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Rhodium(III)-Catalyzed C–H Activation Mediated Synthesis of Isoquinolones from Amides and Cyclopropenes

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Abstract

We have developed a synthesis of 4-substituted isoquinolones from the Rh(III)-catalyzed, C–H activation mediated, coupling of *O*-pivaloyl benzhydroxamic acids and 3,3-disubstituted cyclopropenes. Experiments suggest the formation of a [4.1.0] bicyclic-system, which can open under acidic conditions to generate the desired isoquinolone.

Keywords

C–H activation; heterocycles; isoquinolone; cyclopropene; donor-acceptor cyclopropane

Isoquinolones are a ubiquitous motif found in numerous medically interesting targets.¹ An approach to access this core is the Rh(III)-catalyzed coupling of amides with alkynes to provide 3,4-disubstituted isoquinolones.² Early reports by our group^{2c} and others^{2b,d} found that terminal alkynes were incompatible with the oxidative reaction conditions because of unwanted Glaser-type couplings. In contrast, when an internal oxidant is utilized, terminal alkynes can be used to provide 3-substituted isoquinolones in excellent yield.^{2e} Glorius expanded on this work by using MIDA-boronate terminal alkynes to access 3-MIDA boronate-substituted isoquinolones.^{2f} Absent from these reports is the ability to access 4-substituted isoquinolones (Figure 1).

We imagined this substitution pattern could be accessed through formation of an intermediate donor–acceptor cyclopropane.³ We were intrigued by some recent reports on the use of nitrogen donors on activated cyclopropanes.⁴ We speculated that 3,3-disubstituted-cyclopropenes could be coupled to benzhydroxamic acids to generate a [4.1.0] bi-cyclic heterocycle. In the presence of either a carboxylic acid or the Lewis acidic Rh(III) catalyst, the resultant cyclopropane could be opened to generate a 4-substituted isoquinolone (Figure 1). In contrast to previous examples which used alkynylation to achieve isoquinolones, our approach requires an alkenylation. This reactivity has previously been reported independently by Fagnou^{2e} and Glorius,⁵ and further developed by Rovis and Ward,⁶ Cramer,⁷ and Molander.⁸

Equation 1

We were pleased to find that *O*-pivaloyl benzhydroxamic acid **1a** could be coupled to activated cyclopropene **2a** in MeOH with CsOAc (200 mol %) and [RhCp*Cl₂]₂ (1 mol %) to provide the desired 3-substituted isoquinolone **3a** in excellent yield (99%) (Equation 1).

The reaction scope is illustrated in Table 1. A variety of *para*-substituents are tolerated providing product in excellent yield (Table 1, **3b-3e, 3h**). Substitution at the *meta*-position provides variable levels of selectivity. Methyl substituted starting materials offer product in >10:1 regioselectivity in the C–H activation, favoring activation distal to the substituent (Table 1, **3f**). In contrast, methoxy-substituents provide product, but at a 1.1:1 mixture of regioisomers (Table 1, **3g**). Highly electron rich gallic acid derivatives provide product in excellent yield (Table 1, **3i**). Finally, when *di*-ethyl malonate based cyclopropene is used, the desired product is isolated in exquisite yield without transesterification.

Unfortunately, our attempts to increase the scope of the cyclopropene component to include simple *mono*-activated cyclopropenes failed to provide the desired 4-substituted isoquinolone. We were, however, able to isolate the [4.1.0] bicyclic intermediate in 60% yield as a 1.4:1 ratio of inseparable diastereomers (Scheme 1).

Disappointed that the cyclopropane did not open under the reaction conditions, we sought an alternative method to open the donor-acceptor cyclopropane. When cyclopropanes **4a** and **4b** were submitted to a 2:1 mixture of 4M HCl in 1,4 dioxane/DCM and heated to 60 °C for 2 hours, the desired isoquinolone **5** was furnished in 95% yield (Scheme 2).

Based on these experiments, we propose that a Rh(III) catalyzed olefination occurs as described by Fagnou and Glorius to afford the [4.1.0] bi-cycle. We suggest that pivalic acid or [RhCp*Cl₂]₂, acting as a Lewis acid, catalyzes the opening of the donor acceptor cyclopropane to generate an acyl-imine, which tautomerizes to form the desired isoquinolone. In the absence of two activating groups, a stronger acid is required to achieve opening.

In conclusion, we have discovered a method to access 4-substituted isoquinolones from cyclopropenes and amides under Rh(III) catalysis. Isolation of a [4.1.0] bicycle supports the mechanism occurs in two discrete steps.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

References

1. For a review of isoquinolone synthesis; see: Glushkov VA, Shklyayev YV. *Chem. Heterocycl. Compd.* 2001; 37:663.
2. a Guimond N, Gouliaras C, Fagnou K. *J. Am. Chem. Soc.* 2010; 132:6908. [PubMed: 20433170] b Mochida S, Umeda N, Hirano K, Satoh T, Miura M. *Chem. Lett.* 2010; 39:744. c Hyster TK, Rovis T. *J. Am. Chem. Soc.* 2010; 132:10565. [PubMed: 20662529] d Song G, Chen D, Pan C-L, Crabtree RH, Li X. *J. Org. Chem.* 2010; 75:7487. [PubMed: 20923219] e Guimond N, Gorelsky SI, Fagnou K. *J. Am. Chem. Soc.* 2011; 133:6449. [PubMed: 21452842] f Wang H, Grohmann C, Nimphius C, Glorius F. *J. Am. Chem. Soc.* 2012; 134:19592. [PubMed: 23146122]
3. a Reissig H-U, Zimmer R. *Chem. Rev.* 2003; 103:1151. [PubMed: 12683780] b Yu M, Pagenkopf BL. *Tetrahedron.* 2005; 61:321. c Rubin M, Rubina M, Gevorgyan V. *Chem. Rev.* 2007; 107:3117. [PubMed: 17622181] d Carson CA, Kerr MA. *Chem. Soc. Rev.* 2009; 38:3051. [PubMed: 19847340] e De Simone F, Waser J. *Synthesis.* 2009:3353. f Campbell MJ, Johnson JS, Parsons AT, Pohlhaus PD, Sanders SD. *J. Org. Chem.* 2010; 75:6317. [PubMed: 20863142]
4. a De Simone F, Waser J. *Synlett.* 2009:593. b De Simone F, Gertsch J, Waser J. *Angew. Chem. Int. Ed.* 2010; 49:5767. c de Nanteuil F, Waser J. *Angew. Chem. Int. Ed.* 2011; 50:12075. d Benfatti F, de Nanteuil F, Waser J. *Org. Lett.* 2012; 14:386. [PubMed: 22188445] e Benfatti F, de Nanteuil F, Waser J. *Chem. Eur. J.* 2012; 18:4844. [PubMed: 22422718]
5. a Rakshit S, Grohmann C, Besset T, Glorius F. *J. Am. Chem. Soc.* 2011; 133:2350. [PubMed: 21275421] b Wang H, Glorius F. *Angew. Chem. Int. Ed.* 2012; 51:7318.
6. Hyster TK, Knörr L, Ward TR, Rovis T. *Science.* 2012; 338:500. [PubMed: 23112327]
7. Ye B, Cramer N. *Science.* 2012; 338:504. [PubMed: 23112328]
8. Presset M, Oehlrich D, Rombouts F, Molander GA. *Org. Lett.* 2013; 15:1528. [PubMed: 23496033]
9. **General Procedure for the synthesis of 3a** A 1.5 dram vial was charged with a stir bar, **1a** (0.2 mmol), [RhCp*Cl₂]₂ (1 mol %), CsOAc (0.4 mmol), and MeOH (1 mL). After stirring for 30 seconds, cyclopropene **2a** (0.22 mmol) was added and the reaction mixture was allowed to stir for 8 hours at 23 °C. Upon completion, as determined by TLC, the reaction mixture was concentrated. The crude residue was purified via column chromatography (2:1 Hexanes/EtOAc with 1% Et₃N) to provide the isoquinolone **3a** as a white solid (99% yield).

• 3-Substituted Isoquinolones (Fagnou and Glorius)

• Proposed 4-Substituted Isoquinolones

Figure 1.
Proposed approach to access mono-substituted isoquinolones

Scheme 1.
mono-activated cyclopropenes

Scheme 2.
Cyclopropane Opening

Table 1

Isoquinolone Scope^a

^aReaction conditions: Amides (1 equiv), cyclopropene (1.1 equiv), $[\text{RhCp}^*\text{Cl}_2]_2$ (1 mol %), CsOAc (200 mol %), MeOH (0.2 M), 23 °C, 8 hours.

^bProduct provided as a 1.1:1 ratio of C-H activation regioisomers.