JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

COMMUNICATION

pubs.acs.org/JACS

Rhodium-Catalyzed Acylation with Quinolinyl Ketones: Carbon−Carbon Single Bond Activation as the Turnover-Limiting Step of Catalysis

Colin M. Rathbun and Jeffrey B. Johnson*

Department of Chemistry, Hope College, Holland, Michigan 49423, United States

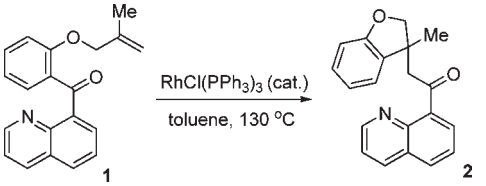
Supporting Information

ABSTRACT: The rhodium-catalyzed intramolecular carboacylation of quinolinyl ketones serves as an ideal subject for the mechanistic study of carbon−carbon bond activation. Combined kinetic and NMR studies of this reaction allowed the identification of the catalytic resting state and determination of the rate law, $^{12}C/^{13}C$ kinetic isotope effects, and activation parameters. These results have identified the activation of a ketone−arene carbon−carbon single bond as the turnover-limiting step of catalysis and provided quantitative detail into this process.

The transition metal-catalyzed activation and functionalization of carbon−carbon single bonds presents a significant challenge for organic chemists.[1] Despite the ubiquity of these bonds, the development of useful methodologies remains largely unrealized, due in part to the inherent challenges of carbon−carbon bond stability and relative steric inaccessibility. Successful methodologies typically rely upon strategies such as ring strain[2] and enforced proximity[3,4] to achieve transition metal-catalyzed activation.[5,6] In recent years, the field has been expanding to less specialized substrates, and additional emphasis has been placed upon coupling activation with a functionalization step, most notably the insertion of alkenes and alkynes into the activated bond. Such a process can form two new carbon−carbon bonds and holds the potential for the construction of two stereocenters, leading to a rapid increase of molecular complexity.[7,8] Recent advances by several groups have demonstrated the potential of these new methods for the manipulation of carbon−carbon single bonds in methodologies that extend well beyond traditional retrosynthetic disconnects.

In accordance with the scarcity of carbon−carbon bond-activation methodology, mechanistic studies of these transition metal-catalyzed transformations are relatively sparse. To date, studied systems have been primarily limited to reactions utilizing strained substrates or the activation of carbon−nitrile bonds.[9,10] To address this shortcoming and to develop a greater understanding of the carbon−carbon bond-activation process within a catalytic cycle, we initiated a mechanistic investigation of the rhodium-catalyzed carboacylation reaction of quinolinyl ketones reported by Douglas and co-workers (Scheme 1).[7] Upon initial examination, we found this system to be particularly amenable for kinetic study due to its clean conversion with complete specificity. Our mechanistic study, including the determination of the rate law, activation parameters, and $^{12}C/^{13}C$ kinetic isotope effects, has provided heretofore unknown mechanistic detail into this unique and promising transformation and provides a quantitative measurement of the activation energy of a transition metal-catalyzed carbon−carbon single bond activation.

Scheme 1



Investigation of the intramolecular carboacylation reaction focused on the conversion of the parent substrate, quinolinyl ketone **1**, to compound **2** and utilized ^{1}H NMR spectroscopy to monitor reaction progress. In order to achieve air-free conditions and the elevated temperature required for reaction, the kinetic experiments were performed in toluene-d_8 in resealable NMR tubes. The NMR tubes were immersed in an oil bath heated to 130 °C and periodically removed for spectrum acquisition and measurement of substrate and product concentrations.

The kinetic observation of this reaction immediately yielded a surprise: a plot of the concentration of **1** versus time revealed the linear consumption of starting material through at least 80% conversion, clearly indicating that the reaction rate was independent of starting material concentration (Figure 1). The reaction rate displayed zero-order dependence upon substrate and first-order dependence upon catalyst concentration for rhodium concentrations between 0.004 and 0.02 M (4−20 mol %). These combined results provide an overall first-order rate law where $k = 4.98 \times 10^{-4}$ s^{-1} (eq 1).

$$-\frac{d[1]}{dt} = k[\mathrm{Rh}]^1[1]^0 \qquad (1)$$

Due to the similarity of the quinoline in both **1** and **2**, it is notable that no obvious product inhibition was observed during the kinetic run. To further test for inhibition, a series of kinetic runs were initiated with typical concentrations of quinolinyl ketone **1** (0.082 M) and catalyst (0.024 M) but with 0.297 M of added product **2**, conditions that mirror reaction conditions at 80% completion (inset, Figure 1). In these reactions, the initial

Received: October 27, 2010
Published: January 27, 2011

dx.doi.org/10.1021/ja109686v | J. Am. Chem. Soc. 2011, 133, 2031–2033

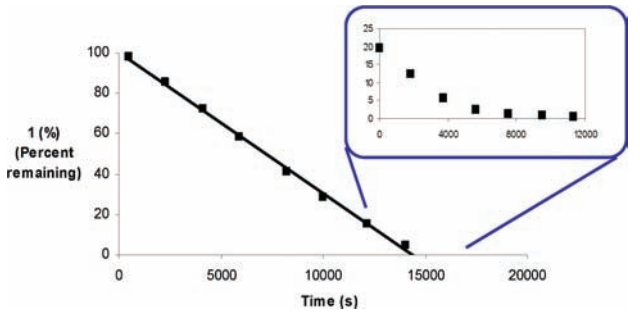
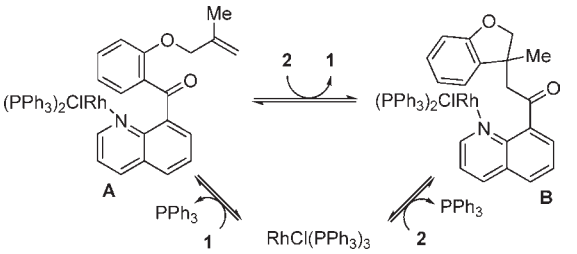


Figure 1. Plot of substrate (**1**) conversion versus time for the reaction of **1** (0.097 M) catalyzed by 0.0104 M $RhCl(PPh_3)_3$ in toluene-d_8 at 130 °C. Inset shows the results of a second experiment performed under identical conditions with the addition of 0.297 M product (**2**).

Scheme 2



rate of reaction matched the independent runs relatively closely (3.58×10^{-4} s^{-1} vs 4.98×10^{-4} s^{-1}).[11] As the reaction proceeds, however, the reaction demonstrates a rate dependence upon starting material, which accurately fits a first-order decay. These results suggest that the previously observed zero-order dependence on substrate **1** stems from saturation kinetics. Substrate **1** binds the rhodium catalyst much more tightly than does the product, resulting in the equilibrium of rhodium-containing species in solution lying completely toward complex **A** (Scheme 2). Sufficiently high concentrations of **2**, however, result in competitive binding to rhodium and increasing concentrations of intermediate **B**. Under such conditions, small variations in the concentrations of **1** and **2** influence the relative concentrations of **A** and **B** and thus the rate of reaction, leading to first-order substrate dependence and product inhibition (Scheme 2).[12]

To probe the influence of PPh_3 upon the rate of reaction, a series of kinetic runs were performed with exogenous PPh_3 concentrations between 0 and 0.108 M. Addition of PPh_3 causes reaction inhibition while simultaneously resulting in a change in the dependence on quinolinyl ketone **1**, which displays first-order kinetics under these conditions. The rate dependence upon the concentration of PPh_3 is approximately inverse first-order, as increasing concentrations of PPh_3 in a ratio of up to 5 equiv to catalyst results in increasing inhibition.

The combined observed data are consistent with competition of PPh_3 with both substrate **1** and product **2** for binding at the metal center, suggesting that $RhCl(PPh_3)_3$ must lose an equivalent of PPh_3 prior to catalysis. In the absence of exogenous PPh_3, the zero-order dependence can be rationalized with the assignment of intermediate **A**, a rhodium−quinoline complex, as the resting state of catalysis, with only minimal concentrations of **B** and $RhCl(PPh_3)_3$ (Scheme 2). The addition of PPh_3, however,

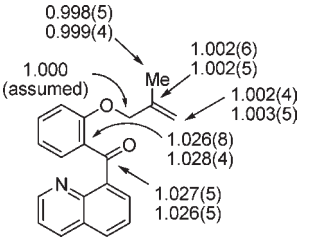


Figure 2. Observed $^{12}C/^{13}C$ kinetic isotope effects for select carbons during the carboacylation of **1**.

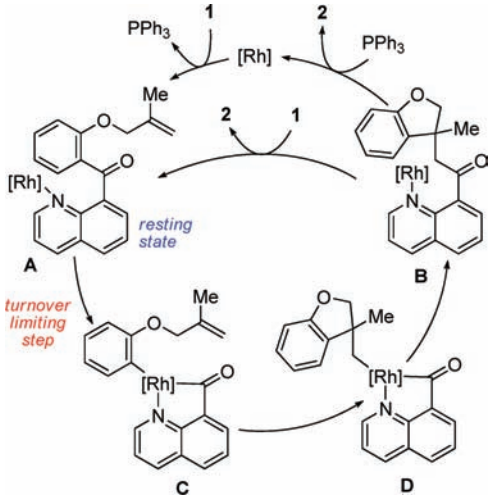
causes a shift in the equilibrium from **A** back toward $RhCl(PPh_3)_3$, resulting in a reduced reaction rate.

Due to the intramolecular nature of this reaction, it is impossible to probe the relative energies of the proposed activation (oxidative addition), alkene insertion, and reductive elimination steps by traditional kinetic means. Numerous studies support the assumption that reductive elimination of a carbon−carbon bond should occur very quickly relative to activation and insertion,[13,14] and thus we focused on differentiating between turnover-limiting activation and insertion. We turned to the Singleton method[15] to measure the $^{12}C/^{13}C$ kinetic isotope effects, thus allowing us to ascertain the potential involvement of the ketone and/or the alkene in the turnover-limiting step of catalysis. Turnover-limiting activation of the carbon−carbon bond would be expected to result in isotope effects on the ketone and α-carbons with little effect on the alkene carbons. In contrast, rate limiting alkene insertion should result in kinetic isotope effects on the alkene carbons and on the adjacent aromatic carbon, with little effect on the ketone. Two gram scale reactions were run to approximately 90% conversion, and the reisolated starting material was examined for ^{13}C content using quantitative ^{13}C NMR spectroscopy. The $^{12}C/^{13}C$ kinetic isotope effects were determined for a number of carbons, including the ketone and adjacent α carbons and the alkene, with the results summarized in Figure 2.[16] Significant isotope effects were observed at the ketone and aromatic carbons (1.027 ± 0.005 and 1.026 ± 0.005 for the ketone, and 1.026 ± 0.008 and 1.028 ± 0.004 for the aromatic carbon), while negligible isotope effects on the alkene carbons (less than 1.003 in all experiments) suggest the lack of involvement in the rat-limiting step. Taken together, these results suggest that carbon−carbon bond activation is the turnover-limiting step of catalysis.[17] The observation of kinetic isotope effect on both the ketone and aromatic carbons provides clear support for an oxidative addition-type activation of the carbon−carbon single bond and the intermediacy of a rhodium−acyl−arene species (intermediate **C** in Scheme 3.)[10]

These results, in conjunction with the previously determined rate law, are consistent with the catalytic cycle provided in Scheme 3. Under typical reaction conditions, the reaction follows saturation kinetics, and **A** is the resting state of catalysis; with sufficient product concentration, inhibition is observed. The addition of exogenous PPh_3 pushes the equilibrium of rhodium-containing species toward $RhCl(PPh_3)_3$ and changes the rate law to one that displays first-order dependence on the quinolinyl ketone. The nature of the intermediates **C** and **D** cannot be directly probed as they occur following the turnover-limiting step, and the understanding of the relationship of **A**, **B**, and $RhCl(PPh_3)_3$ is limited to inferences from the inhibitory nature of excess product and PPh_3 on the rate of reaction.

dx.doi.org/10.1021/ja109686v |*J. Am. Chem. Soc.* 2011, 133, 2031–2033

Scheme 3



Finally, quantitative information about carbon−carbon single bond activation as the turnover-limiting step of catalysis was obtained through kinetic runs performed between 110 and 140 °C. These results led to the determination of the activation parameters, $\Delta H^{\ddagger} = 27.8 \pm 1.0$ kcal/mol and $\Delta S^{\ddagger} = -4.3 \pm 2.4$ eu. The relative neutrality of the activation entropy is consistent with **A** as the resting state and the activation of **A** to generate **C** as the turnover limiting step, as little change in the overall molecular organization would be expected in this sequence.

Herein we have provided quantitative insight into the mechanism of transition metal-catalyzed carbon−carbon bond activation by Wilkinson's catalyst. From a resting state of a rhodium-quinolinyl species, the reaction proceeds via turnover-limiting activation of a Csp^2-Csp^2 ketone−aryl bond as indicated by the $^{12}C/^{13}C$ kinetic isotope effect determination. The quantitative measurement of the energy requirement for carbon−carbon bond activation within the context of the catalytic cycle provides a means by which to gauge future catalysts and will prove valuable in the process of developing more general and synthetically applicable carbon−carbon bond-activation methodology.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures, including spectral and kinetic data. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author
jjohnson@hope.edu

■ ACKNOWLEDGMENT

We thank the Camille and Henry Dreyfus Foundation and the Research Corporation for funding. J.B.J. also thanks the Towsley Foundation for support. We also gratefully acknowledge funding for instrumentation from the NSF (CHE-0922623).

■ REFERENCES

(1) (a) Murakami, M.; Ito, Y. In *Activation of Unreactive Bonds and Organic Synthesis*; Murai, S., Ed.; Springer: Berlin, 1999; p 97. (b) Crabtree, R. H. *Chem. Rev.* **1985**, *85*, 245.

(2) (a) Müller, C.; Lachicotte, R. J.; Jones, W. D. *Organometallics* **2002**, *21*, 1975. (b) Kondo, T.; Kaneko, Y.; Taguchi, Y.; Nakamura, A.; Okada, T.; Shiotsuki, M.; Ura, Y.; Wada, K.; Mitsudo, T. *J. Am. Chem. Soc.* **2002**, *124*, 6824. (c) Ashida, S.; Murakami, M. *Bull. Chem. Soc. Jpn.* **2008**, *81*, 885 and references therein.

(3) (a) Jun, C.-H.; Moon, C. W.; Lee, D.-Y. *Chem.—Eur. J.* **2002**, *8*, 2422. (b) Park. Y. J.; Park, J.-W.; Jun. C.-H. *Acc. Chem. Res.* **2008**, *41*, 222 and references therein.

(4) (a) Salem, H.; Ben-David, Y.; Shimon, L. J. W.; Milstein, D. *Organometallics* **2006**, *25*, 2292. (b) Rybtchinski, B.; Milstein, D. *Angew. Chem., Int. Ed.* **1999**, *38*, 870 and references therein.

(5) For leading references, see: (a) Nečas, D.; Kotora, M. *Curr. Org. Chem.* **2007**, *11*, 1566. (b) Murakami, M.; Makino, M.; Ashida, S.; Matsuda, T. *Bull. Chem. Soc. Jpn.* **2006**, *79*, 1315. (c) Jun, C.-H. *Chem. Soc. Rev.* **2004**, *33*, 610.

(6) Significant advances have been made in the activation of C−CN bonds. For leading references, see: (a) Hirata, Y.; Yada, A.; Morita, E.; Nakao, Y.; Hiyama, T.; Ohashi, M.; Ogoshi, S. *J. Am. Chem. Soc.* **2010**, *132*, 10070. (b) Nakao, Y.; Yada, A.; Hiyama, T. *J. Am. Chem. Soc.* **2010**, *132*, 10024. (c) Najara, C.; Sansano, J. M. *Angew. Chem., Int. Ed.* **2009**, *48*, 2452. (d) Nakao, Y.; Ebata, S.; Yada, A.; Hiyama, T.; Ikawa, M.; Ogoshi, S. *J. Am. Chem. Soc.* **2008**, *130*, 12874. (e) Watson, M. P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2008**, *130*, 12594. (f) Nishihara, Y.; Inoue, Y.; Itazaki, M.; Takagi, K. *Org. Lett.* **2005**, *7*, 2639.

(7) (a) Dreis, A. M.; Douglas, C. J. *J. Am. Chem. Soc.* **2009**, *131*, 412. (b) Wentzel, M. T.; Reddy, V. J.; Hyster, T. K.; Douglas, C. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 6121.

(8) For examples of enantioselective C−C activation, see: (a) Nishimura, T.; Matsumura, S.; Maeda, Y.; Uemura, S. *Chem. Commun.* **2002**, 50. (b) Matsuda, T.; Shigeno, M.; Makino, M.; Murakami, M. *Org. Lett.* **2006**, *8*, 3379. (c) Matsuda, T.; Shigeno, M.; Murakami, M. *J. Am. Chem. Soc.* **2007**, *129*, 12086. (d) Seiser, T.; Cramer, N. *Angew. Chem., Int. Ed.* **2010**, *49*, 10163. (e) Trost, B. M.; Xie, J. *J. Am. Chem. Soc.* **2008**, *130*, 6231. (f) Reddy, V. J.; Douglas, C. J. *Org. Lett.* **2010**, *12*, 952 and ref 6e.

(9) (a) Ateşin, T. A.; Li, T.; Lachaize, S.; García, J. J.; Jones, W. D. *Organometallics* **2008**, *27*, 3811. (b) Li, T.; García, J. J.; Brennessel, W. W.; Jones, W. D. *Organometallics* **2010**, *29*, 2430. (c) Evans, M. E.; Li, T.; Jones, W. D. *J. Am. Chem. Soc.* **2010**, *132*, 16278.

(10) For kinetic studies on a related stoichiometric system, see: (a) Suggs, J. W.; Jun, C.-H. *J. Am. Chem. Soc.* **1984**, *106*, 3054. (b) Suggs, J. W.; Jun, C.-H. *J. Am. Chem. Soc.* **1986**, *108*, 4679.

(11) These values assume a first-order dependence upon rhodium throughout the reaction.

(12) The reason for stronger binding of **1** is unclear. Alkene coordination is not apparent in ^{1}H NMR spectra taken of stoichiometric solutions of $RhCl(PPh_3)_3$ and substrate **1** in toluene-d_8 at 80 °C.

(13) For leading references, see: (a) Brown, J. M.; Cooley, N. A. *Chem. Rev.* **1988**, *88*, 1031. For discussion within a catalytic cycle, see: (b) Espinet, P.; Echavarren, A. M. *Angew. Chem.,Int. Ed.* **2004**, *43*, 4704. (c) Denmark, S. E.; Sweis, R. F. *J. Am. Chem. Soc.* **2004**, *126*, 4876. (d) Jones, G. D.; Martin, J. L.; McFarland, C.; Allen, O. R.; Hall, R. E.; Haley, A. D.; Brandon, R. J.; Konovalova, T.; Desrochers, P. J.; Pulay, P.; Vicic, D. A. *J. Am. Chem. Soc.* **2006**, *128*, 13175.

(14) For an exception, see: Johnson, J. B.; Bercot, E. A.; Rowley, J. M.; Coates, G. W.; Rovis, T. *J. Am. Chem. Soc.* **2007**, *129*, 2718.

(15) (a) Singleton, D. A; Thomas, A. A. *J. Am. Chem. Soc.* **1995**, *117*, 9357. (b) Frantz, D. E.; Singleton, D. A.; Snyder, J. P. *J. Am. Chem. Soc.* **1997**, *119*, 3383.

(16) See Supporting Information for complete results and the experimental method.

(17) This interpretation of the observed kinetic isotope effects assumes the rapid exchange of **1** with intermediate **A** relative to C−C activation. In contrast, slow exchange would be expected to result in negligible kinetic isotope effects.