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Rhodium-Catalyzed Highly Enantioselective Direct Intermolecular Hydroacylation of 1,1-Disubstituted Alkenes with Unfunctionalized Aldehydes

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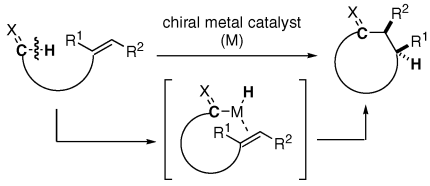
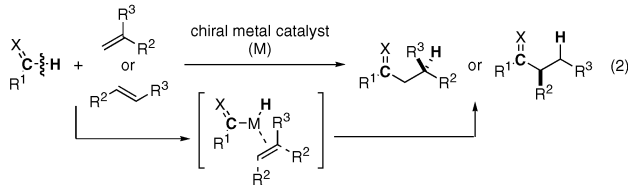
Transition metal catalyzed vinylic or aromatic sp^2 C−H bond alkylations with alkenes have been extensively studied, and a number of efficient methods are available.[1] However, the majority of enantioselective variants are intramolecular reactions (eq 1).[2] Although a number of efficient intermolecular sp^2 C−H bond alkylations with alkenes have been reported, the successful enantioselective reactions using disubstituted alkenes have been limited to those with highly reactive norbornenes (eq 2).[3−6] Transition metal catalyzed hydroacylations of alkenes with aldehydes, which involve aldehyde sp^2 C−H bond activation as a key step, are also in the same situation. Although large numbers of enantioselective intramolecular hydroacylations of disubstituted alkenes have been reported,[7] only two examples of intermolecular variants have been succeeded to date.[8,9] Bolm and Stemmler demonstrated the first enantioselective intermolecular hydroacylation of disubstituted alkenes, while substrates were limited to salicylaldehydes and norbornenes.[8] Willis and co-workers recently reported a notable success by using disubstituted allenes instead of disubstituted alkenes.[9] Although this report is the most successful achievement in this area, substrates were still limited to *β-S*-aldehydes and aryl-substituted allenes.[9]

Intramolecular approach (many precedents)



(1)

Intermolecular approach (few precedents using norbornenes)

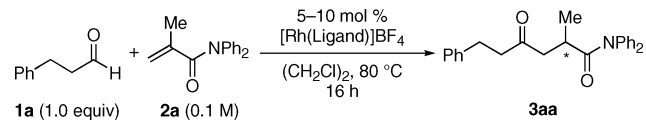


(2)

In the above two successful examples, functionalized aldehydes were employed to stabilize the key acylrhodium intermediates with aldehyde chelation control, which suppresses competitive rhodium-catalyzed reductive decarbonylation.[10,11] Our research group recently developed a cationic rhodium(I)/dppb complex-catalyzed direct intermolecular hydroacylation of *N,N*-dialkylacrylamides with unfunctionalized aldehydes presumably through the stabilization of acylrhodium intermediates with alkene chelation to rhodium instead of aldehyde chelation.[12] Here, we achieved highly enantioselective direct intermolecular hydroacylation of *1,1-disubstituted alkenes* with *unfunctionalized aldehydes* by using a cationic rhodium(I)/QuinoxP* complex as a catalyst.

We first screened chiral bisphosphine ligands in the reaction of hydrocinnamaldehyde (**1a**) and *N,N*-diphenylmethacrylamide (**2a**) as shown in Table 1. The study revealed that not only enantioselectivity but also product yields were highly dependent on the ligands, which

Table 1. Screening of Chiral Bisphosphine Ligands[a]

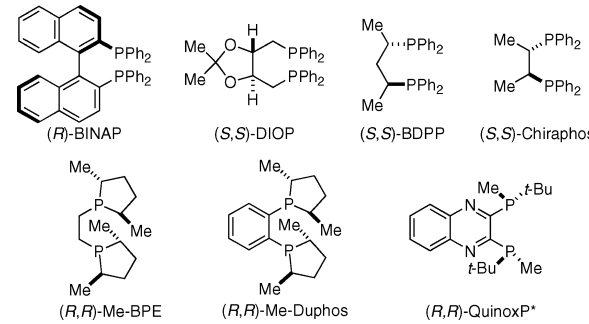


1a (1.0 equiv) **2a** (0.1 M) **3aa**

entry	ligand	catalyst (%)	convn (%)	yield (%)	ee (%)
1	(*R*)-BINAP	10	58	14	35 (+)
2	(*S,S*)-DIOP	10	44	29	22 (−)
3	(*S,S*)-BDPP	10	1	<1	−
4	(*S,S*)-Chiraphos	10	89	<1	−
5	(*R,R*)-Me-BPE	10	6	<1	−
6	(*R,R*)-Me-Duphos	10	92	66	88 (+)
7[b]	(*R,R*)-QuinoxP*	10	90	74	99 (+)
8[b,c]	(*R,R*)-QuinoxP*	5	>99	87	98 (+)

[a] $[Rh(cod)_2]BF_4$ (0.0050 mmol), ligand (0.0050 mmol), **1a** (0.050 mmol), **2a** (0.050 mmol), and $(CH_2Cl)_2$ (0.5 mL, 0.1 M) were used. The active catalysts were generated in situ by hydrogenation. [b] $[Rh(nbd)_2]BF_4$ was used. [c] Concentration of **2a**: 0.5 M. **1a**: 1.1 equiv.

is sharp contrast to previously reported enantioselective inter- and intramolecular hydroacylations.[7−9] Although the use of BINAP and DIOP, possessing large bite angles, showed modest catalytic activity for this reaction, both yields and ee values were low (entries 1 and 2). Bisphosphine ligands, possessing smaller bite angles than BINAP and DIOP, were then examined. However, almost no catalytic activities were observed by using BDPP and Me-BPE (entries 3 and 5), and rapid decarbonylation was observed by using Chiraphos (entry 4). Pleasingly, monoaryl-bisphosphine ligands were found to be highly effective (entries 6 and 7), and both high yield and ee value were achieved by using QuinoxP*[13] as a ligand (entry 7). Furthermore, employing a high substrate concentration allowed reducing the catalyst loading to 5 mol % (entry 8).



A series of aldehydes **1a**−**h** and acrylamides **2a**−**d** was subjected to the above optimal reaction conditions as shown in Table 2. *N,N*-Diphenyl- (**2a**), *N*-methyl-*N*-phenyl- (**2b**), and *N,N*-dibenzylmethacrylamides (**2c**) reacted with **1a** to yield the corresponding *γ*-ketoamides in high yields with excellent ee values (entries 1−3). Not only methacrylamides **2a**−**c** but also 2-phenylacrylamide **2d** could be employed (entry 4). With respect to aldehydes, a variety of primary and secondary unfunctionalized aliphatic aldehydes **1b**−**f** reacted with

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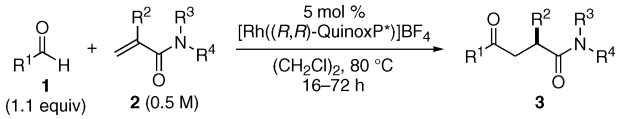
Table 2. Rhodium-Catalyzed Enantioselective Hydroacylation of Acrylamides **2a**−**d** with Aliphatic Aldehydes **1a**−**h**[a]

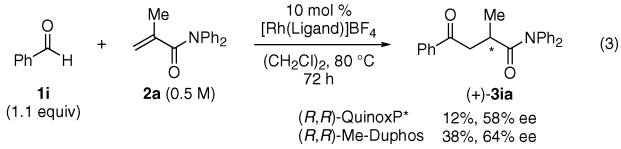


entry	1	R^1	2	R^2	R^3, R^4	yield (%)[b]	ee (%)
1	**1a**	$Ph(CH_2)_2$	**2a**	Me	Ph_2	87	98 (+)
2	**1a**	$Ph(CH_2)_2$	**2b**	Me	Me, Ph	74	96 (+)
3[c]	**1a**	$Ph(CH_2)_2$	**2c**	Me	Bn_2	73	97 (+)
4[c]	**1a**	$Ph(CH_2)_2$	**2d**	Ph	Ph_2	78	99 (+)
5[d]	**1b**	*n*-Pr	**2a**	Me	Ph_2	79	98 (+)
6	**1c**	*n*-C_7H_{15}	**2a**	Me	Ph_2	75	98 (+)
7[d]	**1d**	*i*-Bu	**2a**	Me	Ph_2	74	98 (R, +)
8[c,d]	**1d**	*i*-Bu	**2d**	Ph	Ph_2	80	97 (+)
9[d]	**1e**	*c*-C_5H_9	**2a**	Me	Ph_2	81	98 (+)
10	**1f**	Cy	**2a**	Me	Ph_2	76	98 (+)
11[c]	**1f**	Cy	**2d**	Ph	Ph_2	73	97 (+)
12	**1g**	*t*-Bu	**2a**	Me	Ph_2	0	−
13	**1h**	$BnO(CH_2)_3$	**2a**	Me	Ph_2	74	98 (+)

[a] $[Rh(nbd)_2]BF_4$ (0.025 mmol), (*R*,*R*)-QuinoxP* (0.025 mmol), **1** (0.550 mmol), **2** (0.500 mmol), and $(CH_2Cl)_2$ (1.0 mL) were used. The active catalysts were generated in situ by hydrogenation. [b] Yield based on **2**. [c] Catalyst: 10 mol %. [d] 2 equiv of **1** was used due to its volatility.

2a and **2d** to yield the corresponding γ-ketoamides in high yields with excellent ee values (entries 5−11), while pivalaldehyde (**1g**) failed to react with **2a** (entry 12). Functionalized aldehyde **1h** could also participate in this reaction (entry 13).

Unfortunately, the reaction of benzaldehyde (**1i**) and **2a** was sluggish and enantioselectivity was moderate, but the use of Me-Duphos as a ligand could improve both yield and ee values (eq 3).



(3)

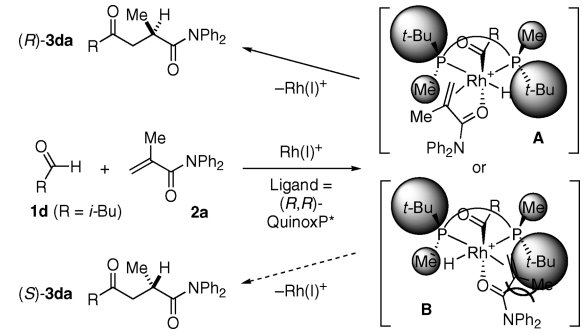
Finally, the reaction of a 1,2-disubstituted alkene, *N*,*N*-diphenylcrotonamide, was investigated, but complete product racemization was observed at 80 °C. Although a transition metal catalyzed hydroacylation of a trisubstituted alkene has not been reported, if the hydroacylation of trisubstituted alkene **2e** with **1a** proceeds, a thermodynamically stable diastereomer would be generated. Pleasingly, hydroacylation product **3ae** was obtained with perfect diastereoselectivity as well as high enantioselectivity, although significantly reduced reactivity was observed (eq 4).

(4)

A possible mechanism for highly selective production of (*R*)-**3da** is shown in Scheme 1. The formation of intermediate **A** might be more favorable than that of intermediate **B** due to the steric interaction between the amide moiety of **2a** and the *tert*-butyl group of (*R*,*R*)-QuinoxP* in intermediate **B**. We believed that strong bidentate coordination of substituted acrylamides to the cationic rhodium might stabilize the acylrhodium intermediate and construct the rigid chiral environment.

In conclusion, we have established that a cationic rhodium(I)/QuinoxP* complex catalyzes the highly enantioselective direct intermolecular hydroacylation of 1,1-disubstituted alkenes with unfunctionalized aldehydes. Future work will focus on establishment of the enantio- and diastereoselective hydroacylation of trisubstituted alkenes with aldehydes.

Scheme 1



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Supporting Information Available: Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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