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Rhodium(III) catalyzed synthesis of isoquinolone fused azabicycles through C–H activation of *N*-pivaloyloxy benzamides

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ABSTRACT

Herein we describe an efficient one pot strategy toward highly functionalized isoquinolone fused azabicycles having great synthetic potential via C–H activation of *N*-pivaloyloxy benzamides under very mild conditions. The reaction is accomplished at room temperature within one hour in good to excellent yields and is found to be compatible with a range of diazabicyclic olefins and benzamides. The present strategy offers an easy route for the synthesis of biologically relevant compounds which possess multiple points for divergent synthesis. N–N bond cleavage of synthesized compounds may enable their significant role as effective precursors for the preparation of diaminocyclopentane fused isoquinolones.

Isoquinolone is one of the nitrogen-containing heterocycles and is a highly valuable structural skeleton of many biologically important natural products and pharmaceutical agents.[1] Transition metal catalyzed C–H bond activation reactions of various aromatic substrates containing the nitrogen based functional group as the directing group have been explored for the construction of these biologically relevant molecules.[2,3] The metal catalyzed C–H functionalization protocols allow the synthesis of a variety of heterocyclic compounds in an atom-economic way by making use of readily accessible starting materials with less generation of toxic waste.[4] Fagnou and co-workers and Wang and co-workers have independently mentioned the annulation of norbornadiene with hydroxamic acid derivatives during their detailed studies with alkenes under rhodium[3a] and ruthenium[2h] catalysis, respectively. But these reactions required prolonged reaction time and elevated temperature. Apart from these reports, there have been no serious efforts taken for the C–H activation of benzamides with bicyclic systems. Design and synthesis of biologically active scaffolds with appendages for further functionalization are highly promising strategy in medicinal chemistry. In the present manuscript, we wish to discuss the results of our studies on the annulation reaction of various diazabicyclic olefins through the C–H activation of *N*-pivaloyloxy benzamides.

Transition metal or Lewis acid catalyzed ring-opening reactions of diazabicyclic alkenes have been extensively investigated by different research groups[5–8] including our laboratory,[9] for the synthesis of a variety of cyclopentanoids.[10] Remarkably, heteroannulation or carboannulation of diazabicyclic alkenes is a versatile and powerful one-pot strategy for the construction of a wide variety of biologically significant skeletons.[11,12] We have developed a number of palladium and rhodium catalyzed synthetic transformations of strained diazanorbornene analogues toward complex polycyclic molecules.[12,13] Very recently, we have demonstrated a palladium/Lewis acid mediated domino reaction of pentafulvene derived diazabicyclic olefins with 2-iodoaniline for the synthesis of novel spiropentacyclic motifs with indoline and pyrazolidine fused to cyclopentene core.[12c] We have also developed a proficient one pot strategy for the synthesis of cyclopentene fused chromanone derivatives by the ring opening-ring closing of diazabicyclic alkenes via rhodium catalyzed oxidative coupling of salicylaldehydes.[12b] Our continued interest in the metal catalyzed annulation reactions of diazabicyclic olefins prompted us to investigate the C–H activation of *N*-pivaloyloxy benzamides with diazabicyclic olefins derived from cyclopentadiene as well as pentafulvenes. We disclose herein the rhodium catalyzed synthesis of highly functionalized isoquinolone fused azabicycles under very mild reaction conditions (Scheme 1).

With an idea of synthesizing complex molecular frameworks with multiple points for further functionalization, we initiated our studies by employing azabicyclic alkene **1a** and *N*-pivaloyloxy

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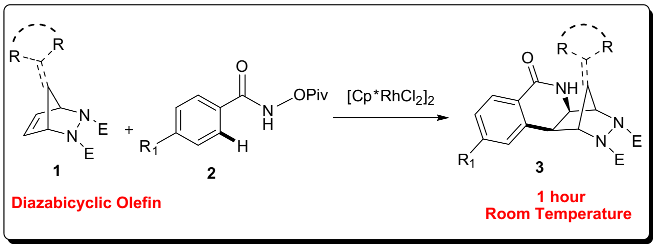
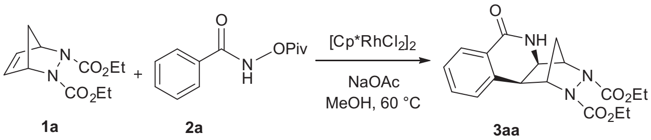


Scheme 1. Present strategy.



Scheme 2. Reaction of diazabicyclic olefin **1a** with *N*-pivaloyloxy benzamide **2a**.

Table 1
Optimization for a suitable catalyst system

Entry	Catalyst	Additive	Solvent	Temp (°C)	Yield (%)
1	$[RhCl_2Cp^*]_2$	NaOAc	MeOH	60	94
2	$[RhCl_2Cp^*]_2$	CsOAc	MeOH	60	89
3	$[RhCl_2Cp^*]_2$	$Cu(OAc)_2{\cdot}H_2O$	MeOH	60	Trace
4	$[RhCl_2Cp^*]_2$	AgOAc	MeOH	60	92
5	$[RhCl_2Cp^*]_2$	NaOAc	MeOH	Rt	96

Reaction conditions: Alkene (1.0 equiv), benzamide (1.0 equiv), catalyst (2.0 mol %), aditive (2.0 equiv), solvent (2 mL), 1 h.

benzamide **2a** as substrates. When **1a** was treated with *N*-pivaloyloxy benzamide **2a** in the presence of $[Cp{*}RhCl_2]_2$ and additive NaOAc in methanol at 60 °C, isoquinolone fused azabicycle **3aa** was obtained in 94% yield (Scheme 2). The structure of the product was established by various spectroscopic techniques[14] (see Supporting information).

Detailed optimization studies were performed for screening various reaction parameters to obtain the best catalyst system (Table 1). The efficiency of various additives such as NaOAc, CsOAc, $Cu(OAc)_2{\cdot}H_2O$ and AgOAc was tested, from which NaOAc gave the highest yield. Among the additives that were examined $Cu(OAc)_2{\cdot}H_2O$ was found to be ineffective for the transformation. A little increase in reaction efficiency was observed, when the reaction was performed at room temperature for one hour (Entry 5). Ultimately, **1a** (1 equiv) and **2a** (1 equiv) in the presence of $[RhCl_2Cp^*]_2$ (2.0 mol %) and NaOAc (2.0 equiv) in methanol at room temperature for 1 h were found to be the optimal catalytic condition for the formation of isoquinolone fused azabicycle **3aa.**[15]

To investigate the scope of the diazabicyclic olefins, different bicyclic olefins **1b–d** were treated with *N*-pivaloyloxy benzamide **2a**. Under the optimized conditions, the reactions proceeded efficiently to afford the highly functionalized isoquinolone derivatives **3ba–da** in good to excellent yields (Table 2).

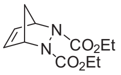
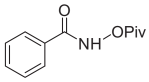
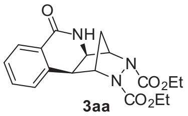
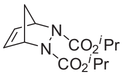
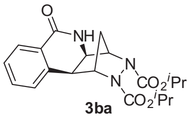
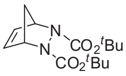
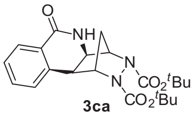
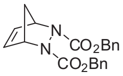
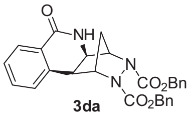
The present strategy was tested with various benzamides to explore the scope and generality of the annulation reaction. Benzamides bearing a range of electron donating and electron withdrawing substituents **2b–f** were smoothly converted into the corresponding isoquinolone derivatives **3ab–cf** in good to excellent yields (Table 3).

In the next stage, we were interested to investigate the developed protocol on the heteroannulation of pentafulvene derived diazabicyclic olefins.[9j] Under the optimal catalytic conditions, treatment of azabicyclic olefin **1e** with *N*-pivaloyloxy benzamide **2a** afforded the isoquinolone fused alkylideneazabicycle **3ea** in 56% yield (Scheme 3).

The scope of pentafulvene derived diazabicyclic olefins was proved by the reaction of substituted benzamides with various pentafulvene derived bicyclic olefins **1e–i**. In all the cases, heteroannulation via C–H activation proceeded smoothly and furnished the corresponding isoquinolone **3ea–if** derivatives in moderate to good yields (Table 4).

It is to be noted that the oxidative cleavage of the exocyclic double bond[9j] followed by N–N bond cleavage[8d] (as described by

Table 2
Scope of various diazabicyclic olefins with **2a**

Entry	Bicyclic olefin	Benzamide	Product	Yield (%)
1	 **1a**	 **2a**	 **3aa**	96
2	 **1b**	**2a**	 **3ba**	88
3	 **1c**	**2a**	 **3ca**	79
4	 **1d**	**2a**	 **3da**	84

Reaction conditions: Bicyclic alkene (1.0 equiv), benzamide (1.0 equiv), $[RhCl_2Cp^*]_2$ (2.0 mol %), NaOAc (2.0 equiv), MeOH (2 mL), rt.