Homogeneous Catalysis

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Chemoselectivity in Catalytic C–C and C–H Bond Activation: Controlling Intermolecular Carboacylation and Hydroarylation of Alkenes**

*Michael T. Wentzel, Venkata Jaganmohan Reddy, Todd K. Hyster, and Christopher J. Douglas**

A major challenge in the development of carbon–carbon σ-bond (C–C) activation is competitive activation and functionalization at C–H bonds,[1] which are typically more accessible to metal catalysts (Figure 1). As a result, catalytic C–C or *ortho*-C–H activation of ketones is controlled by the appropriate choice of catalyst and solvent.

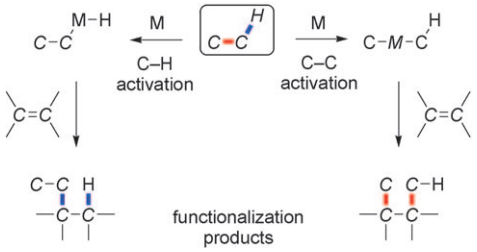
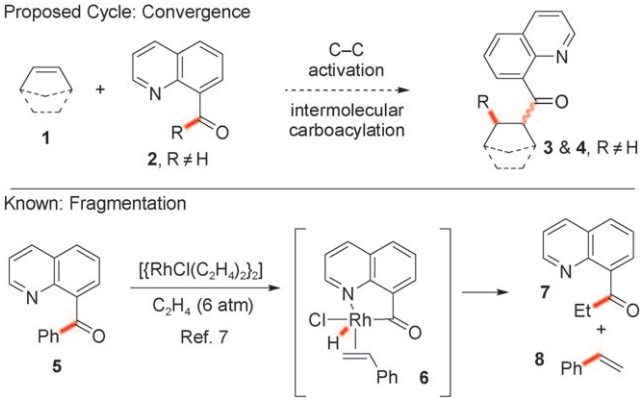


Figure 1. C–C and C–H activation reactions.

C–C activation and functionalization is an under-developed strategy in synthetic organic chemistry.[2] We are aware of only a few prior studies in which competitive C–C and C–H activation pathways can be controlled. A series of reports from Nakao, Hiyama et al. elegantly demonstrated that nickel-catalyzed aryl C–CN or *ortho*-C–H activation can be controlled by ligand or substrate choice.[3] In both cases an alkyne was inserted into the activated bond. Jones and co-workers studied competitive C–CN and C–H activation reactions in allyl cyanides.[4] Milstein and co-workers have extensively studied C–C and C–H activation in toluene-based pincer systems.[5]

As organic substrates for C–C and C–H bond activation become more complex, controlling competing pathways becomes critically important. To this end, we are investigating direct inter- and intramolecular[6] alkene carboacylation with unstrained ketones by C–C activation. Herein, we report that

Our success with intramolecular carboacylation[6] led us to contemplate an intermolecular variant (**1** + **2**→**3** + **4**, Scheme 1) for convergent syntheses. Previously, C–C activa-



Scheme 1. Catalytic C–C activation reactions with 8-acylquinolines.

tion of **5** with $[\{RhCl(C_2H_4)_2\}_2]$ and excess C_2H_4 yielded fragmentation products **7** and styrene (**8**) via a Rh-H intermediate (**6**).[7] This unusual hydroacylation provides the products in good yield, but C_2H_4 was the only alkene capable of this reaction.[8]

We chose [2.2.1]bicycloheptenes for initial study to avoid intermediates with accessible *syn*-β-hydrides. We heated equimolar amounts of **5** and norbornene for 24 h in the presence of rhodium catalysts (Table 1). Although Wilkinson's catalyst was ineffective (entry 1), $[\{RhCl(C_2H_4)_2\}_2]$ resulted in the formation of a new product (**10**).[9,10] This C–H activation is likely directed by the oxygen atom of the ketone. In CH_3CN, the conversion decreased, but a small amount of carboacylation product **9** formed (entry 3).[11,12] A switch to $[Rh(cod)_2]OTf$ provided higher conversion, but poor chemoselectivity (entry 5). A solvent screen (entries 6–9) showed that the product distribution depended on the solvent, with THF providing complete selectivity for **9** (entry 9). It is remarkable that one can select exclusive C–C or C–H activation and functionalization by the appropriate choice of catalyst and solvent. The addition of phosphine ligands to the $[Rh(cod)_2]OTf$/THF reactions decreased the yield without affecting the **9**/**10** ratio (entries 10 and 11). In all cases, **9** and **10** were obtained with good diastereocontrol (>95:5 by ^1H NMR spectroscopy). Excess alkene (10 equiv)

[*] M. T. Wentzel, V. J. Reddy, T. K. Hyster,[+] Prof. C. J. Douglas
Department of Chemistry, University of Minnesota
Twin Cities, 207 Pleasant St. SE, Minneapolis, MN 55455 (USA)
Fax: (+1) 612-626-7541
E-mail: cdouglas@umn.edu

[+] UMN Undergraduate Research, 2007–2008.

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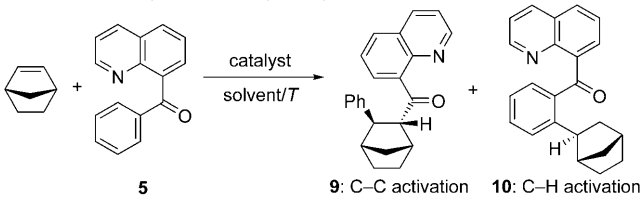
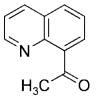
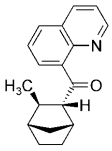
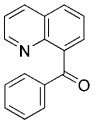
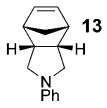
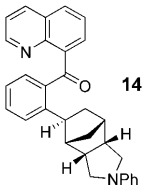
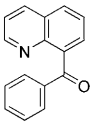
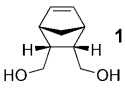
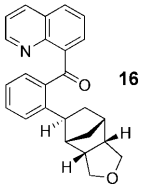
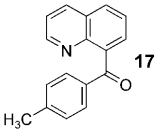
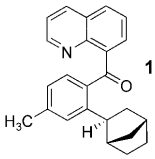
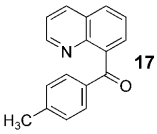
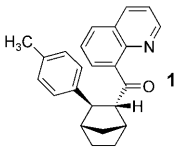
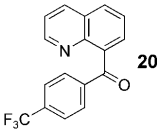
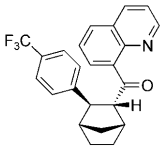
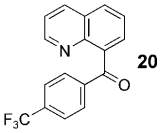
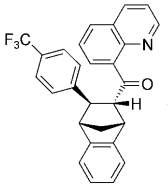
Table 1: Carboacylation and hydroarylation with **5**.



Entry	Catalyst[b]	Solvent	*T*	Yield, **9**/**10**[a]
1	$[Rh(PPh_3)_3]Cl$	$PhCH_3$	130 °C	>10%, –
2	$[\{RhCl(C_2H_4)_2\}_2]$[c]	$PhCH_3$	130 °C	**79%, 0:1**
3	$[\{RhCl(C_2H_4)_2\}_2]$[c]	CH_3CN	100 °C	35%, ≈1:20
4	$[Rh(cod)_2]BF_4$	$PhCH_3$	130 °C	38%, 1:6
5	$[Rh(cod)_2]OTf$	$PhCH_3$	130 °C	56%, 4:5
6	$[Rh(cod)_2]OTf$	$PhCF_3$	130 °C	44%, 1:5
7	$[Rh(cod)_2]OTf$	$(CH_2Cl)_2$	130 °C	62%, 1:7
8	$[Rh(cod)_2]OTf$	CH_3CN	100 °C	41%, 5:3
9	$[Rh(cod)_2]OTf$	THF	100 °C	**50%, 1:0**
10	$[Rh(cod)_2]OTf$	THF[d]	100 °C	20%, 1:0
11	$[Rh(cod)_2]OTf$	THF[e]	100 °C	12%, 1:0

[a] Yields and ratios by ^{1}H NMR spectroscopy with an internal standard. [b] Catalyst loading 10 mol% unless otherwise noted. [c] 5 mol% catalyst used. [d] With 20 mol% PPh_3. [e] With 20 mol% $P(t\text{Bu})_3$. The values in bold show the most selective reactions. cod = 1,5-cyclooctadiene, THF = tetrahydrofuran, OTf = trifluoromethane sulfonate.

Table 2: Variation of the quinoline and alkene substrates.

Quinoline	Alkene	Cond.[a]	Products	Yield[b]
 **11**		A	 **12**	39% (60%)
 **5**	 **13**	A	 **14**	44% (65%)
 **5**	 **15**	A	 **16**	41% (60%)
 **17**		A	 **18**	44% (64%)
 **17**		B	 **19**	30%, (66%), **18**/**19**; 1:1
 **20**		B	 **21**	24%
 **20**	 **22**	B	 **23**	24%

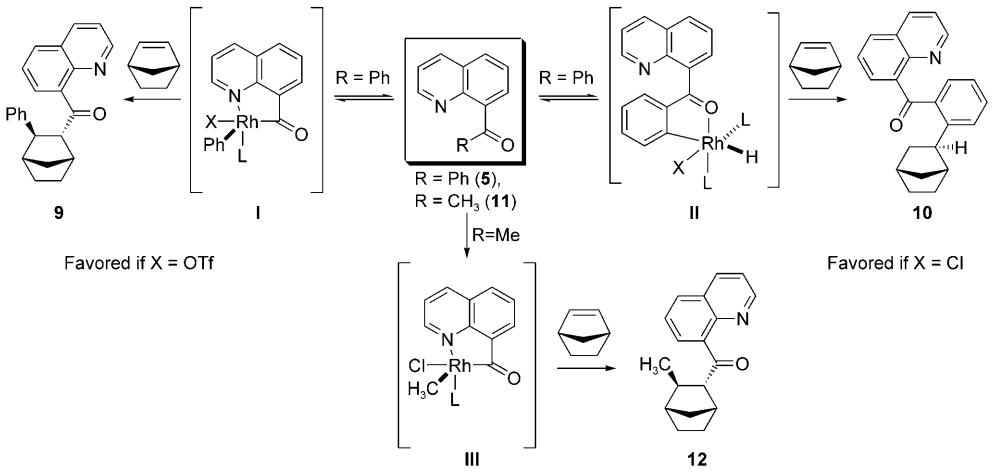
[a] Conditions A: $[\{RhCl(C_2H_4)_2\}_2]$ (5 mol%), $PhCH_3$, 130 °C, 24 h. Conditions B: $[Rh(cod)_2]OTf$ (10 mol%), THF, 100 °C, 24 h. [b] Yields after chromatography, (%) yields based on recovered starting material.

did not improve the yields of **9** and **10** under the conditions shown for entries 9 and 2, respectively.

We examined other 8-acylquinolines with bridged cycloalkenes (Table 2). We used the optimized conditions from Table 1 to examine substituent effects rather than reoptimize each substrate pair. Exchanging the 8-benzoyl group for acetyl resulted in C–H activation products being avoided altogether, even when $[\{RhCl(C_2H_4)_2\}_2]$ was used in $PhCH_3$ (conditions A). The use of functionalized alkenes (**13** and **15**) increased the propensity of **5** to undergo hydroarylation rather than carboacylation. Alkenes **13** and **15** did not undergo carboacylation even with [Rh(cod)]OTf in THF (conditions B). Diol **15** underwent spontaneous cyclization to a THF ring along with concurrent hydroarylation. By adding a *para*-CH_3 group (**17**, Table 2), selectivity was complete for C–H activation under conditions A, but conditions B gave an approximately 1:1 mixture of **18** and **19**. Changing the CH_3 group of **17** to CF_3 (**20**) suppressed the C–H activation pathway, thus suggesting that more-electron-rich aryl ketones undergo C–H activation more readily under conditions B. When alkene **22** was used, the yield was similar, but the diastereomer ratio decreased (ca. 4:1, *anti*/*syn*).

One hypothesis to explain these data is equilibration of the carboacylation product **9** to the hydroarylation product **10** with $[\{RhCl(C_2H_4)_2\}_2]$ in $PhCH_3$. Since C–C activation is sometimes thought to be reversible,[13] and β-carbon elimination in norbornyl systems is also known,[14,15] we tested this hypothesis by subjecting pure **9** to conditions A. No trace of **10** was detected by ^{1}H NMR spectroscopy, thereby ruling out this rationale.

Based on our findings and previous results, we presume that **5** can form two possible intermediates (**I** and **II**, Scheme 2). Using the same catalyst/solvent combination as used in previous C–C activation studies,[6,7] we exclusively form the product resulting from C–H activation (**10**). Since both **I** and **II** are accessed under these conditions and since **9** and **10** do not equilibrate, we conclude that **II** is simply more apt toward migratory insertion than **I** when chloride is present in a nonpolar solvent. By changing the catalyst counterion (OTf), a mixture of both C–H (**9**) and C–C (**10**) activated products was formed [Table 1, entry 4]. Furthermore, by switching to a more polar solvent (THF) with OTf as the counterion, the C–C activation pathway is selected exclusively. When R = Me (**11**), only C–C activation (**III**) occurs—



Scheme 2. Mechanistic considerations.

despite the use of chloride in a nonpolar solvent—since an intermediate analogous to **II** cannot form.[16]

We have reported the activation of an unstrained C–C σ bond and subsequent intermolecular carboacylation of an olefin that forms two new C–C σ bonds. According to our knowledge, this is the first reported example of its kind. These results provide a basis for controlling C–C and C–H activation reaction pathways, which will help in the development of future catalytic C–C activation reactions.

Experimental Section

Representative procedure for carboacylation (C–C activation): Quinoline **5** (25.2 mg, 0.11 mmol), norbornene (10.3 mg, 0.11 mmol), and $[Rh(cod)_2]OTf$ (5.2 mg, 0.011 mmol) were suspended in THF (0.325 mL). The reaction vessel was sealed under N_2 with a Teflon-lined screw-cap, heated to 100 °C, and maintained for 24 h. The reaction was allowed to cool to room temperature and filtered through Celite with the aid of ethyl acetate (5 mL). The filtrate was concentrated and the resulting residue was analyzed by ^1H NMR spectroscopy with 4-methoxyacetophenone as an internal standard (50% yield from **5**). Concentration and purification by column chromatography (ethyl acetate/hexanes) provided **9** as an oil (18.0 mg, 0.55 mmol, 50%): see the Supporting Information for details.

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[8] The authors did not specify the alkenes examined, reporting, "The exchange reaction with alkenes other than ethylene was not efficient." See Ref. [7].

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[12] See the Supporting Information.

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