Homogeneous Catalysis

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Branch-Selective Intermolecular Hydroacylation: Hydrogen-Mediated Coupling of Anhydrides to Styrenes and Activated Olefins**

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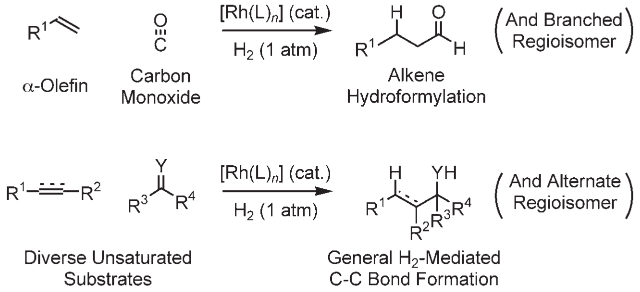
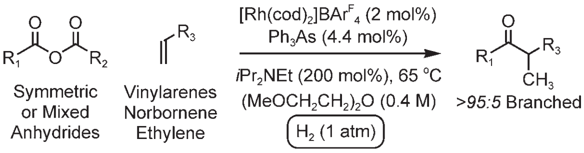
Alkene hydroformylation is the largest volume application of homogeneous metal catalysis and the prototypical example of hydrogen-mediated C–C bond formation.[1] Remarkably, while hydroformylation is practiced on a vast scale, systematic efforts toward the development of hydrogenative C–C coupling reactions that extend beyond carbon monoxide insertion have only recently been described.[2,3] Ideally, it would be desirable to couple two or more organic molecules simply through their exposure to gaseous hydrogen in the presence of a metal catalyst. This goal represents the primary focus of research in our laboratory.[2]



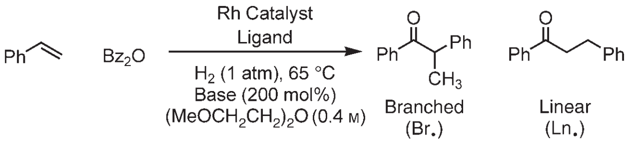
In connection with ongoing efforts toward the development of hydrogen-mediated C–C coupling reactions, we herewith disclose studies on the hydrogen-mediated reductive coupling of carboxylic anhydrides, including mixed anhydrides, to styrenes and activated olefins, and thus generate a protocol for intermolecular alkene hydroacylation.[3b,4–7] Notably, we find that cationic rhodium catalysts ligated by triphenylarsine (Ph_3As)[8] enable formation of branched hydroacylation products with exceptionally high levels of regiocontrol [Eq. (1)]. The significance of these findings is twofold. First, while catalytic systems for intramolecular hydroacylation involving aldehydes as acyl donors are well developed,[4] corresponding intermolecular hydroacylations[5–7] are far more limited in scope because of competitive decarbonylation of aldehydes.[9] Secondly, prior to the results reported herein, the catalytic reductive coupling of alkenes to carbonyl compounds has only been achieved intramolecularly by cyclization of olefinic aldehydes.[10]



(1)

Our initial studies focused on the reductive coupling of styrene and benzoic anhydride. Such hydroacylations find precedent in the reaction of acid chlorides and ethylene mediated by stoichiometric quantities of $[RhH(PPh_3)_3(CO)]$,[11a] the reductive coupling of dienes and acid chlorides catalyzed by palladium and mediated by silane,[11b] and, most importantly, a single report by Miura and coworkers of the hydrogen-mediated coupling of benzoic anhydride to styrene catalyzed by $[RhCl(cod)]_2$ (cod = cycloocta-1,5-diene) with $(PhO)_3P$ as the ligand. Under these conditions, a 3:1 mixture of branched and linear products is obtained in 30% yield.[3b] However, it was found that increased catalyst loading did little to improve the yield of the coupling product (Table 1, entries 1 and 2). A survey of

Table 1: Optimization of hydrogen-mediated intermolecular hydroacylation.[a]



Entry	Catalyst (mol%)	L (mol%)	Base	Yield [%]	Br./Ln.
1	$[\{RhCl(cod)\}_2]$ (0.5)	PhO_3P (2)	iPr_2NEt	30	3:1
2	$[\{RhCl(cod)\}_2]$ (5)	PhO_3P (20)	iPr_2NEt	45	3:1
3	$[\{RhCl(cod)\}_2]$ (5)	Ph_3P (20)	iPr_2NEt	15	6:1
4	$[\{RhCl(cod)\}_2]$ (5)	Fur_3P (20)	iPr_2NEt	22	> 95:5
5	$[\{RhCl(cod)\}_2]$ (5)	Ph_3As (20)	iPr_2NEt	57	> 95:5
6	$[\{RhCl(cod)\}_2]$ (5)	Ph_3Bi (20)	iPr_2NEt	trace	
7	$[\{RhOMe(cod)\}_2]$ (5)	Ph_3As (20)	iPr_2NEt	67	> 95:5
8	$[Rh(cod)_2]OTf$ (5)	Ph_3As (12)	iPr_2NEt	79	> 95:5
9	$[Rh(cod)_2]OTf$ (5)	Ph_3As (12)	Li_2CO_3	63	> 95:5
10	$[Rh(cod)_2]BF_4$ (5)	Ph_3As (12)	iPr_2NEt	82	> 95:5
11	$[Rh(cod)_2]PF_6$ (5)	Ph_3As (12)	iPr_2NEt	85	> 95:5
12	$[Rh(cod)_2]SbF_6$ (5)	Ph_3As (12)	iPr_2NEt	84	> 95:5
13	$[Rh(cod)_2]BAr^F_4$ (5)	Ph_3As (12)	iPr_2NEt	93	> 95:5
14	$[Rh(cod)_2]BAr^F_4$ (2)	Ph_3As (4.4)	iPr_2NEt	93	> 95:5

[a] Cited yields are of isolated material. For the experiments above, 400 mol% of styrene and 100 mol% of Bz_2O were used. However, under the conditions cited in entry 13, but using 100 mol% of styrene and 200 mol% of Bz_2O, an 87% yield of the branched reductive coupling product was obtained. See the Supporting Information for detailed experimental procedures.

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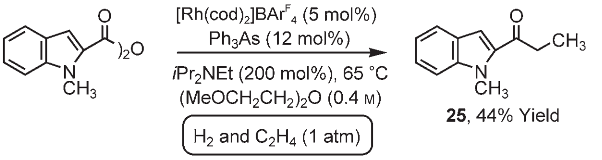
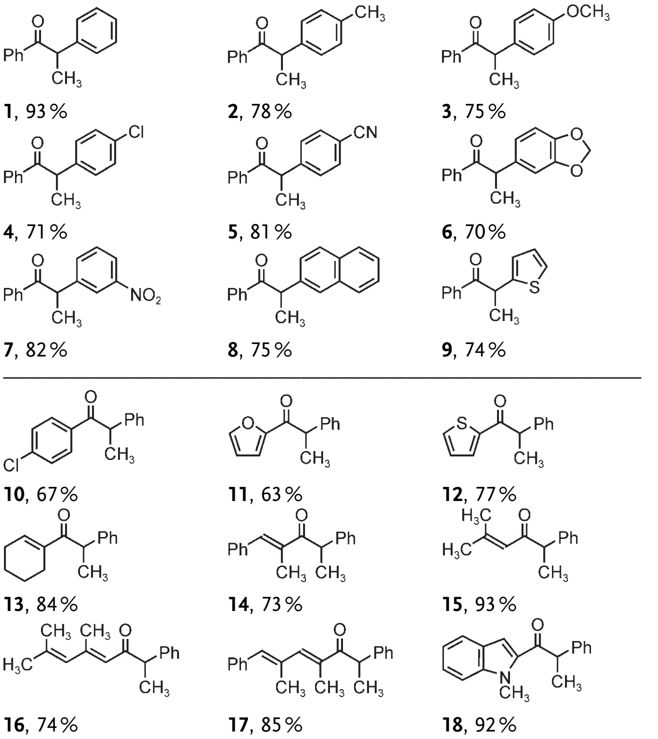
monodentate ligands proved more fruitful. Whereas Rh catalysts ligated by PPh_3 gave only a 15% yield of the coupling product, more electron-deficient ligands $(2\text{-Fur})_3P$ (Fur = furanyl) and Ph_3As provided the branched coupling product as a single regioisomer and, for the latter case, in substantially improved yield (Table 1, entries 3–5). Given these results, the ligand Ph_3As was screened against a series of Rh^I sources (Table 1, entries 7–13). It was found that cationic Rh^I complexes were especially effective precatalysts. Indeed, upon use of $[Rh(cod)_2]BAr^F_4$ as precatalyst ($Ar^F = 3,5\text{-}(CF_3)_2C_6H_3$), the coupling product is obtained in 93% yield as a single regioisomer (Table 1, entry 13). Enhanced reactivity conferred through the use of noncoordinating counterions, and in particular $BAr^F_4{}^-$, has been noted for cationic Rh^I- and Ir^I-based hydrogenation catalysts.[12] Catalyst loading could be reduced to 2 mol% without any decline in the yield (Table 1, entry 14). Notably, the present second-generation catalytic system (Table 1, entries 13 and 14) provides better yields and better regioselectivities at less than half the catalyst loading than the original catalytic system described in the pioneering study by Miura and co-workers (Table 1, entries 1 and 2).

Various substrate combinations were explored under these optimized conditions. It was found that substituted styrenes and related vinylarenes reductively couple to benzoic anhydride in good to excellent yield with complete regiocontrol favoring the branched product (Table 2, top). As demonstrated by the formation of product **7**, arenes containing nitro groups are not subject to reduction under the conditions of hydrogen-mediated coupling. Simple aliphatic alkenes gave diminished yields of the reductive coupling product and exhibit incomplete levels of regioselection.[13] To further assess the scope of the reaction, different carboxylic anhydrides were hydrogenated in the presence of styrene. Aromatic, heteroaromatic, and α,β-unsaturated anhydrides couple in good to excellent yield and with complete branch-selective regiocontrol (Table 2, bottom). Notably, α,β-unsaturated coupling products **14–17**, are not subject to over-reduction under the conditions of hydrogen-mediated coupling. Aliphatic anhydrides, such as acetic anhydride, provide diminished yields of the coupling product.[13] As demonstrated by the formation of **19–24** (Table 3), norbornene also couples readily to heteroaromatic and α,β-unsaturated carboxylic anhydrides. Of greater interest, gaseous ethylene participates in the coupling. For example, the 2-carboxyindole anhydride shown in Equation (2) (chosen because of the low volatility of the product) is converted into the corresponding ethyl ketone in an unoptimized 44% yield simply by using a balloon containing roughly equal volumes of hydrogen and ethylene gas.



(2)

Table 2: Hydrogen-mediated coupling of Bz_2O to different vinylarenes (top) and hydrogen-mediated coupling of different anhydrides to styrene (bottom).[a]

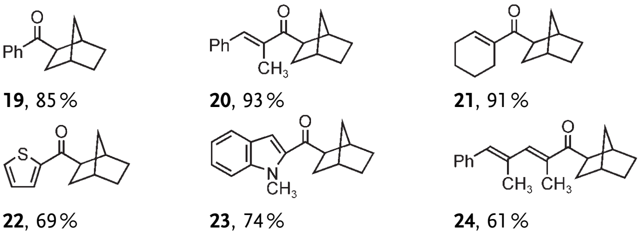


1, 93%; **2**, 78%; **3**, 75%; **4**, 71%; **5**, 81%; **6**, 70%; **7**, 82%; **8**, 75%; **9**, 74%

10, 67%; **11**, 63%; **12**, 77%; **13**, 84%; **14**, 73%; **15**, 93%; **16**, 74%; **17**, 85%; **18**, 92%

[a] Cited yields are of isolated material. In all cases, >95:5 regioselection is observed. See the Supporting Information for detailed experimental procedures.

Table 3: Hydrogen-mediated coupling of assorted carboxylic anhydrides to norbornene.[a]



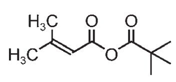
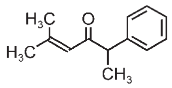
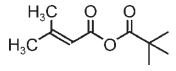
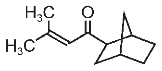
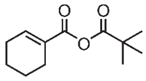
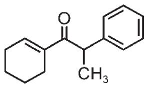
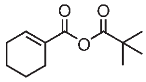
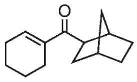
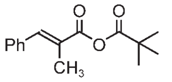
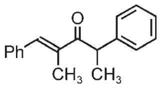
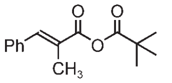
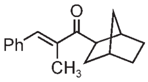
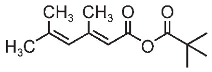
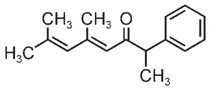
19, 85%; **20**, 93%; **21**, 91%; **22**, 69%; **23**, 74%; **24**, 61%

[a] Cited yields are of isolated material. See the Supporting Information for detailed experimental procedures.

Coupling to mixed anhydrides would be desirable for more highly functionalized carboxylic acid precursors. Accordingly, mixed anhydrides derived from trimethylacetic acid (pivalic acid) and various α,β-unsaturated acids were prepared and subjected to the optimized conditions for coupling to styrene and norbornene. Gratifyingly, transfer of the α,β-unsaturated acyl moiety was observed exclusively. Complete levels of branch regioselectivity were also observed in coupling reactions to styrene (Table 4).

To gain insight into the catalytic mechanism, the coupling of benzoic anhydride and styrene was conducted in a deuterium atmosphere. Deuterium is incorporated primarily at the β position, but the extent of incorporation is base-

Table 4: Hydrogen-mediated coupling of mixed anhydrides to styrene and norbornene.[a]

Entry	Mixed anhydride	Product	Yield [%]
1			71
2			62
3			70
4			86
5			80
6			84
7			73

[a] Cited yields are of isolated material. In all cases involving styrene, >95:5 regioselection is observed. See the Supporting Information for detailed experimental procedures.

dependant. When iPr$_2$NEt or Li$_2$CO$_3$ are used as the base, 0.4 and 0.8 deuterium atoms are incorporated, respectively. These data are consistent with the catalytic mechanism **A** (Scheme 1) initially proposed by Miura and co-workers[3b] which involves heterolytic activation of hydrogen by way of the dihydride. Incomplete incorporation of deuterium may result from reversible coordination and hydrometalation of styrene. Furthermore, dehydrogenation of iPr$_2$NEt may compete with hydrogen activation, thus contributing further to the incomplete incorporation of deuterium. Dissociation of the weakly coordinating ligand Ph$_3$As prior to hydrometalation may direct the formation of the branched alkyl rhodium intermediate, as this would allow the resulting coordinatively unsaturated Rh center to interact with the adjacent arene. However, the regio-determining hydrometalation of mechanism **A**, which occurs prior to any interaction with the anhydride, is inconsistent with the fact that different acyl donors, such as the *O*-2-pyridyl ester, exhibit different levels of regioselection. It is known that low-valent rhodium complexes undergo oxidative addition to carboxylic anhydrides under mild conditions to afford acyl metal carboxylates.[14] Hence, catalytic mechanism **B**, which involves oxidative addition of an anhydride followed by insertion of styrene and hydrogenolytic cleavage of the rhodium–carbon bond is herewith proposed to account for the changes in the regiochemistry arising from the use of different acyl derivatives.

In summary, we have reported a regioselective intermolecular hydroacylation of vinylarenes in which symmetric and mixed carboxylic anhydrides are used as acyl donors. High levels of branch selectivity are promoted through the use of cationic rhodium catalysts ligated by triphenylarsine. Future studies will focus on the hydrogen-mediated coupling of simple α-olefins to aliphatic carboxylic anhydrides and acid chlorides, as well the development of enantioselective variants involving chirally modified triphenylarsine ligands.

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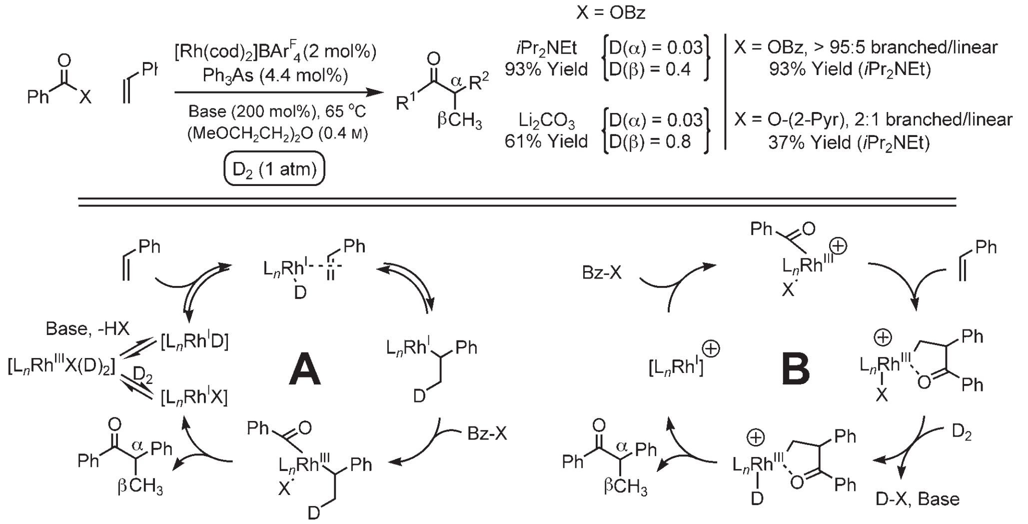

Scheme 1. Plausible catalytic mechanism as supported by deuterium labeling studies. Bz = benzyl.

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