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Rhodium(III)-Catalyzed C−H Activation: Ligand-Controlled Regioselective Synthesis of 4-Methyl-Substituted Dihydroisoquinolones

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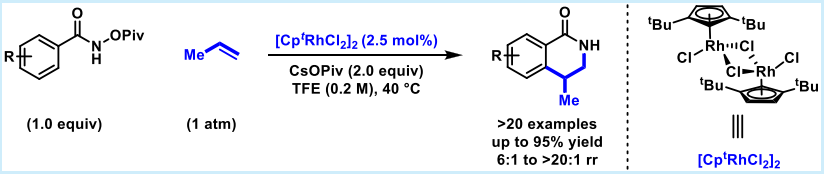
Supporting Information



ABSTRACT: Rh-catalyzed C−H functionalization of *O*-pivaloyl benzhydroxamic acids with propene gas provides access to 4-methyl-substituted dihydroisoquinolones. Good to excellent levels of regioselectivity are achieved using [Cp^{t}RhCl$_2$]$_2$ as a precatalyst under optimized conditions. Thorough examination of aryl/heteroaryl *O*-pivaloyl hydroxamic acid substrates, ligand effects on C−H site selectivity, alkene scope, and demonstration of scale are discussed within.

Tetrahydroisoquinolines (THIQs) and their dihydroisoquinolone analogues are privileged scaffolds found within naturally occurring alkaloids[1] and numerous drug discovery programs[2] (Figure 1). For example, Palonosetron is a 5-HT$_3$ antagonist approved for the treatment of chemotherapy-induced nausea and vomiting.[3] Gliquidone, a prescribed antidiabetes treatment, also bears this structural motif.[4] Further survey of the literature reveals that 4-methyl-substituted derivatives are commonly prepared during lead optimization campaigns.[5] Strategic incorporation of small substituents in drug design (e.g., the colloquial "magic methyl")[6] has the potential to dramatically improve the bioactivity, pharmacokinetics, and off-target selectivity for a given lead or series while increasing lipophilic efficiency.[7] Motivated by the need for efficient access to diverse 4-methyl-substituted dihydroisoquinolones on one of our projects at Pfizer, our objective in the present study was to enable a direct regioselective method for their synthesis.

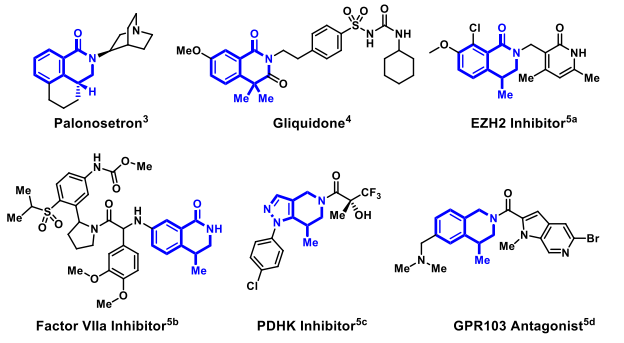


Figure 1. Representative examples of bioactive molecules bearing the 4-substituted isoquinoline motif.[3−5]

Transition-metal-catalyzed C−H alkylation reactions utilizing alkenes represent a powerful class of C−C bond-forming transformations within organic chemistry.[8] Over the past decade, Rh(III)-catalyzed C−H functionalization, in particular, has emerged as an effective approach for the synthesis of small molecules due to the functional group tolerance and mild reaction conditions often employed.[9] In 2011, Fagnou[10a] and Glorius[10b] independently reported the first annulations of *O*-pivaloyl benzhydroxamic acids with π-unsaturates (Scheme 1a). Following these seminal reports, significant progress has been made toward rendering alkene insertions of this type regio-[11] and stereoselective.[12] Of these studies, we were particularly inspired by the work of Rovis et al.,[11b,d] wherein they describe a ligand-directed strategy for the regioselective insertion of alkyl-substituted alkenes, giving rise to 4-substituted dihydroisoquinolones (Scheme 1b). Though annulations of gaseous olefins were not described in their study and remain largely unexplored in this context, our laboratory was intrigued by the possibility of employing propene as an atom-economical C3 carbon source to synthesize pharmaceutically relevant 4-methyl-substituted dihydroisoquinolones. Therefore, we focused this investigation on evaluating the regioselectivity and optimal conditions for propene delivery using rhodium-based catalysts in this transformation.

We began by benchmarking our optimization efforts with reaction conditions previously reported in the literature[10a,11d] to test the feasibility of our desired annulation reaction with *O*-

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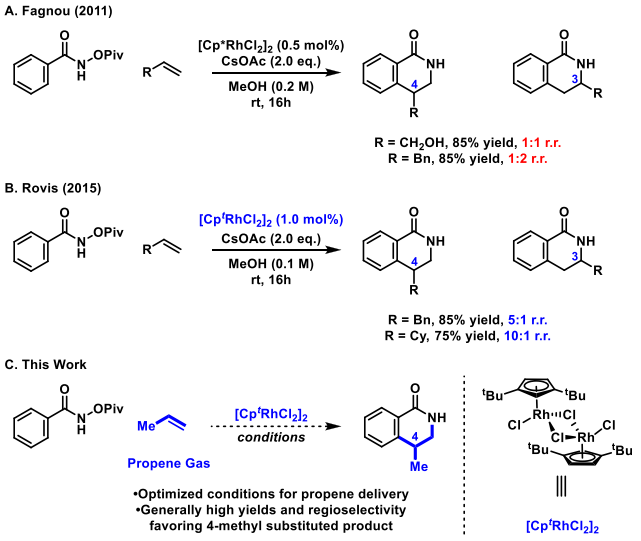
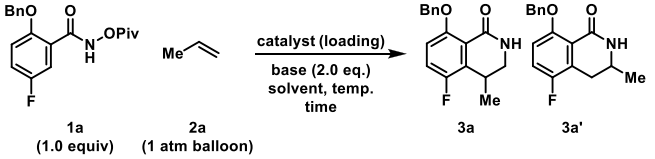
Scheme 1. Rh(III)-Catalyzed Annulation of *O*-Pivaloyl Hydroxamic Acids with Alkenes via C−H Activation[10,11b]



pivaloyl hydroxamic acid **1a** and propene gas **2a** (Table 1). Under identical conditions, using cesium acetate (CsOAc) as the base and methanol as the reaction solvent, the reactivity and regioselectivity of $[Cp^*RhCl_2]_2$ and $[Cp^tRhCl_2]_2$ catalysts were compared at room temperature (entries 1 and 2). We found that $[Cp^*RhCl_2]_2$ gave slightly higher yield (11%); however, no appreciable regioselectivity for the formation of **3a** was achieved (entry 1). On the other hand, by employing the $[Cp^tRhCl_2]_2$ catalyst utilized by Rovis and co-workers,[11b,d] the dihydroisoquinolone product **3a** could be accessed in ⩾20:1 regioselectivity (entry 2). At this stage, we performed NMR analysis of the isolated product (entry 2), and through 2D $^{19}F-^{1}H$ heteronuclear (NOE) correlation spectroscopy, we were able to confirm the structure as the 4-methyl-substituted regioisomer **3a**. Excited by the excellent regioselectivity obtained for our model substrate, we proceeded with a high-throughput optimization study to identify the ideal base and solvent to be used with $[Cp^tRhCl_2]_2$ for the insertion of propene **2a** (entry 3). Several of the weak bases we examined displayed promising conversions with cesium pivalate (CsOPiv), performing slightly better than the others. Most notably, however, we observed that 2,2,2-trifluoroethanol (TFE) was unique in its capacity to deliver the desired product **3a** in high conversion.[13] From a practical perspective, we felt the increased pressure (2 atm propene) and high dilution (0.01 M TFE) used in our high-throughput screening platform should be modified for transitioning these conditions to laboratory scale. Harnessing the optimized components of CsOPiv and TFE, we turned our attention to evaluating the effect of temperature and reaction duration at a more conventional reaction concentration (0.2 M TFE). Additionally, we utilized a balloon filled with propene as our preferred method for gas delivery. At room temperature, we observed catalyst turnover to be sluggish with a significant amount of starting material left unreacted. Despite this fact, we obtained a promising 7-fold improvement in isolated yield after the reaction was stirred for 48 h under an atmosphere of propene (entry 4). By moderately increasing the temperature to 40 °C, we achieved full conversion of starting material after 18 h, furnishing a 68% yield of **3a** after flash column chromatography (entry 5). Last, we note that our procedure for setting up the reaction is relatively straightforward and does not require rigorous exclusion of oxygen or moisture.

With the reaction conditions optimized to our satisfaction, we sought to examine the scope and limitations of this reaction (Scheme 2). A diverse set of *O*-pivaloyl benzhydroxamic acids **1** were prepared and examined under these conditions en route to 4-methyl-substituted dihydroisoquinolones **3**. The simplest expression of these involved synthesis of **3b**, which was achieved in 76% yield and 17:1 regioisomeric ratio (rr). Electron-withdrawing (examples **3c** and **3e**) as well as electron-donating (example **3d**) substituents were tolerated *para* to the hydroxamate. Substitution *ortho* to the site of C−H insertion was also tolerated, exemplified by example **3f**, albeit with a small loss of regiocontrol typically observed. As illustrated with our model substrate **1a**, *ortho*-substitution of the hydroxamate with benzyloxy, fluoro, and methyl groups delivered synthetically useful amounts of our desired products **3g−i**. In these cases, however, we believe electrostatic repulsion and steric hindrance can both play a role in disrupting the concerted metalation−deprotonation event by increasing the dihedral angle between the hydroxamate−metal complex and arene C−H bond.[14] Ultimately, we observed diminished conversions as these effects became more pronounced. To further highlight this observation, we prepared 2-chloro-*N*-(pivaloyloxy)benzamide **1j** and submitted it to the reaction conditions, wherein we found that only a trace of product **3j** could be detected. Heterocyclic substrates containing furan or thiophene motifs performed exceptionally well under these conditions to furnish products **3k−3m** in excellent yield and regioselectivity. Nitrogen-containing heterocycles, however, proved to be more challenging with pyrazole **1n**

Table 1. Selected Optimization Experiments for Rh(III)-Catalyzed Annulations with Propene Gas[a]



entry	catalyst	loading (mol %)	base	solvent	temp (°C)	time (h)	yield (%)	rr
1	$[Cp^*RhCl_2]_2$	1.0	CsOAc	MeOH (0.1 M)	23	18	11	1.3:1
2	$[Cp^tRhCl_2]_2$	1.0	CsOAc	MeOH (0.1 M)	23	18	5	>20:1
3				high-throughput optimization[b]				
4	$[Cp^tRhCl_2]_2$	2.5	CsOPiv	TFE (0.2 M)	23	48	38	15:1
5	$[Cp^tRhCl_2]_2$	2.5	CsOPiv	TFE (0.2 M)	40	18	68	11:1

[a]Regioisomeric ratios (rr) were determined by ^{1}H NMR analysis of the crude reaction mixtures, and percent yields correspond to isolated products. [b]See Supporting Information for details.

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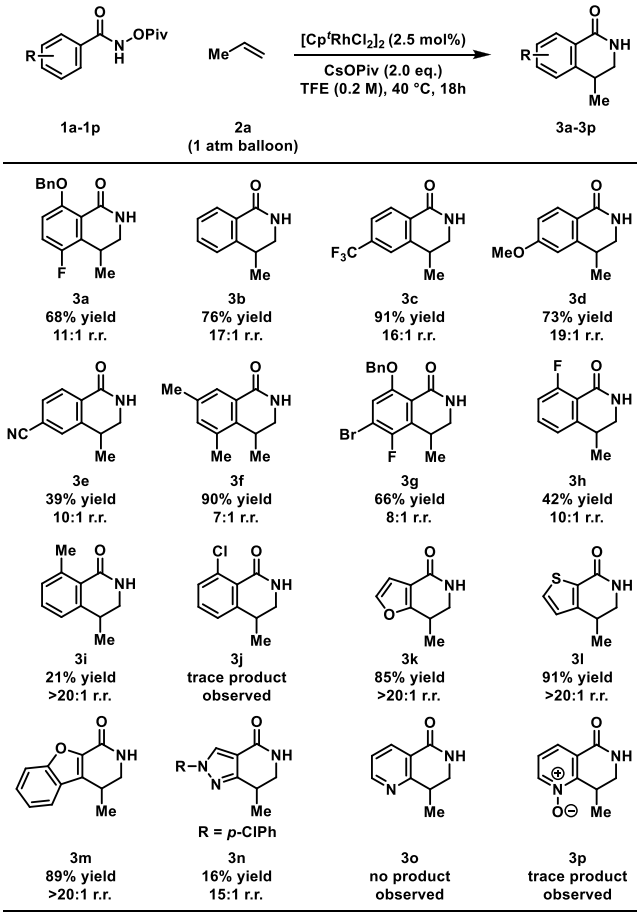
Scheme 2. *O*-Pivaloylhydroxamic Acid Scope[a,b]

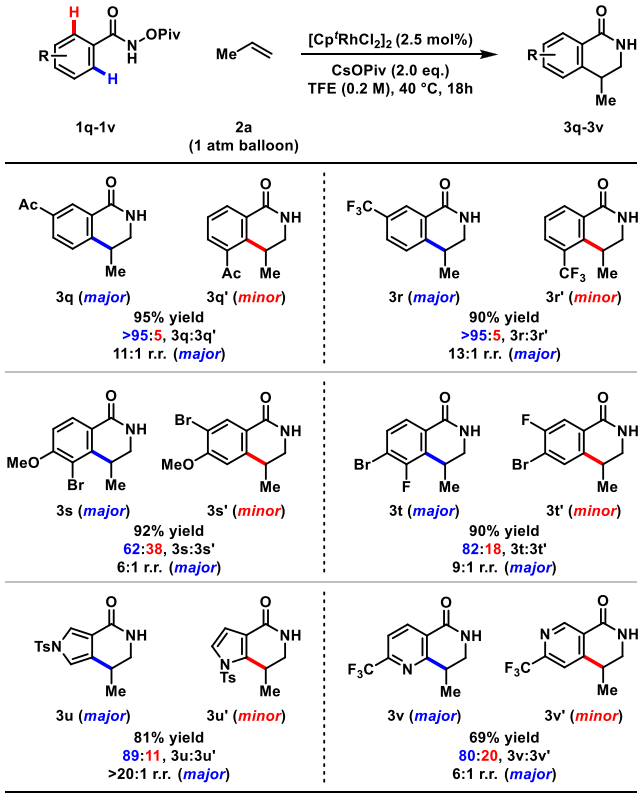


[a]All reactions were run on a 0.3 mmol scale unless otherwise noted. [b]Regioisomeric ratios (rr) were determined by ^{1}H NMR analysis of the crude reaction mixtures, and percent yields correspond to isolated products.

providing a modest 16% isolated yield of the desired tetrahydropyrazolopyridinone **3n**. Nicotinic acid derivative **1o** and its *N*-oxide analogue **1p**, known to be successful substrates in previous studies employing the prototypical $[Cp^*RhCl_2]_2$ catalyst,[11h] were not successful under these conditions.

To further explore the scope of this transformation, we prepared several additional substrates possessing two potential sites for C−H activation (Scheme 3). In general, we found the Handy method useful as starting point for predicting C−H site selectivity a priori (e.g., **3k**, Scheme 2).[15] However, when bulky substituents are introduced proximally to one of the potential sites for activation, this analysis can fail. For example, substrates bearing *meta*-acetyl **1q** or *meta*-trifluoromethyl **1r** groups were found to react preferentially at the least sterically encumbered position, overriding the innate preference for activation of the most deshielded C−H bond, thus delivering propene adducts **3q**−**3r** in excellent yield, regioselectivity, and C−H site selectivity. Reducing the molecular volume of the group *ortho* to the most acidic C−H bond restores selectivity for that position as the predominant site for activation, as demonstrated by examples **3s**−**3t**. Of particular significance to medicinal chemists, we demonstrated that pyrrolopyridinone **3u** could be accessed efficiently in good regio-/site selectivity. Additionally, though nicotinates **1o** and **1p** were ineffectual, we were pleased to find that CF_3-substituted nicotinate **1v** was a competent

Scheme 3. Examination of C−H Site Selectivity[a,b]

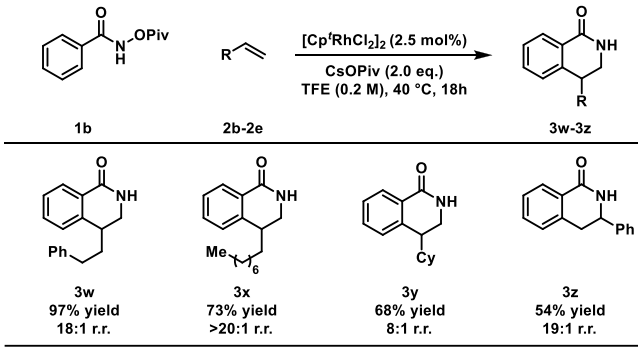


[a]All reactions were run on a 0.3 mmol scale unless otherwise noted. [b]Regioisomeric ratios (rr) were determined by ^{1}H NMR analysis of the crude reaction mixtures, and percent yields correspond to isolated products.

reaction partner, enabling access to naphthyridinone **3v** through preferential activation at the 2-position.

Having surveyed the scope of *O*-pivaloyl benzhydroxamic acids, we briefly evaluated additional olefinic substrates under our optimized conditions (Scheme 4). Here, we found that alkyl-substituted terminal alkenes delivered the 4-substituted dihydroisoquinolones **3w**−**3y** in yields and regioselectivities comparable to those described by Rovis[11b,d] and have unambiguously assigned the structure of **3w** through X-ray

Scheme 4. Olefin Substrate Scope[a,b]



[a]All reactions were run on a 0.3 mmol scale unless otherwise noted. [b]Regioisomeric ratios (rr) were determined by ^{1}H NMR analysis of the crude reaction mixtures, and percent yields correspond to isolated products.

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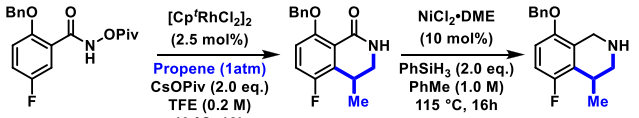
crystallography (CCDC 1916101). Additionally, we found that the ligand-mediated regiocontrol provided by the $[Cp^tRhCl_2]_2$ catalyst could not overcome the electronic bias of styrene, thus the 3-substituted congener **3z** was obtained in this instance. Styrenes are known to display this inherent regiochemical preference.[10]

To conclude our study, we sought to establish that our optimized procedure could be performed successfully on >1 g of substrate, a 10-fold increase from our standard conditions, with the objective of facilitating multistep syntheses (Scheme 5). For

Scheme 5. Gram-Scale Synthesis[a]



1a: 1.04 g, 3.00 mmol

3a: 571 mg, 2.00 mmol; 66% yield, 10:1 rr

4a: 70% yield

[a]Regioisomeric ratios (rr) were determined by ^{1}H NMR analysis of the crude reaction mixtures, and percent yields correspond to isolated products.

demonstration of scale, we used 3 mmol of our model substrate **1a** following the general procedure which delivered >500 mg of dihydroisoquinolone **3a** in 66% yield and 10:1 regioselectivity. This result compares favorably with the reactions we performed on a smaller scale. Moreover, dihydroisoquinolone **3a** could be readily reduced under mild conditions, providing tetrahydroisoquinoline **4a** in good yield.[16]

In summary, we have developed a convenient method for annulation of *O*-pivaloyl benzhydroxamic acids with propene gas for the regioselective synthesis of 4-methyl-substituted dihydroisoquinolones via C−H activation. A diverse set of functional groups including halides, ketones, nitriles, and heterocycles was tolerated. Examination of the effects that influence regioselectivity for olefin insertion and site selectivity for C−H activation has provided a better understanding for predicting the fate of novel substrates. We envision that this methodology will directly impact ongoing medicinal chemistry programs, aiding rapid analogue synthesis and fragment-based drug discovery approaches focused on the versatile isoquinoline motif. Furthermore, we believe these conditions will serve as a useful platform for adaptation to larger-scale applications later in the drug development process.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02029.

Experimental procedures; characterization data and copies of NMR spectra for all novel compounds (PDF)

Accession Codes

CCDC 1916101 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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