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A Metallacycle Fragmentation Strategy for Vinyl Transfer from Enol Carboxylates to Secondary Alcohol C−H Bonds via Osmium- or Ruthenium-Catalyzed Transfer Hydrogenation

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Supporting Information

ABSTRACT: A strategy for catalytic vinyl transfer from enol carboxylates to activated secondary alcohol C−H bonds is described. Using XPhos-modified ruthenium(0) or osmium(0) complexes, enol carboxylate−carbonyl oxidative coupling forms transient β-acyloxy-oxametallacycles, which eliminate carboxylate to deliver allylic ruthenium(II) or osmium(II) alkoxides. Reduction of the metal(II) salt via hydrogen transfer from the secondary alcohol reactant releases the product of carbinol C−H vinylation and regenerates ketone and zero-valent catalyst.

Carbonyl vinylation is a convergent method for the synthesis of allylic alcohols that often relies on the stoichiometric use of vinylmetal reagents (Scheme 1, eq 1).[1] Metal-catalyzed alkyne−carbonyl reductive coupling[2,3] bypasses discrete use of vinylmetal reagents; however, with the exception of hydrogen-mediated processes,[3] stoichiometric reductants that are metallic, pyrophoric, and mass-intensive are often required (Scheme 1, eq 2).[2] More recently, redox-neutral alcohol−alkyne vinylations have been developed using ruthenium[4a,b] and nickel catalysts (Scheme 1, eq 3).[4c] Despite these important advances, efficient catalysts for the reductive coupling of acetylene and terminal alkynes to carbonyl partners remain elusive.[5] The E1cB-type fragmentation of metallacycles bearing leaving groups vicinal to the metal potentially offers an alternate strategy for vinyl transfer, which, to date, has only been realized in *stoichiometric* reactions of early transition metals.[6,7] Here, we introduce a general strategy for *catalytic* vinyl transfer from enol carboxylates to activated ketones based on oxidative coupling−metallacycle fragmentation pathways (Scheme 1, eq 4).[8] This method enables direct vinylation of secondary alcohol C−H bonds in vicinally dioxygenated systems (e.g., α-hydroxy esters, 1,2-diols), including the introduction of unsubstituted vinyl moieties.

Scheme 1. Convergent Methods for the Synthesis of Allylic Alcohols through Vinyl Transfer

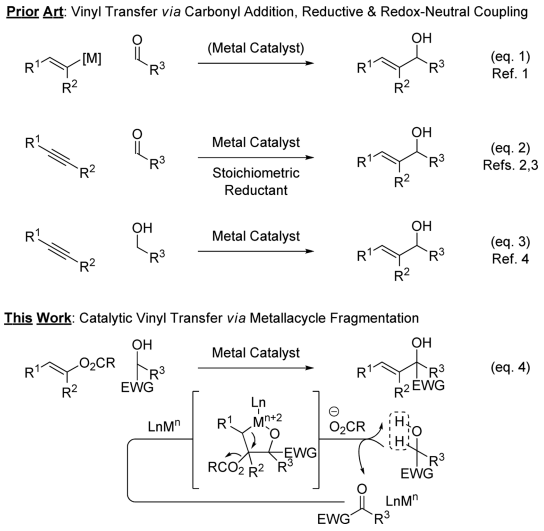
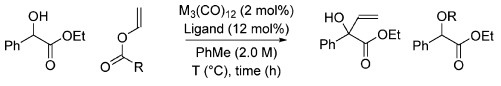
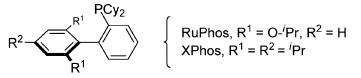


Table 1. Selected Optimization Experiments in the Redox-Triggered C−H Vinylation of Ethyl Mandelate 1a[a]



1a (100 mol%) — *O*-Ac-**2a**, R = Me; *O*-Piv-**2a**, R = ^{t}Bu — **3a** — *O*-Ac-**1a**, R = Ac; *O*-Piv-**1a**, R = Piv

Entry	**2a** (mol%)	M	Ligand	T (°C)	time (h)	**3a**:*O*-Ac/Piv-**1a**
1	*O*-Ac-**2a** (500)	-	-	130	20	trace (0:1)
2	*O*-Ac-**2a** (500)	-	XPhos	130	20	trace (0:1)
3	*O*-Ac-**2a** (500)	Ru	XPhos	130	20	29 (1:1)
4	*O*-Ac-**2a** (500)	Os	XPhos	130	20	85 (9.5:1)
5	*O*-Piv-**2a** (500)	Os	XPhos	130	24	75 (>20:1)
6	*O*-Piv-**2a** (500)	Os	XPhos	140	24	86 (>20:1)
⇨ **7**	*O*-Piv-**2a** (300)	**Os**	**XPhos**	**140**	**24**	**83** (>20:1)
8	*O*-Piv-**2a** (200)	Os	XPhos	140	24	76 (>20:1)
9	*O*-Piv-**2a** (300)	Os	RuPhos	140	24	72 (>20:1)
10	*O*-Piv-**2a** (300)	Os	PCy_3	140	24	50 (>20:1)
11	*O*-Piv-**2a** (300)	Os	PCy_2Ph	140	24	28 (>20:1)
12	*O*-Piv-**2a** (300)	Os	-	140	24	trace (>20:1)



[a]Yields are of material isolated by silica gel chromatography. See Supporting Information for further experimental details.

Initial experiments involving the reaction of ethyl mandelate **1a** with vinyl acetate **2a** were inspired by established conditions for ruthenium(0)-catalyzed C−C couplings of activated secondary alcohols with 1,3-dienes[9] and earlier studies by Chatani and Murai on the ruthenium(0)-catalyzed Pauson−Khand reaction of vicinal dicarbonyl compounds.[10] Control experiments in the absence of the precatalyst components revealed small quantities of acyl transfer to form *O*-Ac-**1a** (Table 1, entries 1 and 2). In the presence of $Ru_3(CO)_{12}$ and XPhos, ethyl mandelate **1a** and vinyl acetate **2a** reacted to form

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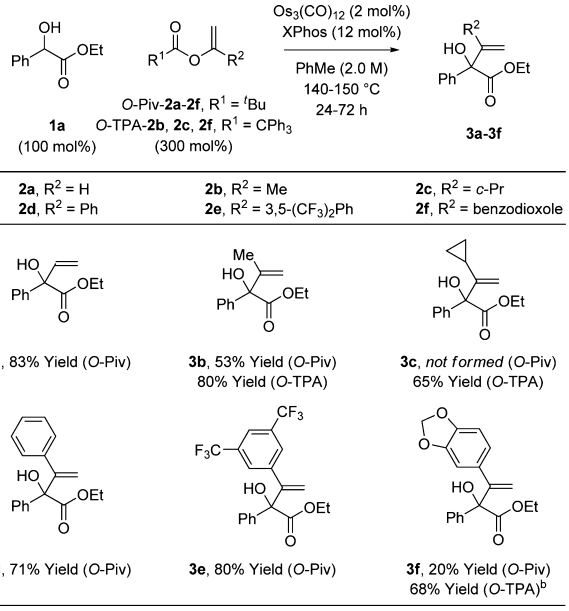
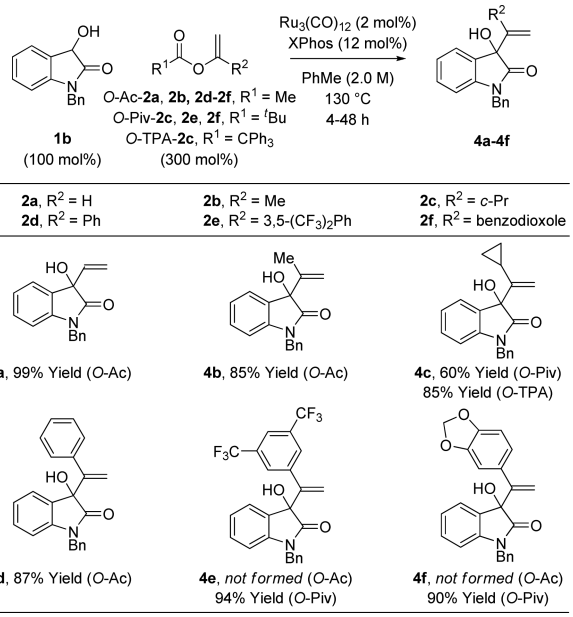
Table 2. Osmium-Catalyzed Vinyl Transfer from Enol Carboxylates 2 to Ethyl Mandelate 1a to Form 3a–3f[a]



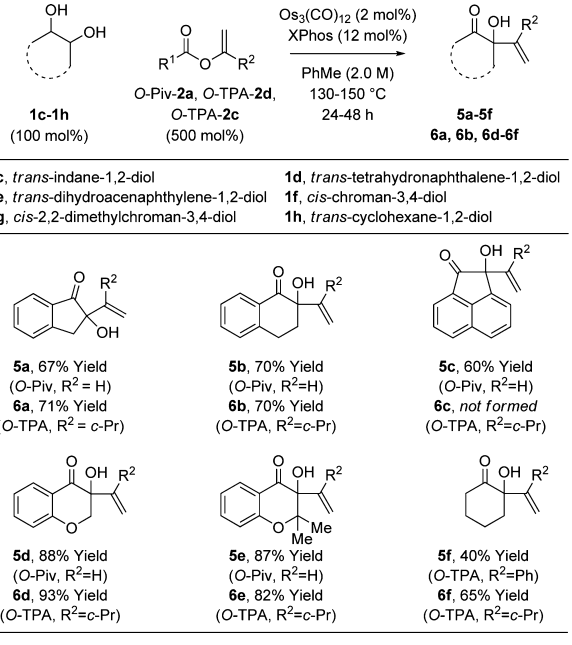
[a]Yields are of material isolated by silica gel chromatography. [b]$Os_3(CO)_{12}$ (4 mol%) and XPhos (24 mol%), isolated yield based on recovered starting material. See Supporting Information for further experimental details.

Table 3. Ruthenium-Catalyzed Vinyl Transfer from Enol Carboxylates 2 to 3-Hydroxy-2-oxindole 1b to Form 4a–4f[a]



[a]Yields are of material isolated by silica gel chromatography. See Supporting Information for further experimental details.

Table 4. Osmium-Catalyzed Vinyl Transfer from Enol Carboxylates 2 to 1,2-Diols 1c–1h to Form 5a–5f and 6a, 6b, 6d–6f[a]



[a]Yields are of material isolated by silica gel chromatography. See Supporting Information for further experimental details.

a 1:1 mixture of the desired product of vinyl transfer **3a** and *O*-Ac-**1a** in a combined 29% isolated yield (Table 1, entry 3). Remarkably, the use of $Os_3(CO)_{12}$ and XPhos under otherwise identical conditions provided an 85% isolated yield of vinyl transfer product **3a** and *O*-Ac-**1a** in a 9.5:1 ratio (Table 1, entry 4). The enhanced performance of osmium(0) catalyst[11] can be understood on the basis of π-backbonding.[12] In an effort to suppress competing formation of *O*-Ac-**1a**, the use of vinyl pivalate **2a** was explored (Table 1, entries 5 and 6). The reaction of ethyl mandelate **1a** with vinyl pivalate **2a** produced adduct **3a** in 75% isolated yield with complete suppression of competing acyl transfer pathways (Table 1, entry 5). A modest increase in temperature improved the isolated yield of **3a** to 86% (Table 1, entry 6). Variation in the loading of **2a** was explored under these conditions (Table 1, entries 6–8), and a loading of 300 mol% was deemed optimal (Table 1, entry 7). Further variation in ligand did not avail further improvement (Table 1, entries 9–11). In the absence of ligand, only trace quantities of **3a** were observed (Table 1, entry 12).

To assess the generality of this process with respect to the vinyl donor, ethyl mandelate **1a** was subjected to these optimal conditions in the presence of vinyl pivalates *O*-Piv-**2a–2f** (Table 2). Although the unsubstituted vinyl pivalate *O*-Piv-**2a** is an efficient partner for vinyl transfer, the use of more highly substituted vinyl pivalates *O*-Piv-**2b–2f** was less efficient due to competing *O*-acylation. The use of the corresponding triphenyl acetates *O*-TPA-**2b**, -**2c**, and -**2f** suppresses transesterification, delivering the desired products of vinyl transfer **3b**, **3c**, and **3f** in moderate to excellent yields (Table 2). *N*-Benzyl-3-hydroxy-2-oxindole **1b** was subjected to a parallel set of vinyl transfer experiments (Table 3). Dehydrogenation of **1b** gives rise to a highly reactive isatin that readily engages in oxidative coupling, allowing the parent ruthenium(0) catalysts to be employed and attenuating competitive transesterification that previously accompanied use of vinyl acetates. Nevertheless, in certain cases the vinyl pivalates are required to enforce better partitioning of *O*-acylation and C–C coupling pathways. For example, the enol acetates *O*-Ac-**2e** and *O*-Ac-**2f** fail to deliver the desired adducts **4e** and **4f**, respectively, due to competing acyl transfer. In contrast, the corresponding vinyl pivalates *O*-Piv-**2e** and *O*-Piv-**2f** deliver adducts **4e** and **4f** in 94% and 90% yields, respectively. The yield of **4c** was increased from 60% to 85% by suppression of *O*-acylation when using triphenyl acetate

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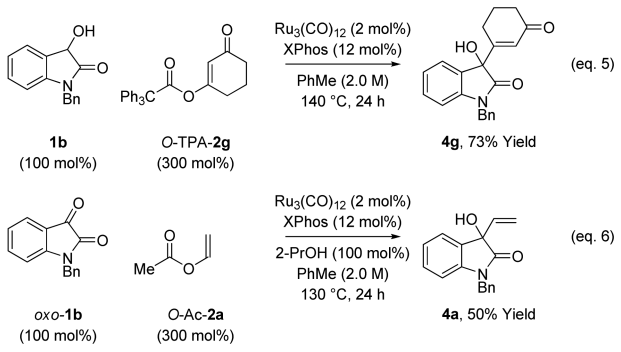
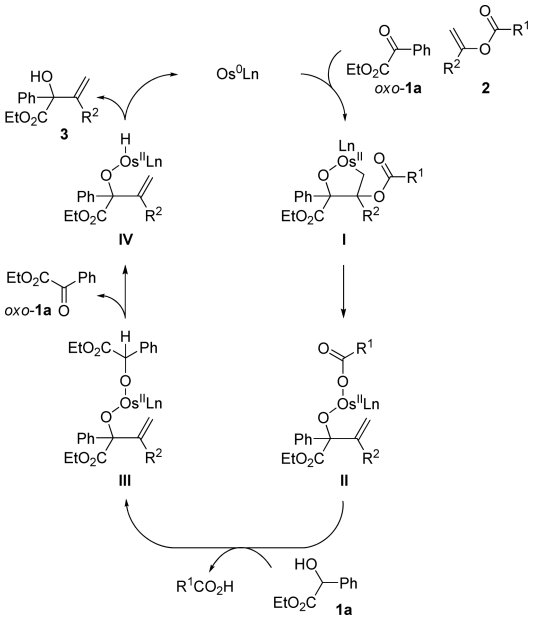
O-TPA-**2c**. The conversion of 3-hydroxy-2-oxindole **1b** to adduct **4g** demonstrates the feasibility of transferring trisubstituted alkenes that are activated in the form of conjugated enones (eq 5). Finally, vinyl transfer can be performed from the dicarbonyl oxidation level, as illustrated in the reductive coupling of *oxo*-**1b** with vinyl acetate **2a** (eq 6).



Vicinal diols, which can form 1,2-diketones as reactive intermediates, were explored as electrophilic partners in vinyl transfers using *O*-Piv-**2a**, *O*-TPA-**2d**, and *O*-TPA-**2c** (Table 4). The reactions of vicinal diols **1c**−**1h** are oxidative and require excess vinyl donor as sacrificial hydrogen acceptor. It was found that aryl-substituted diols **1c**−**1g** react with *O*-Piv-**2a** to form adducts **5a**−**5e** in moderate to good yields. For non-symmetric diols **1c**, **1d**, **1f**, and **1g**, the vinyl transfer proceeds in a completely regioselective manner and can be explained on the basis of our prior density functional theory calculations in related alkyne−diol C−C couplings.[13] The more highly substituted triphenyl acetate *O*-TPA-**2c** reacts with aryl-substituted diols **1c**, **1d**, **1f**, and **1g**, delivering adducts **6a**, **6b**, **6d**, and **6e** in up to 93% isolated yield. Adduct **6c** was not formed, presumably due to steric issues. Simple aliphatic diols, such as cyclohexane diol **1h**, participate in vinyl transfer, as illustrated in the formation of adducts **5f** and **6f**. Here, somewhat modest yields were observed due to competitive transesterification. Phenyl-(2-pyridyl)-methanol and related heteroaromatic secondary alcohols do not participate in vinyl transfer under the aforesaid conditions.

A plausible catalytic mechanism is illustrated for the coupling of ethyl mandelate **1a** with enol carboxylate **2** to form adducts **3** (Scheme 2). Prior mechanistic studies involving the use of $Ru_3(CO)_{12}$ precatalysts[9d] suggested intervention of a discrete mononuclear osmium(0) complex modified by XPhos. Osmium(0)-mediated oxidative coupling of *oxo*-**1a** with enol carboxylate **2** provides a transient β-acyloxy-oxametallacycles, **I**. Related ruthenium(0)-mediated carbonyl−alkene oxidative couplings find precedent in the work of Chatani and Murai[10] and our own studies.[9,13] The regioselectivity of oxidative coupling is likely driven by formation of a less hindered primary carbon−osmium bond. Reversible oxidative coupling, as demonstrated in a related system,[9d] might correct errors in regioselectivity. The β-carboxy-oxaosmacycle **I** undergoes fragmentation to form the osmium(II) carboxylate **II**,[7j,k] which upon substitution by ethyl mandelate **1a** delivers the osmium(II) alkoxide complex **III**. The intermediate **III** undergoes β-hydride elimination to furnish the α-ketoester *oxo*-**1a** and the osmium(II) hydride **IV**, which upon O−H reductive elimination provides the product of vinyl transfer **3** to close the catalytic cycle.

Scheme 2. Proposed General Catalytic Mechanism Involving Oxidative Coupling−Metallacycle Fragmentation



In summary, we report a broad, new strategy for catalytic vinyl transfer from enol carboxylates to activated secondary alcohol C−H bonds via metallacycle fragmentation under the conditions of ruthenium(0)- and osmium(0)-catalyzed transfer hydrogenation. This method is applicable to a range of activated secondary alcohols and vicinal diols **1c**−**1h**. Future studies will focus on the development of related C−C bond-forming transfer hydrogenations that directly convert lower alcohols to higher alcohols in the absence of stoichiometric organometallic reagents.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b04688.

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Notes

The authors declare no competing financial interest.

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