C–O Activation

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Insertion of an Alkene into an Ester: Intramolecular Oxyacylation Reaction of Alkenes through Acyl C–O Bond Activation**

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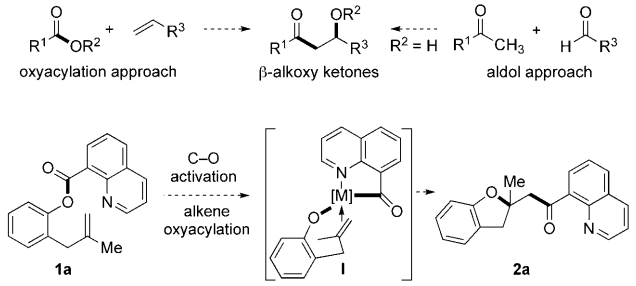
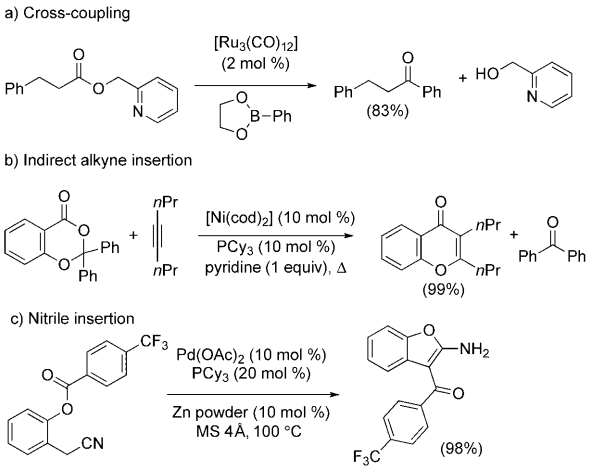
β-Alkoxyketones are common intermediates in organic synthesis. An unusual approach to this class of compounds could be the insertion of a C=C bond into an ester, a potentially atom economical process (Scheme 1). This alkene "oxyacylation" could be an alternative to the aldol reaction.[1] Atom economy and ester manipulation, however, are rarely compatible: esters usually fragment after reactions with nucleophiles, or decarbonylate when activated with transition metals.[2] In the rare cases when the acyl C–O bond is activated and decarbonylation is suppressed, the acyl metal alkoxide complexes can undergo additional transformations,[3,4] but only with the expulsion of an alcohol (Scheme 2a)[3b–f] or ketone (Scheme 2b).[3a] We are aware of one example where acyl C–O activation provided products containing the original atoms: Ohe's recent Pd-catalyzed nitrile insertion into an acyl C–O bond, followed by rearrangement (Scheme 2c).[4] The challenge of productive acyl C–O bond activation is accentuated by the frequent reports of the reverse reaction: when acyl metal alkoxides are accessed by other means, they readily undergo reductive elimination to form esters.[5]



Scheme 1. Alkene oxyacylation.

We postulated that a chelating group would prevent decarbonylation by stabilizing the acyl metal complex, **I**. Our approach was akin to stoichiometric acyl C–O bond activation strategies[6–8] in which metal chelating groups were used.[6] We employed quinoline as a chelating group based on our previous successes in acyl C–C bond activation.[9] We designed an intramolecular reaction to avoid problems with regioselectivity and to increase local concentrations of alkene. Activation of **1a** to **I**, followed by migratory insertion and reductive elimination would provide **2a**, containing a cyclic ether with a ketone in a 1,3-relationship and a new fully substituted carbon center.



Scheme 2. Processes involving acyl C–O activation.

Here, we report the first example of alkene insertion into the acyl C–O bond of an ester. Beginning with **1a**, we screened Rh complexes containing various counterions (Cl, BF_4, OTf), with $[Rh(cod)_2]OTf$ (cod = cyclooctadiene) providing encouraging results (Table 1, entries 1–3). A byproduct observed in our initial study was the phenol **3a**, resulting from a formal hydrolysis of **1a**, though attempts to rigorously exclude water did not decrease the formation of **3a**. Switching to 1,2-dicholorethane as solvent, $[Rh(cod)_2]BF_4$ showed good conversion, but gave a 1:1 mixture of **2a**:**3a** (Table 1, entries 4, 5). The addition of bidentate phosphine ligands, particularly dppp, was effective at maintaining high conversion. Using the $[Rh(cod)_2BF_4]$/dppp catalyst system at higher temperature suppressed the formation of **3a** (Table 1, entries 8–11).

Using the conditions from Table 1, entry 11, we examined the scope of oxyacylation (Table 2). Both electron-donating and electron-withdrawing substituents on the aromatic linker gave products **2b–g** in good yields (Table 2, entries 1–6), although longer reaction times were required for electron-

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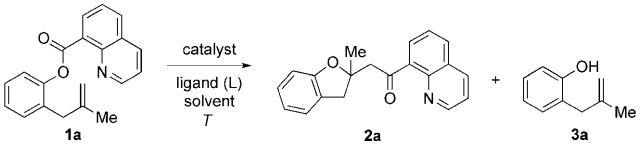
Table 1: Optimization of reaction conditions.[a]



Entry	Catalyst	L	Solvent	T [°C]	Yield of **2a** (**3a**)
1	$[Rh(PPh_3)_3Cl]$	–	PhMe	130	–
2	$[\{Rh(C_2H_4)_2Cl\}_2]$	–	PhMe	130	–
3	$[Rh(cod)_2]OTf$	–	PhMe	130	20% (37%)[b]
4	$[Rh(cod)_2]OTf$	–	DCE	110	complex mixture
5	$[Rh(cod)_2]BF_4$	–	DCE	110	40% (40%)[b]
6	$[Rh(cod)_2]BF_4$	dppe	DCE	130	–
7	$[Rh(cod)_2]BF_4$	dppb	DCE	130	40%[b]
8	$[Rh(cod)_2]BF_4$	dppp	DCE	90	25% (25%)[b]
9	$[Rh(cod)_2]BF_4$	dppp	DCE	110	65% (32%)[b]
10	$[Rh(cod)_2]BF_4$	dppp	DCE	130	82%[c]
11[d]	$[Rh(cod)_2]BF_4$	dppp	DCE/PhMe	150	85%[c]

[a] Entries 1–5: Rh catalyst 20 mol%, 0.1 M **1a**, 24 h, entries 6–11: $[Rh(cod)_2]BF_4$ (10 mol%), ligand (12 mol%), 0.05 M **1a**, 24 h. [b] Determined by ^1H NMR spectroscopy. [c] Yield after chromatography. [d] Conditions used for further substrate evaluation. Legend: dppe = 1,2-bis(diphenylphosphino)ethane, dppp = 1,3-bis(diphenylphosphino)propane, dppb = 1,4-bis(diphenylphosphino)butane, DCE = 1,2-dichloroethane.

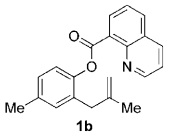
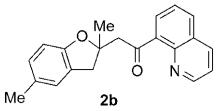
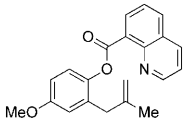
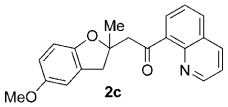
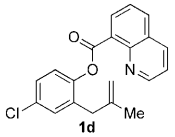
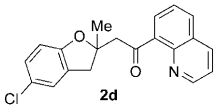
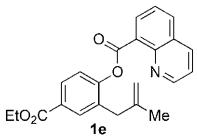
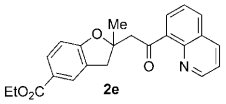
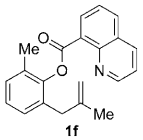
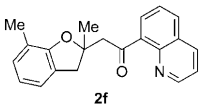
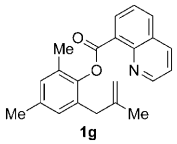
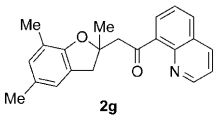
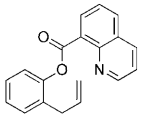
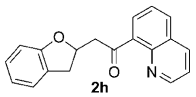
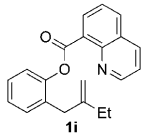
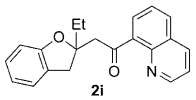
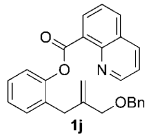
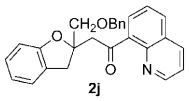
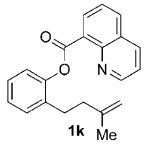
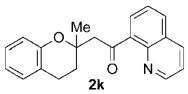
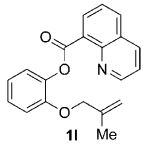
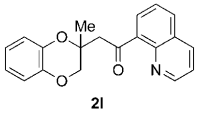
donating groups (entries 1, 2). In the presence of another ester group, acyl C–O bond activation occurred exclusively for the 8-quinoline carboxylate ester, leaving the other ester untouched (Table 2, entry 4). Substitution at the 6-position of the aromatic linker accelerated the reaction, presumably due to the restricted rotation of the acyl group (Table 2, entries 5, 6). Replacing alkene substituents with Et and CH_2OBn provided products **2i** and **2j** in good yield (Table 2, entries 8, 9). An alkene substituent is required for oxyacylation to occur; for R = H (**1h**), oxyacylation product **2h** was not observed, possibly due to facile β-hydride elimination (Table 2, entry 7).

Chromans could also be formed (Table 2, entry 10). For allylic ether **1l**, we observed oxyacylation at 130 °C, but at higher temperatures (150 °C) the product from Claisen rearrangement was formed predominantly (Table 2, entry 11).

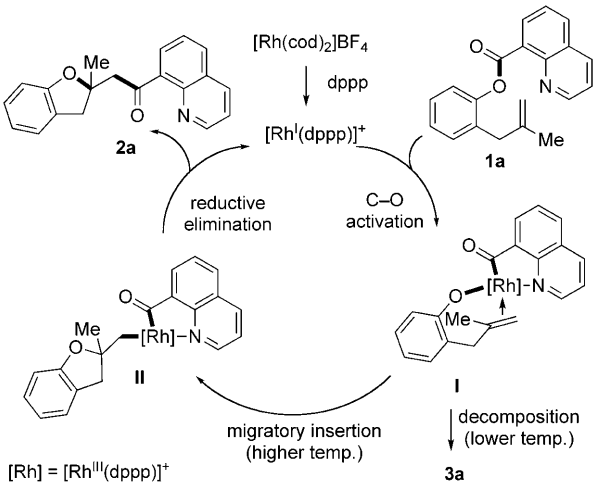
Based on the above results, we propose the following reaction mechanism (Scheme 3). Coordination to the quinoline nitrogen directs rhodium to insert into the acyl C–O bond, forming intermediate **I**. Migratory insertion of the alkene into the metal–oxygen bond,[10] followed by reductive elimination provides **2a**. A by-product observed in this reaction was phenol **3a**, which we presume is a decomposition product from intermediate **I**. Hartwig et al. reported similar decomposition of related rhodium alkoxide complexes.[11] When the reaction temperature was increased, oxyacylation product **2a** was favored and the formation of **3a** was minimized (Table 1, entires 8–11), suggesting that migratory insertion to form **II** is turnover-limiting.

In conclusion, we have reported the first direct insertion of an alkene into an acyl C–O bond to provide β-alkoxy ketones bearing a fully substituted carbon center. Decarbon-

Table 2: Reaction scope.[a]

Entry	Substrate	Product	Yield [%][b]
1[c]	 **1b**	 **2b**	79
2[c]	 **1c**	 **2c**	60[d]
3	 **1d**	 **2d**	65
4	 **1e**	 **2e**	78
5	 **1f**	 **2f**	90
6	 **1g**	 **2g**	81
7	 **1h**	 **2h**	–
8	 **1i**	 **2i**	78
9	 **1j**	 **2j**	51
10	 **1k**	 **2k**	85
11	 **1l**	 **2l**	25[e]

[a] Conditions: $[Rh(cod)_2]BF_4$ (10 mol%), dppp (12 mol%), PhMe/DCE = 8:2, 150 °C, 24 h. [b] Yield after chromatography. [c] 36 h. [d] 14% recovered **1c**, 70% **2c** based on recovered starting material (brsm). [e] 130 °C, 50% recovered **1l**, 50% **2l** brsm.



Scheme 3. Mechanistic hypothesis for oxyacylation.

ylation was suppressed by the use of a quinoline chelating group. Our results demonstrate that ester manipulation can indeed be atom economical. Current efforts focus on discovering other directing groups to expand the utility of this methodology.

Experimental Section

Representative procedure: In a nitrogen-filled glove box, a 1 dram reaction vial (Chemglass, polytetrafluoroethylene-lined cap) was charged with $[Rh(cod)_2]BF_4$ (0.01 mmol, 0.1 equiv), 1,3-bis(diphenylphosphino)propane (0.012 mmol, 0.12 equiv), and DCE (0.4 mL). The mixture was stirred at room temperature for 1 h and then transferred to a 1 dram vial containing ester **1a** (30.6 mg, 0.1 mmol, 1 equiv) and toluene (1.6 mL). The reaction mixture was maintained at 150 °C for 24 h. The mixture was then removed from the glove box and concentrated. The crude product was purified by flash column chromatography (gradient, EtOAc:Hex) to afford the product **2a** (26 mg, 0.085 mmol, 85 %).

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