Ligand design for Rh(III)-catalyzed C–H activation: an unsymmetrical cyclopentadienyl group enables a regioselective synthesis of dihydroisoquinolones†

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We report the regioselective synthesis of dihydroisoquinolones from aliphatic alkenes and O-pivaloyl benzhydroxamic acids mediated by a Rh(III) precatalyst bearing sterically bulky substituents. While the prototypical Cp* ligand provides product with low selectivity, sterically bulky Cp\textsubscript{t} affords product with excellent regioselectivity for a range of benzhydroxamic acids and alkenes. Crystallographic evidence offers insight as to the source of the increased regioselectivity.

C–H activation mediated processes have provided a unique retrosynthetic approach to access a variety of substituted heterocycles.\(^1\) One tactic that has received increased attention is the coupling of π-components with heteroatom containing molecules.\(^2\) A variety of transition metals are capable of catalyzing this type of transformation, providing access to dozens of heterocyclic motifs.\(^1\)–\(^3\) A challenge for these methods is controlling the regioselectivity of migratory insertion across alkenes and alkynes after the metallacycle forming C–H activation (eqn 1).

Steric and electronic effects are understood to control migratory insertion of unsymmetrical alkynes in Rh(III) catalyzed isoquinolone syntheses (eqn 1). When the substituents are electronically similar, the larger group resides β to Rh in the metallacycle to avoid unfavorable steric interactions (selectivity is generally >10 : 1).\(^4\) When the substituents are electronically different, the more electron-donating group prefers being α- to rhodium in the metallacycle, presumably to stabilize the electron poor metal.\(^5,6\) The type of C–H bond being activated also plays an important role in the regioselectivity of migratory insertion; aromatic substrates typically provide synthetically useful regioselectivities when electronically different alkynes are used (>10 : 1) but alkanyl C–H activation leads to products with lower regioselectivities, presumably due to minimal steric interactions during migratory insertion.\(^7,8\) We found that sterically bulky di-\textit{tert}-butylcyclopentadienyl ligand (Cp\textsubscript{t}) enhances the regioselectivity of the alkyne migratory insertion event in these cases, delivering regioselectivities (>10 : 1) modestly above those achievable by Cp* ligated Rh complexes (<6 : 1). However, when the alkyne migratory insertion was poorly selective with RhCp* (<3 : 1), RhCp\textsubscript{t} complex was ineffective at providing synthetically useful levels of selectivity. Furthermore, the Cp\textsubscript{t} ligand was only effective with aryl substituted alkynes, presumably because of strong steric interactions between the ligand and alkyne in the insertion event.

Possible Migratory Insertion Products (1)

Previous Intermolecular Coupling with Alkenes (3) (ref 5h)

Previous Intramolecular Coupling with Alkenes (3) (ref 14a)

Proposed Ligand Controlled Alkyne Migratory Insertion (4)

Migratory insertion of alkenes to access heterocycles using C–H activation chemistry is still relatively rare, with seminal studies by Glorius and Fagnou reporting the synthesis of dihydroisoquinolones.\(^9\)–\(^11\) Similar to alkenes, alkanyl electron-
donating groups favor the position adjacent to the metal in the metallacycle delivering high regioselectivity. In contrast to alkenes, aliphatic alkene afford product with poor regioselectivity (2 : 1) (eqn 2).\textsuperscript{9,10} We hypothesized competing steric and electronic effects cause the low regioselectivity, with steric effects favoring the formation of a 4-substituted product and electronics favoring the formation of a 3-substituted product.\textsuperscript{11}

As a temporary solution to this problem, our group and others have employed tethering strategies to increase the regioselectivity of the migratory insertion event (eqn 3).\textsuperscript{11,12} Of course, regioselectivity controlled by the ligand on Rh would be the optimal solution to the selectivity problem (eqn 4). Consequently, we focused our attention toward developing an intermolecular variant of this reaction that would provide product with improved regioselectivity.

As a model system, we explored the impact ligands have on the coupling of O-pivaloyl-benzhydroxamic acid 1a with 1-decene 2a to provide dihydroisoquinolones 3a and 3a'. When Cp* is used as a ligand, the desired products are isolated in excellent yield but poor selectivity (2.4 : 1 3a : 3a') (Table 1, entry 1).

To determine the effect that ligand electronics have on product regioselectivity, we employed an electron deficient 1-trifluoromethyl-2,3,4,5-tetramethylcyclopentadienyl ligand originally developed by Gassman (CpCF\textsubscript{3})\textsuperscript{17} and found that this catalyst provides 3a and 3a' products in good yield but without an increase in selectivity (2.4 : 1) (Table 1, entry 2).\textsuperscript{18,19} Since ligand electronics did not appear to affect product regioselectivity, we tested an electron rich, sterically bulky di-phenyltri-methyl Cp ligand (Cp\textsuperscript{t}) and were pleased to find a remarkable increase in selectivity from 2.4 : 1 to 12 : 1 (3a : 3a').

Having demonstrated that Cp\textsuperscript{t} is able to substantially increase the regioselectivity of alkene migratory insertion, we explored the scope of O-pivaloyl benzhydroxamic acids amenable to this reaction. We were pleased to find para-substituted benzhydroxamic acids are well tolerated (50–76% yields) with both Cp* and Cp\textsuperscript{t} ligands. Notably, the low regioselectivity of <2.2 : 1 seen using [RhCp*Cl\textsubscript{2}]\textsuperscript{2} is dramatically improved with [RhCp'Cl\textsubscript{2}]\textsuperscript{2} giving excellent regioselectivities of >14 : 1 (Table 2, entries 1–4). Electron rich amides derived from gallic acid provide product in excellent yield and regioselectivity (Table 2, entry 5). Finally, heterocyclic amides are both well tolerated under the reaction conditions and responsive to the sterically bulky ligand, providing product with excellent regioselectivity (Table 2, entries 6–7).

\textit{meta}-Substituents also provide exquisite levels of regioselectivity for alkene migratory insertion when Cp\textsuperscript{t} is used (>15 : 1) (Table 3). Interestingly, when Cp\textsuperscript{t} is used the C–H activation occurs exclusively at the 6-position; we suggest that this selectivity is the result of steric interactions between the 2-substituent and metal complex during concerted metallation deprotonation. Surprisingly, when Cp\textsuperscript{t} is used, the regioselectivity of the C–H activation actually decreases to afford a mixture of 2- and 6-substituted products. While on the surface the decrease of selectivity appears counterintuitive, it can be explained by the uneven distribution of steric bulk in the Cp\textsuperscript{t} ligand, which we will comment on subsequently. Not only is this decrease in selectivity mechanistically intriguing, it also offers

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|}
\hline
Entry & Starting material & Cp* & Cp'  \\
\hline 1 & X = CF\textsubscript{3} (1b) & 50 & 1.5 : 1 19 : 1  \\
2 & X = Cl (1c) & 76 & 2.2 : 1 19 : 1  \\
3 & X = OMe (1d) & 70 & 1.9 : 1 16 : 1  \\
4 & X = Ph (1e) & 75 & 1.7 : 1 14 : 1  \\
5 & X = OMe (1f) & 95 & 1.9 : 1 15 : 1  \\
6 & X = CF\textsubscript{3} (1g) & 84 & 2.5 : 1 19 : 1  \\
7 & X = OMe (1h) & 88 & 1.8 : 1 19 : 1  \\
\hline
\end{tabular}
\caption{Amide scope\textsuperscript{a}}
\end{table}

\textsuperscript{a} Reaction conditions: amide (0.2 mmol), 1-decene (0.2 mmol), precatalyst (1 mol%), CsOAc (200 mol%), MeOH (0.1 M).
an exciting opportunity to potentially reverse the regioselectivity of C–H activation.

We next explored the alkene tolerance of the method. Allyl benzene 2b furnishes a 1.6 : 1 ratio of dihydroisoquinolone with RhCp* (Table 4, entry 1). When Cp' is employed, the regioselectivity increases to 4.5 : 1. Reducing the temperature to 0 °C further increases regioselectivity to 5.1 : 1. Placing an electron-donating group on the aromatic ring increases the selectivity of insertion (Table 4, entry 2). Aryl electron withdrawing substituents do not, however, provide a change in regioselectivity relative to phenyl (Table 4, entry 3). When the aromatic ring is moved further from the alkene the regioselectivity observed with Cp* increases and yields remain high (Table 4, entries 4 and 5). Ester and ketone functional groups are tolerated without a detrimental impact on regioselectivity (Table 4, entry 6, 9, and 10). Unfortunately, alkenes bearing stereocenters are ineffective at inducing diastereoselectivity with either ligand (Table 4, entries 6 and 8). Vinyl cyclopropanes participate with good levels of regioselectivity but poor diastereoselectivity (Table 4, entry 8). Unprotected alcohols provide product in excellent yield with no sign of oxidation (Table 4, entry 7).

![Fig. 1 Impact of ligand on reaction of vinyl cyclohexane.](image)
the 3-substituted dihydroisoquinolone 4a was isolated in 90% yield with 11 : 1 regioselectivity (Fig. 1). However, when the same reaction was catalyzed by [RhCp*Cl]2, the opposite isomer 4b was isolated in 75% yield and 10 : 1 (4b : 4a) regioselectivity. Given this unexpected discovery, we were interested in gleaning insight into how Cp* influences regioselectivity of alkene migratory insertion. A competition experiment between vinyl cyclohexane 2m and 1-decene 2a run to 10% conversion favored the formation of dihydroisoquinolone 3a in >19 : 1 ratio as determined by 1H NMR. This experiment suggests that enhanced steric interactions between the substrate and ligand slow the rate of migratory insertion.

To investigate the steric differences between the RhCp* and RhCp’ systems X-ray analysis was conducted on a 5-membered RhCp’ metallacycle. While we were unable to obtain a 5-membered rhodacycle from our system, Jones and coworkers previously characterized 5-membered rhodacycle 5a from N-benzylidenemethanamine and [RhCp*Cl]2.21 We found that a similar metallacycle 5b derived from [RhCp’Cl]2 could be obtained in crystalline form under identical conditions and was evaluated by single crystal X-ray diffraction.

A comparison of the bond lengths and angles reveals several notable differences between our Cp’ rhodacycle and the Cp* rhodacycle reported by Jones (Fig. 2). The Rh–Cp centroid distance in 5b is 0.011 Å longer than 5a which is either the result of increased steric interactions, or an artifact of Cp’ being a less electron-donating ligand. While there are subtle differences in many bond lengths and angles, the most striking difference is the angle C3–Rh–Cl, which is 98.03° in 5b while only 90.09° in 5a. The angle increase is likely the result of steric interactions caused by the tert-butyl moiety being situated directly over the Rh–Cl bond. As alkene exchange presumably occurs with Cl, we suggest that steric interactions between the t-butyl of the ligand and the alkene substituent affect both the alkene coordination and 1,2-insertion events.

Based on the X-ray crystal structure and regioselectivity data, we propose the following model for regioselectivity of the 1,2-migratory insertion of alklenes, where steric contributions from the t-butyl groups influence both alkene coordination and insertion events to give high selectivity. With small alkyl alklenes, we propose that steric interactions from one t-butyl of Cp’ disfavor alkene coordination (I) and subsequent insertion to give the β-substituted product 3a* (Fig. 3). Coordination of the alkene with the steric bulk oriented away from the t-butyl group finds minimized steric interactions during coordination (II). Subsequent migratory insertion from II places the alkyl substituent α to Rh in the transition state, which we propose is able to stabilize a buildup of partial positive charge, making the α-substituted product 3a both sterically and electronically favored with Cp’. In the case of the Cp* ligand with small alkyl alklenes, neither steric nor electronic interactions dominate so low selectivity is observed.

However if the size of the alkene substituent is significantly increased, as in the case of vinyl cyclohexane, then Cp’ favors the opposite regioisomer. While certainly a puzzling result, we propose the selectivity can be explained by Cp’ rotation such that the t-butyl groups both occupy the space above the metallacycle. Cp’ rotation gears the O-piv toward the alkene coordination site disfavoring alkene coordination to this side (IV) favoring the α-substituted product 3a. At the same time, alkene coordination (III) with the cyclohexyl opposite the O-piv minimizes steric interactions enabling insertion of the large alkene and preferential formation of β-substituted product 3a*. While not conclusive, the observation that cyclohexyl alkene reacts significantly slower than n-octyl alkene suggests that migratory insertion of the cyclohexyl alkene proceeds through a higher energy and potentially highly ordered transition state, such as Cp’ rotation.

Fig. 2 X-Ray analysis.

Fig. 3 Rationale for selectivity.
Conclusions

In conclusion, we found that sterically bulky di-tert-butyl
cyclopentadienyl ligand (Cp') is effective at increasing regiose-
licity of alkene migratory insertion in the synthesis of dihy-
droisoquinolines by Rh(m) C–H activation catalysis. In contrast
to previous cases where Cp* delivers modest levels of regiose-
licity of migratory insertion (with alkynes), Cp' renders
previously non-selective reactions (with alkynes) highly regio-
selective. Furthermore, ligand control (Cp* vs. Cp') enables the
highly selective synthesis of two regioisomeric products with
vinylcyclohexanes. Finally, crystallographic evidence lends
support for a possible explanation of the enhanced regiose-
lectivity.

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