

Table 3. Rh(III)-catalyzed synthesis of 1*H*-isoindoles from α-substituted benzylamines[a]



Entry	α-substituted benzylamine **9**	Isolated yield of **6** (%)
		
1	**9a**; R^2 = Me	**6a**; R^2 = Me, 71%
2	**9b**; R^2 = Ph	**6d**; R^2 = Ph, 75%
3	**9c**; R^2 = *n*-Hex[b]	**6e**; R^2 = *n*-Hex, 61%
4	**9d**; R^2 = Cy[c]	**6f**; R^2 = Cy, 59%
5	 **9e**	 **6k**, 68%

[a]Reaction conditions: **1** (0.2 mmol), **2a** (3.2 equiv), **4** (5 mol%), **5** (2 equiv), 1,2-dichloroethane (200 mg), M.W. (microwave) at 120 °C for 10 min. [b]Hex = hexyl. [c]Cy = cyclohexyl.

The proposal that the mechanism for this process proceeds via intramolecular 1,4-addition of the benzylamine moiety in **7f** to the *ortho*-acrylic ester group stimulated thoughts about another approach for 1*H*-isoindole synthesis. Specifically, we envisaged that benzylamines might participate in Rh(III)-catalyzed reactions with acrylates to produce 1*H*-isoindoles. In a test of this proposal, we observed that reaction of α-methylbenzylamine (**9a**) with acrylate **2a** (3.2 equiv based on **9a**) in the presence of **4** (5 mol%) and **5** (2 equiv) at 120 °C for 10 min under MW irradiation, lead to formation of 1H-isoindole **6a** in a 71% isolated yield (Table 3, entry 1). Reactions of other benzylamines possessing benzylic aryl (**9b** and **9e**), alkyl (**9c**) and cyclohexyl (**9d**) substituents also produced fairly good yields of the corresponding 1*H*-isoindoles, **6** (entries 2-5).

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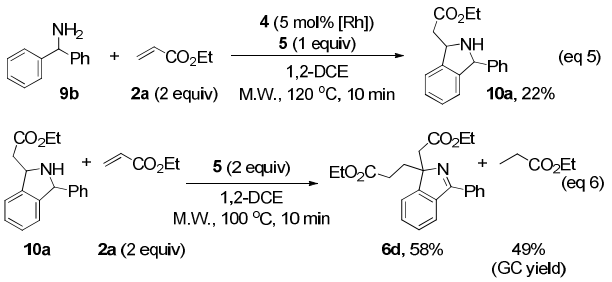
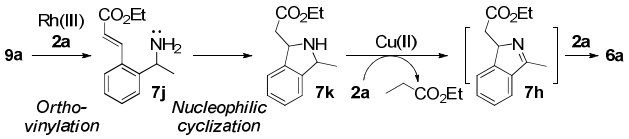


Interestingly, reaction of benzylamine **9b** with **2a** (2 equiv) in the presence of Rh(III) catalyst **4** and 1 rather than 2 equivalents of Cu(II) **5** produced isoindoline **10a** in 22% isolated yield (eq 5). This observation suggests that **10a** is an intermediate in the overall 1*H*-isoindole forming pathway. Furthermore, microwave-promoted reaction of **10a** with acrylic ester **2a** (2 equiv) at 100 °C using oxidant **5** formed **6d** in a 58% yield, along with a 49% GC yield[12] of ethyl propionate, the hydrogenated form of ethyl acrylate (eq 6).



SCHEME 2. Proposed mechanism of synthesizing 1*H*-isoindole from α-substituted benzylamine.

Based on the above results, it is possible to propose that the mechanism for formation of 1*H*-isoindole **6a** from α-substituted benzylamines **9a** and **2a** is the one shown in Scheme 2. In the route, amine-directed *ortho*-vinylation of benzylamine with acrylic ester by Rh(III)/Cu(II) takes place to form **7j**, which participates in intramolecular conjugate addition to generate isoindoline **7k**.[13] Dehydrogenation of **7k** promoted by **2a** then produces **7h** and ethyl propionate, the former of which undergoes 1,4-addition to acrylate **2a** to produce 1*H*-isoindole **6a**.[14]

In the study described above, we developed a novel, one-pot, 3-component, microwave assisted *N*-annulation reaction of aryl ketones with acrylate esters in the presence of ammonium acetate or benzylamine that produces 1*H*-isoindoles. The process has wide ketone and acrylate substrate scopes and it efficiently generates various 1*H*-isoindoles containing a quaternary carbon center.

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12 GC yield of ethyl propionate was determined using mesitylene as an internal standard.

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14 When **9f** [(R)-(+)-α-methylbenzylamine] is employed as a starting material in this reaction, 1*H*-isoindole **6a** is obtained in racemic form in a 70% isolated yield (Scheme 2). This result supports the proposal that dehydrogenation of **7k** takes place to afford 1*H*-isoindole **6a** through the intermediate **7h**.