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Catalytic Carbon−Carbon σ Bond Activation: An Intramolecular Carbo-Acylation Reaction with Acylquinolines

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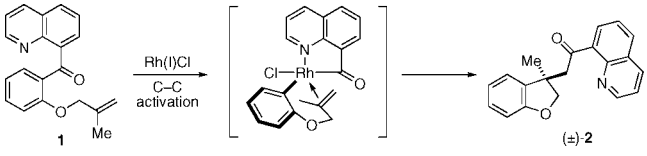
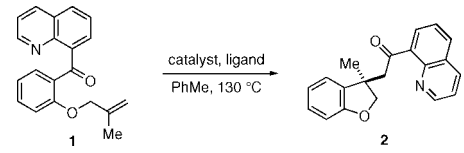
Carbon−carbon sigma-bond activation has emerged as a contemporary challenge for organometallic chemistry.[1] Similar to the recent emergence of C−H activation in synthetic chemistry, C−C σ bond activation could change the way chemists approach the construction of complex molecules by allowing nontraditional retrosynthetic disconnections.[2] To be an effective synthetic strategy, the activation of a C−C σ bond should result in metal−carbon bonds that can be converted into a more complex product. The most common C−C σ bond activation processes involve either the release of ring strain or aromatization to overcome the high kinetic barriers associated with the activation step.[3,4] An alternative strategy is to utilize functional groups to direct a metal to a particular C−C bond, allowing activation to take place. In the 1980s, it was demonstrated that rhodium can be directed by the nitrogen of a quinoline to activate the C−C bond of a ketone at the 8-position.[5] Since then, a variety of additional systems that exploit chelation-assisted C−C activation have been discovered.[1] Catalytic activation and functionalization of unstrained C−C bonds by these methods, however, are often fragmentation reactions, wherein one metal carbon bond is converted into a low value byproduct.[6−8] For example, 8-benzoylquinoline can be catalytically fragmented under ethylene pressure to deliver styrene and ethyl quinolinyl ketone via hydroacylation.[9] Developing processes that allow atom economical[10] use of unstrained C−C σ bonds as versatile synthons for the construction of complex molecules remains a contemporary challenge. Herein, we report a rhodium-catalyzed C−C σ bond activation process that performs the first direct alkene carboacylation starting from a ketone, which allows the construction of an all-carbon quaternary center (Scheme 1).[11]

Scheme 1



In our initial attempts to convert alkene **1** to benzofuran **2**, we found that many combinations of rhodium(I) complexes and phosphines would catalyze the transformation in good to excellent yields (Table 1). An exception was the use of BINAP, which favored alkene isomerization rather than C−C activation and cyclization. Omitting phosphine ligands from the reaction mixture did not prevent cyclization. With 5 mol % $\{RhCl(C_2H_4)_2\}_2$ or Wilkinson's catalyst, benzofuran **2** was formed in excellent yield (entries 1 and 3).[12] Attempts to use other late-metal alkene complexes such as Pd_2dba_3 or $Ni(COD)_2$ did not result in the formation of **2** according to ^{1}H NMR analysis of the crude reaction mixtures, returning only **1**. Lowering the $RhCl(PPh_3)_3$ loading to 2 mol % gave a slightly lower yield after 48 h, with the remainder of the material being unreacted **1**.

Table 1. Optimization of Catalytic Conditions



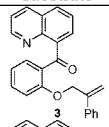
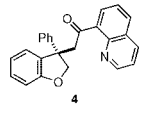
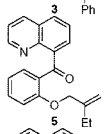
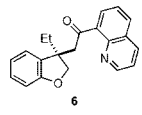
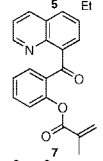
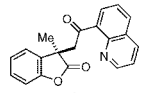
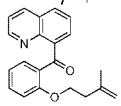
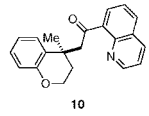
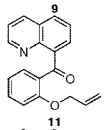
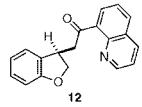
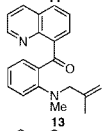
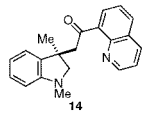
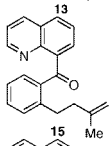
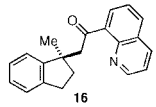
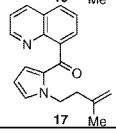
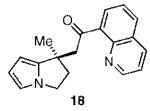
entry	catalyst	mol %	L_n	yield **2** (%)
1	$\{RhCl(C_2H_4)_2\}_2$	5	none	*95*
2	$Rh(OTf)(COD)_2$	5	none	62
3	$RhCl(PPh_3)_3$	10	none	*96*
4	$RhCl(PPh_3)_3$	2	none	90[a]
5	$\{RhCl(C_2H_4)_2\}_2$	5	PCy_3	62
6	$\{RhCl(C_2H_4)_2\}_2$	5	PMe_3	53
7	$Rh(OTf)(COD)_2$	5	PMe_3	72
8	$Rh(OTf)(COD)_2$	5	BINAP	<5[b]
9	Pd_2dba_3	5	none	0
10	$Ni(COD)_2$	5	none	0
11	Pd_2dba_3	5	PPh_3	0[a,c]
12	$Ni(COD)_2$	5	PPh_3	0

[a] As determined using ^{1}H NMR spectroscopy after 48 h. [b] The major product resulted from alkene isomerization to an enol ether. [c] Cleavage of the allyl ether to the corresponding phenol was the major product.

With identification of the optimal reaction conditions, the scope of the reaction was investigated (Table 2). Styrenyl alkene **3** was also an excellent substrate, and cyclization provided product **4**, which contains a diaryl all-carbon quaternary center (entry 1). The reaction tolerated electron-deficient alkenes, as methacrylate ester **7** cyclized to benzofuranone **8** in 80% yield (entry 3). The cyclization of **7** required the addition of a small amount (10 mol %) of hydroquinone to inhibit thermal polymerization of the methacrylate ester. The tether length between the activated C−C σ bond could be extended allowing for the synthesis of a dihydrobenzopyran **10** from alkene **9** in 81% yield (entry 4). Although we expected competitive pathways involving beta-hydrogen elimination to complicate cyclizations involving alpha-olefins such as **11** (entry 5), this did not appear to be the main problem with the substrate. Rather, cleavage of the allyl ether to the phenol in substrate **11** proved to be the dominant decomposition pathway. A 25% yield of the corresponding dihydrobenzofuran **12** was obtained from reaction of **11** when $Rh(OTf)(COD)_2$ was the catalyst. A substrate in which the alkene was tethered by a nitrogen (entry 6) cyclized very slowly with $\{RhCl(C_2H_4)_2\}_2$ as the catalyst, with **13** reaching ~10% conversion to **14** after 48 h (^{1}H NMR). Wilkinson's catalyst proved optimal for this nitrogen-tethered substrate, providing dihydroindole **14** in good yield. The alkene did not require a heteroatom linker, as dihydroindene **16** was prepared in 93% yield from substrate **15** (entry 7). The aryl ketone

10.1021/ja8066308 CCC: $40.75

Table 2. Intramolecular C−C Activation/Carboacylation Reactions[c]

entry	substrate	cond.	product	% yield[a]
1	 **3**	A	 **4**	94
2	 **5**	A	 **6**	82
3	 **7**	A	 **8**	80[b]
4	 **9**	A	 **10**	81
5	 **11**	B	 **12**	25
6	 **13**	C	 **14**	75
7	 **15**	A	 **16**	93
8	 **17**	A	 **18**	63

[a] Isolated yield after chromatography with SiO_2. [b] Reaction stopped after 24 h. [c] Condition A: 5 mol% $\{RhCl(C_2H_4)_2\}_2$, PhMe, 130 °C, 48 h. Condition B: 5 mol% $Rh(OTf)(COD)_2$, PhMe, 130 °C, 24 h. Condition C: 10 mol% $RhCl(PPh_3)_3$, PhMe, 130 °C, 24 h.

group was also replaced with a pyrrole (**17**, entry 8) providing dihydropyrrolizine **18** in 63% yield after cyclization of **17**.

The origins of the diminished reactivity of the phosphine-free catalysts with the anthranilic ketone-derived substrate (**13**) are unclear. We speculate that the C−C activation step is slower in the series because the ketone is less electrophilic, owing to electron donation from the 2-amino group. The addition of triphenylphosphine ligands might make the rhodium catalyst more nucleophilic, allowing the metal to attack the carbonyl and initiate the C−C activation. An alternative hypothesis is that the anthranilic ketone functional group sequesters the catalyst by nonproductive coordination, inhibiting C−C activation. To test this latter hypothesis, we mixed **1** and **13** and heated the mixture in the presence of 5 mol % $\{RhCl(C_2H_4)_2\}_2$. Analysis of the crude reaction mixture by ^1H NMR indicated complete consumption of **1** and the formation of **2**, which disfavors the catalyst deactivation hypothesis.

In summary, we have disclosed a new alkene carboacylation reaction initiated by quinoline-directed, rhodium-catalyzed C−C bond activation. The alkene carboacylation allows for the construction of all-carbon quaternary centers, with a broad substrate scope, providing access to carbocyclic and heterocyclic compounds in good to excellent yields. Current efforts are directed toward both intermolecular and asymmetric carboacylation as well as discovering other new catalytic processes triggered by C−C σ bond activation.

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Supporting Information Available: Experimental procedures, tabulated data, copies of NMR spectra, and copies of 2D NMR for compound **2** are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Compound **2** was characterized by ^1H NMR, ^{13}C NMR, COSY, HMQC, HMBC, IR, and MS. See Supporting Information for details.

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