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Rh(III)-Catalyzed Decarboxylative Coupling of Acrylic Acids with Unsaturated Oxime Esters: Carboxylic Acids Serve as Traceless Activators

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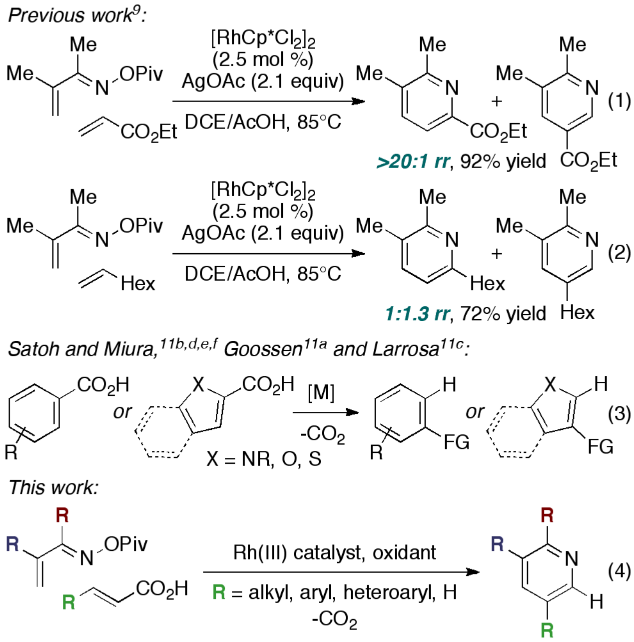
Supporting Information

ABSTRACT: α,β-Unsaturated carboxylic acids undergo Rh(III)-catalyzed decarboxylative coupling with α,β-unsaturated *O*-pivaloyl oximes to provide substituted pyridines in good yield. The carboxylic acid, which is removed by decarboxylation, serves as a traceless activating group, giving 5-substituted pyridines with very high levels of regioselectivity. Mechanistic studies rule out a picolinic acid intermediate, and an isolable rhodium complex sheds further light on the reaction mechanism.

Substituted pyridines are among the most prevalent scaffolds encountered in medicinal chemistry.[1] For this reason, a wealth of research has focused on the construction of these heterocycles.[2] Nonetheless, access to desired substitution patterns often remains a challenge with traditional multicomponent approaches to pyridine synthesis.[3] Classic condensation protocols rely on aldol and Michael-type steps, and the position and identity of product substituents are dictated by the activating groups required for reactivity.[4] Intermolecular [2 + 2 + 2] cycloadditions of nitriles and alkynes often afford regioisomeric mixtures,[5] an obstacle that is typically circumvented by tethering strategies.[6] Novel approaches to diversely substituted pyridines are highly desirable, and several impressive reports highlight the recent advances in this field.[7]

Our efforts in the area of pyridine synthesis have exploited rhodium-catalyzed coupling of α,β-unsaturated oxime esters[8] and alkenes to access 6-substituted pyridines.[9] During the course of this study, we discovered that selectivity depends crucially on the nature of the alkene substrate. Namely, activated alkenes react with exquisite regioselectivity (eq 1) while unactivated alkenes incorporate to give mixtures of regioisomeric products (eq 2). This limitation prompted us to investigate whether the carboxylic acid moiety of acrylic acid derivatives could serve as a 'traceless' activating group.[10] Indeed, this strategy has been utilized by a number of research groups in the context of C−H functionalization (eq 3).[11,12] In these examples, carboxylate ligation imparts selectivity to the C−H activation step, and the acid residue is ultimately cleaved via *in situ* decarboxylation. In a similar manner, we envisioned that the carboxylic acid moiety would direct regioselective alkene incorporation and then be removed by decarboxylation (eq 4).[13] This work would complement our previously reported rhodium-catalyzed pyridine synthesis, since 5-substituted pyridines[14] could be prepared with high selectivity without the constraint of activating group incorporation in the products.



We evaluated the feasibility of the proposed approach in the reaction of α,β-unsaturated *O*-pivaloyl oxime **1a** and crotonic acid (**2a**) (Table 1). An initial screen with catalytic $[RhCp^*Cl_2]_2$ and AgOAc as an oxidant identified hexafluoroisopropanol (HFIP) as the optimal solvent, furnishing the desired **3aa** in 60% yield (entry 1). Importantly, no 6-substituted regioisomer (not shown) was observed. In an effort to avoid superstoichiometric silver reagents, we conducted a screen of other oxidants, which revealed potassium persulfate ($K_2S_2O_8$) to be modestly effective (entry 2). However, the desired pyridine **3aa** was formed in a 1:1 mixture with picolinic acid **4aa**, the nondecarboxylated product of the desired coupling. Addition of a catalytic amount of silver *p*-toluenesulfonate (AgOTs) afforded a 10:1 mixture of products (entry 3), and increasing the amount of AgOTs gave full conversion to **3aa** as a single product (entry 4). Changing to $[RhCp^{CF_3}Cl_2]_2$ (Cp^{CF_3} = tetramethyl(trifluoromethyl)cyclopentadienyl) was necessary for increasing reactivity with aryl acrylic acid substrates such as **2k** (Table 1, entries 5 and 6, and Supporting

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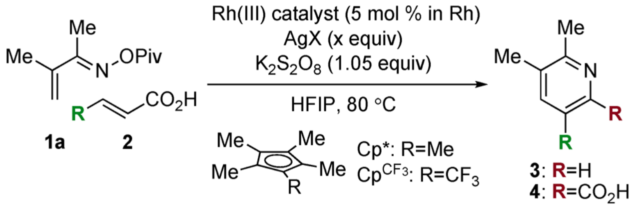
Table 1. Reaction Optimization[a]



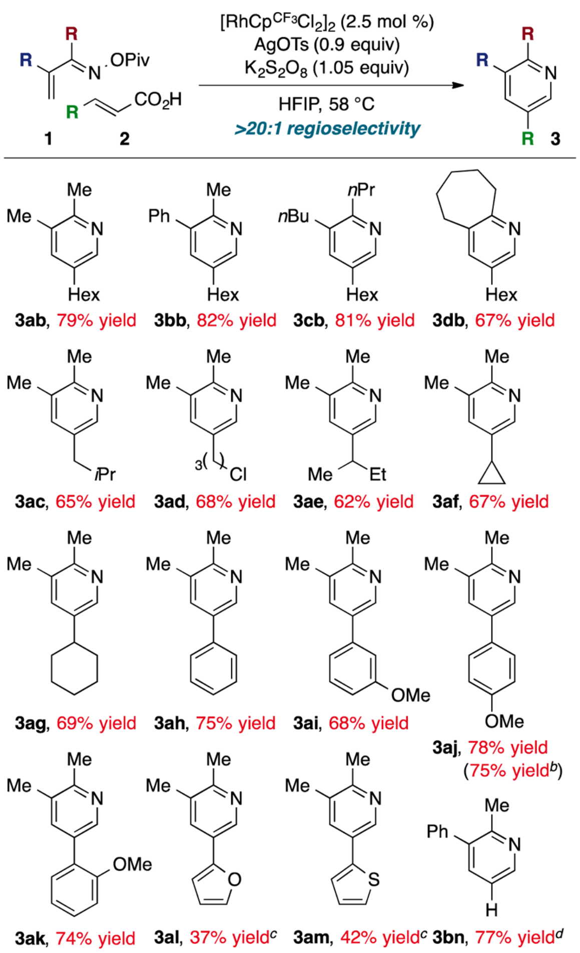
entry	R	catalyst	AgX	equiv	yield (%)[b] 3	yield (%)[b] 4
1	Me (**2a**)	$[RhCp^*Cl_2]_2$	AgOAc	2.1[c]	60	<5
2	Me	$RhCp^*(OAc)_2$	none	–	15	15
3	Me	$RhCp^*(OAc)_2$	AgOTs	0.25	50	5
4	Me	$RhCp^*(OAc)_2$	AgOTs	0.8	80	<5
5	(*m*-OMe)C_6H_4 (**2k**)	$RhCp^*(OAc)_2$	AgOTs	0.8	50	<5
6	(*m*-OMe)C_6H_4	$[RhCp^{CF_3}Cl_2]_2$	AgOTs	0.9	70	<5

[a]1.2 equiv of **2**, 0.3 M. [b]Determined by ^{1}H NMR. [c]Without $K_2S_2O_8$.

Information (SI)), and we thus chose this catalyst for further development.

We examined the scope of the reaction with these optimized conditions (Chart 1). Oxime esters **1** are easily synthesized from the corresponding enones with hydroxylamine hydrochloride and pivaloyl chloride. Knoevenagel condensation of the appropriate aldehyde and malonic acid conveniently accesses acrylic acid derivatives **2**.[15] The reaction of various *α*,*β*-unsaturated *O*-pivaloyl oximes (**1**) and nonenoic acid (**2b**) affords the 5-substituted pyridines in good yields.[16] Both primary and secondary alkyl acrylic acids undergo the desired coupling efficiently; notably, alkyl chloride **2d** is tolerated under the Ag(I) conditions. The acrylic acid may also bear aryl or heteroaryl substitution (**2h**−**2m**). While the alkene contains two possible activating groups in these cases, 5-substituted products are formed with complete regioselectivity. Finally, acrylic acid (**2n**) also undergoes decarboxylative coupling to furnish 2,3-disubstituted **3bn** in good yield.

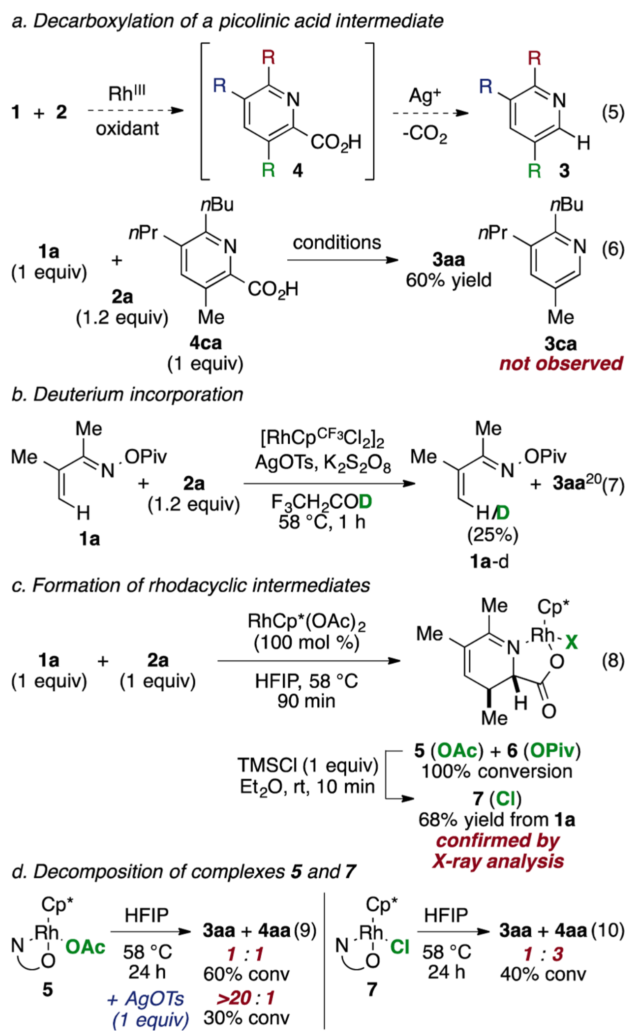
Chart 1. Reaction Scope[a]



[a]Conditions: 1.2 equiv of **2**, 0.3 M. [b] 1 mmol scale. [c] 0.5 equiv of AgOTs. [d] In TFE at 74 °C.

Several key experiments contributed to our current understanding of the reaction mechanism. We initially considered a pathway involving decarboxylation of a picolinic acid intermediate **4** (eq 5, Scheme 1a). Ag(I)-catalyzed decarboxylation is a well-known process[17] and has been demonstrated with aryl[18] and heteroaryl[19] carboxylic acids at elevated temperatures. To test this hypothesis, we synthesized possible intermediate **4ca** and subjected it to the reaction conditions (eq 6). In the event, we observed no formation of decarboxylated **3ca**, ruling out the intermediacy of picolinic acid **4ca**.

Scheme 1. Mechanistic Studies



We gained further mechanistic insight from isotope and stoichiometric experiments (Scheme 1b–d). Reaction of **1a** and **2a** in trifluoroethanol-d_1 performed to ~30% conversion results in partial deuteration at the β-position of the remaining **1a**, an observation consistent with a reversible C–H activation step (eq 7). After a mixture of **1a**, **2a** and a stoichiometric amount of $RhCp^*(OAc)_2$ was heated for 90 min, the major products observed are rhodium carboxylate complexes **5** and **6** (eq 8). Importantly, in **5** and **6**, C–N bond formation and N–O bond cleavage have taken place but decarboxylation has not yet occurred, clarifying the timing of the decarboxylation step. Treatment of **5** and **6** with TMSCl affords chloride complex **7**, an orange solid that is isolated by filtration. The structure given in Scheme 1c was confirmed by single crystal X-ray analysis of **7** (Figure 1). Acetate complex **5** is converted to a 1:1 mixture of

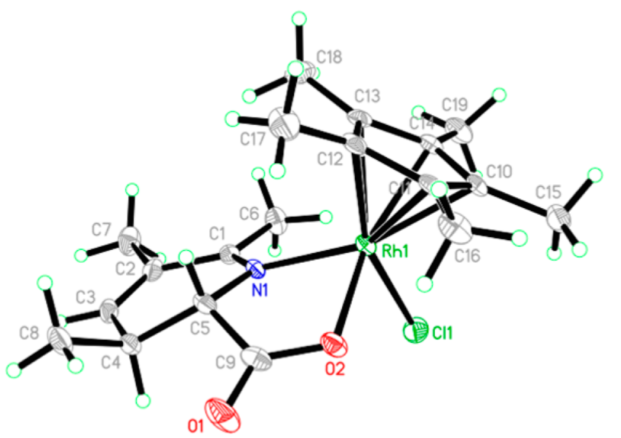


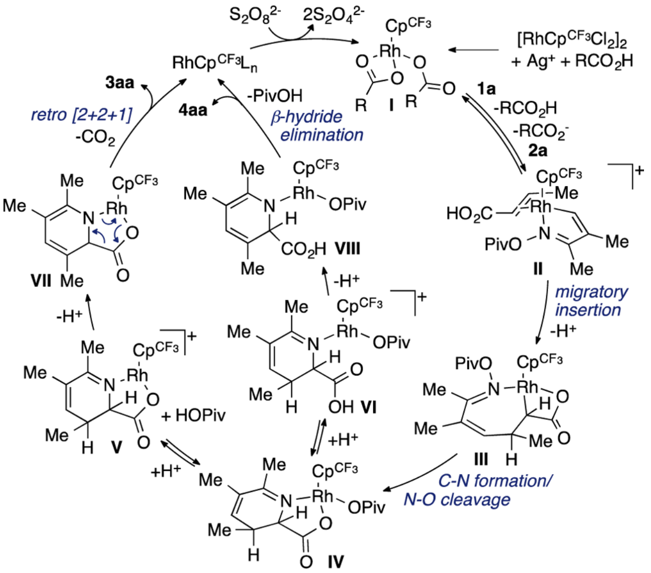
Figure 1. X-ray crystal structure of **7** with thermal ellipsoids drawn at the 50% probability level.

3aa and **4aa** upon heating (eq 9), implicating **5** as a common intermediate of both observed products. In agreement with earlier observations, addition of AgOTs to the reaction leads to exclusive formation of **3aa** (eq 9). Interestingly, heating chloride complex **7** results in a 1:3 mixture of **3aa** and **4aa** (eq 10), suggesting that X ligand identity at this stage influences the divergence of reaction pathways to the two products.

Based on the described mechanistic observations, we propose that pyridine and picolinic acid formation proceeds by the mechanism depicted in Scheme 2. After generation of active catalyst **I**, reversible C–H activation at the β-position of **1a** and ligand exchange provide cationic complex **II**. Migratory insertion and deprotonation give rhodacycle **III**. C–N bond formation and N–O bond cleavage afford intermediate **IV** that is analogous to observable complexes **5** and **6**. From **IV**, proton assisted ionization may occur to liberate either of the two carboxylate ligands, giving cationic complex **V** or **VI**.[21] Deprotonation of **V** leads to metallacycle **VII**, which can undergo a retro [2 + 2 + 1] cycloaddition to extrude CO_2 and provide pyridine **3aa** and a Rh(I) species.[22] Alternatively, deprotonation of **VI** forms intermediate **VIII** from which β-hydride elimination gives picolinic acid **4aa**. Reductive elimination of the resultant Rh(III) hydride gives a Rh(I) complex that is oxidized to regenerate the active catalyst.

In conclusion, we have developed a rhodium-catalyzed decarboxylative coupling of α,β-unsaturated *O*-pivaloyl oximes and acrylic acid derivatives. This method takes advantage of a carboxylic acid as a traceless activating group to produce 5-

Scheme 2. Proposed Mechanism



substituted pyridines with complete regioselectivity. Mechanistic studies suggest that decarboxylation does not occur via a picolinic acid intermediate. We identified significant rhodacyclic intermediates that clarify the order of C–N bond formation and decarboxylation.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, compound characterization, additional experiments, and crystallographic data. This information is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(20) Partial deuteration of the 2-Me and 6-H of **3aa** is also observed; see SI.

(21) The exact role played by Ag^+ in increasing selectivity for **3** is not fully understood at this time.

(22) A stepwise process of CO_2 extrusion and reductive elimination is another possibility.