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Cobalt-Catalyzed Enantioselective Intramolecular Hydroacylation of Ketones and Olefins

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Supporting Information

ABSTRACT: Cobalt−chiral diphoshine catalytic systems promote intramolecular hydroacylation reactions of 2-acylbenzaldehydes and 2-alkenylbenzaldehydes to afford phthalide and indanone derivatives, respectively, in moderate to good yields with high enantioselectivities. The ketone hydroacylation did not exhibit a significant H/D kinetic isotope effect (KIE) with respect to the aldehyde C−H bond, indicating that C−H activation would not be involved in the rate-limiting step.

The catalytic addition of an aldehyde C−H bond across an unsaturated bond, hydroacylation, represents an atom-efficient synthetic approach to carbonyl compounds.[1] Such transformations have been achieved in both inter- and intramolecular settings, conventionally and most extensively using rhodium catalysts.[2] Given the parallelism between the reactivities of cobalt and rhodium in various catalytic transformations including C−H functionalizations,[3,4] the use of more abundant cobalt as alternative catalysts for hydroacylation is a logical idea. Nevertheless, such examples have been rare. In the late 1990s, Brookhart demonstrated intermolecular hydroacylation of vinylsilane using a Cp*Co(I)−bisolefin catalyst.[5] Very recently, Dong developed the intermolecular hydroacylation of 1,3-dienes using a cobalt−diphosphine catalyst, which was proposed to involve, unlike typical rhodium-catalyzed hydroacylations, aldehyde/diene oxidative cyclization as a key step.[6] Besides these intermolecular examples, cobalt-catalyzed intramolecular hydroacylation has been documented for only a few substrates such as 2-vinylbenzaldehyde[5a] and 4-pentenal.[7] We report here that cobalt−chiral diphosphine catalysts[8,9] promote intramolecular hydroacylation reactions of 2-acylbenzaldehyde and 2-alkenylbenzaldehyde derivatives to afford enantioenriched phthalides and indanones (Scheme 1a), respectively, thus serving as viable alternatives to previously developed chiral rhodium catalysts (Scheme 1b,c).[10−13]

The present study commenced with a search for achiral cobalt(I) catalysts generated from cobalt(II) precatalysts and reductants[6,9,14] that can promote intramolecular hydroacylation of 2-acetylbenzaldehyde (**1a**). With a couple of trials, we found that the desired cyclization proceeded in the presence of $CoCl_2$ (10 mol %), dppe (10 mol %), and manganese powder (3 equiv) in acetonitrile at 80 °C, affording the phthalide product **2a** in 95% yield (Table 1, entry 1). With this initial finding, we attempted enantioselective cyclization of **1a** using a variety of chiral diphosphines, which revealed the high sensitivity of the efficiency and enantioselectivity of the reaction to the ligand structure (see the Supporting Information (SI) for full details). Only a few diphosphines promoted the desired cyclization to a reasonable extent (entries 2−4), among which (*R*,*R*)-Ph-BPE exhibited a high enantioselectivity of 95% ee (entry 2). With many other diphosphines, the product **2a** was formed only in low yields or not at all (entries 5−8), although the conversion of **1a** was generally high (up to 90%). In such cases, except for the recovered **1a**, only a trace amount of 3-hydroxyindan-1-one, a byproduct arising from intramolecular aldol reaction of **1a**, was observed by GC analysis (no decarbonylation product was detected). Thus, we speculate that intermolecular aldol condensation of **1a** took place to produce oligomeric products.

Upon further screening of cobalt precatalysts and reductants, we identified the combination of $CoBr_2$ (10 mol %), (*R*,*R*)-Ph-BPE (10 mol %), and indium powder (20 mol %) as the optimum catalytic system, which afforded **2a** in 92% yield with 95% ee (entry 11). The use of other reductants such as manganese and zinc powders did not affect the enantioselectivity but led to lower yields (entries 9 and 10). The catalyst loading could be reduced to 2.5 mol % without a decrease in the yield and

Scheme 1. Enantioselective Intramolecular Hydroacylation of Ketone and Olefin

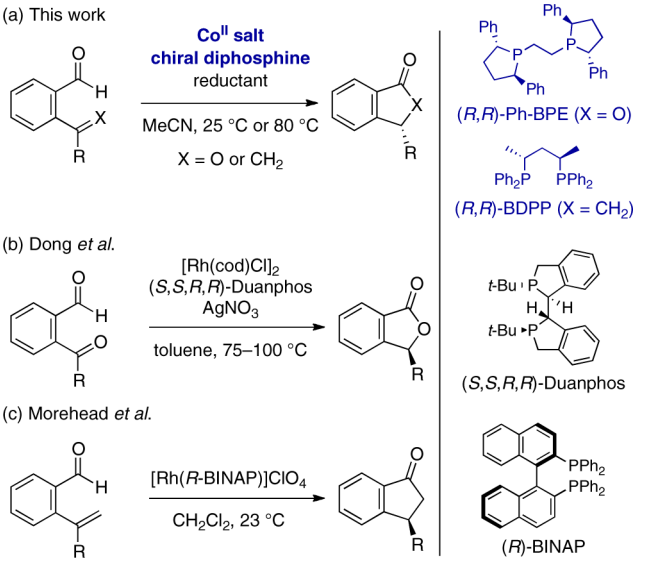

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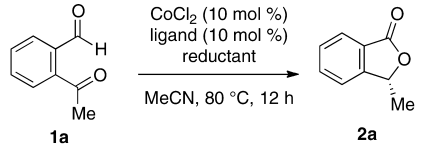
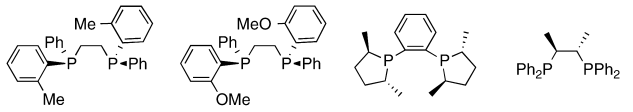
Table 1. Screening of Reaction Conditions for Intramolecular Ketone Hydroacylation[a]

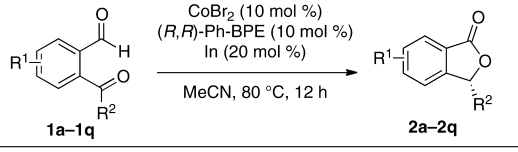


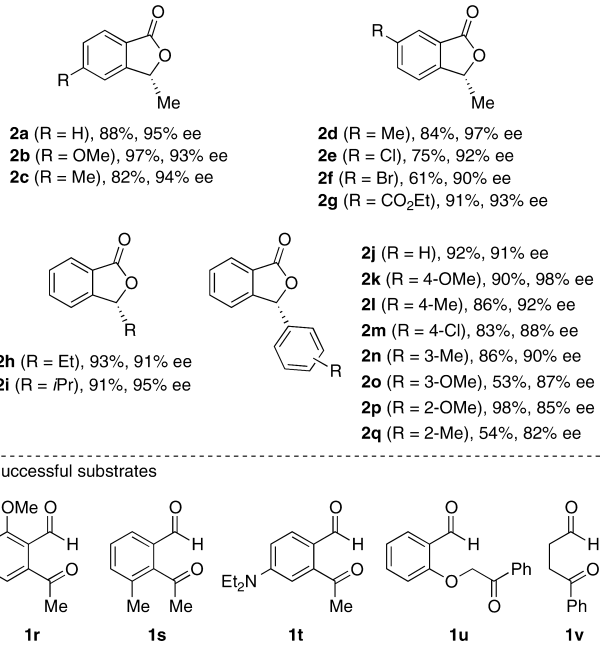


entry	ligand	reductant	yield (%)[b]	ee (%)[c]
1	dppe	Mn (3 equiv)	95	–
2	(*R*,*R*)-Ph-BPE	Mn (1 equiv)	70	95
3	(*R*,*R*,*S*,*S*)-Duanphos	Mn (1 equiv)	37	85
4	(*R*,*R*)-Tol-DIPAMP	Mn (1 equiv)	73	79
5	(*R*,*R*)-DIPAMP	Mn (1 equiv)	4	ND
6	(*R*,*R*)-Me-DuPhos	Mn (1 equiv)	12	ND
7	(*R*,*R*)-BDPP	Mn (1 equiv)	15	ND
8	(*S*,*S*)-Chiraphos	Mn (1 equiv)	0	–
9[d]	(*R*,*R*)-Ph-BPE	Mn (20 mol %)	59	95
10[d]	(*R*,*R*)-Ph-BPE	Zn (20 mol %)	82	95
11[d]	(*R*,*R*)-Ph-BPE	In (20 mol %)	92	95
12[d,e]	(*R*,*R*)-Ph-BPE	In (20 mol %)	95	95

[a]The reaction was performed on a 0.1 mmol scale. [b]Determined by GC. [c]Determined by chiral HPLC analysis. ND = not determined. The absolute stereochemistry was assigned by comparison of the optical rotation with the literature data (see the SI). [d]$CoBr_2$ was used instead of $CoCl_2$. [e]2.5 mol % each of $CoBr_2$ and ligand was used.

Scheme 2. Enantioselective Intramolecular Hydroacylation of Various 2-Acylbenzaldehydes[a]





[a]The reaction was performed on a 0.3 mmol scale. Isolated yields are shown. The ee's were determined by chiral HPLC analysis.

enantioselectivity (entry 12). Note that the reaction was also found to proceed at room temperature at a slower rate.

With the Co–Ph–BPE catalytic system in hand, we explored the scope of the enantioselective intramolecular hydroacylation using various 2-acylbenzaldehyde derivatives (Scheme 2). 2-Acetylbenzaldehydes substituted at the 4- or 5-position participated in the reaction to afford the corresponding phthalides **2b–2g** in moderate to good yields with enantioselectivities of 90% ee or greater. Chloro, bromo, and ester substituents were tolerated (see **2e–2g**). The reaction was found to be sensitive to steric influence and strong electronic perturbation on the benzene ring. Thus, the presence of a substituent at the 3- or 6-position in the substrates **1r** and **1s** shut down the desired hydroacylation reaction. The reaction of 2-acetylbenzaldehyde bearing a 4-diethylamino group **1t** resulted in almost complete recovery of the starting material.[15]

Acyl groups other than the acetyl group also served as internal acceptors for the enantioselective hydroacylation. Ethyl and isopropyl ketone substrates smoothly participated in the reaction to afford the corresponding products **2h** and **2i** in good yields with high enantioselectivities. Diaryl ketone substrates were also amenable to the cyclization reaction, where the enantioselectivity was affected by both the electronic and steric properties of the aroyl group (see **2j–2q**). Compared to the case of the parent benzoyl substrate (**2j**; 91% ee), the enantioselectivity was apparently enhanced with a 4-methoxybenzoyl group (**2k**; 98% ee) and lowered with 4-chloro-, 3-methoxy-, 2-methoxy-, and 2-methylbenzoyl groups (**2m**, **2o–2q**; 82–88% ee). A substrate with a longer tether, **1u**, did not afford the expected 7-membered lactone,[12b,c] while an aliphatic substrate **1v** underwent predominant decarbonylation to afford propiophenone as the major product.

With the successful demonstration of the cobalt-catalyzed enantioselective intramolecular hydroacylation of 2-acylbenzaldehydes, we next turned our attention to the reaction of an analogous olefinic substrate. As we did for the substrate **1a**, we initially identified the combination of $CoCl_2$ (10 mol %), dppp (10 mol %), and zinc powder (1 equiv) as an effective achiral catalytic system for the cyclization of 2-(1-phenylvinyl)benzaldehyde (**3a**) to indanone **4a** in acetonitrile at 80 °C (Table 2, entry 1). Upon subsequent screening of chiral ligands, (*R*,*R*)-BDPP was found to promote the reaction with comparable efficiency with an enantioselectivity of 93% ee (entry 2). Other chiral diphosphines exhibited only modest enantioselectivities (ca. 30–50% ee; entries 3–7) or afforded no desired product (see the SI). GC analysis of such unsuccessful cases indicated the formation of a mixture of products arising from decarbonylation or reduction of the C=O or C=C bond. The reaction with (*R*,*R*)-BDPP proceeded smoothly at room temperature using a lower amount (50 mol %) of zinc powder (entry 8).

During this optimization and subsequent studies, we noted a significant difference between the ketone hydroacylation and the olefin hydroacylation in terms of the appearance of the reaction mixture. In the ketone hydroacylation, a dark brown solution formed immediately upon the addition of MeCN to a heterogeneous mixture of cobalt(II) salt, Ph-BPE, and metal reductant, without a sign of the characteristic blue color of Co(II). On the other hand, the color of the olefin hydroacylation solution was initially light green, which only gradually turned

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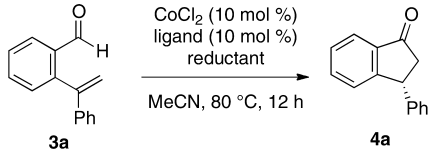
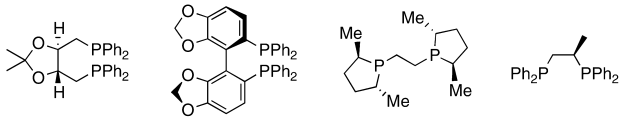
Table 2. Screening of Reaction Conditions for Intramolecular Olefin Hydroacylation[a]





entry	ligand	reductant	yield (%)[b]	ee (%)[c]
1	dppp	Zn (1 equiv)	79	–
2	(*R*,*R*)-BDPP	Zn (1 equiv)	78	93
3	(*R*,*R*)-DIOP	Zn (1 equiv)	87	53
4	(*R*)-SEGPHOS	Zn (1 equiv)	17	52
5	(*R*,*R*,*S*,*S*)-Duanphos	Zn (1 equiv)	50	51
6	(*R*,*R*)-Me-BPE	Zn (1 equiv)	15	42
7	(*R*)-Prophos	Zn (1 equiv)	22	31
8[d]	(*R*,*R*)-BDPP	Zn (50 mol %)	99	97
9[d]	(*R*,*R*)-BDPP	Mn (1 equiv)	0	–
10[d]	(*R*,*R*)-BDPP	In (1 equiv)	0	–

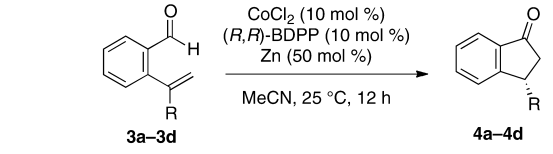
[a]The reaction was performed on a 0.1 mmol scale. [b]Determined by GC. [c]Determined by chiral HPLC analysis. The absolute stereochemistry was assigned by comparison of the optical rotation with the literature data (see the SI). [d]The reaction was performed at room temperature.

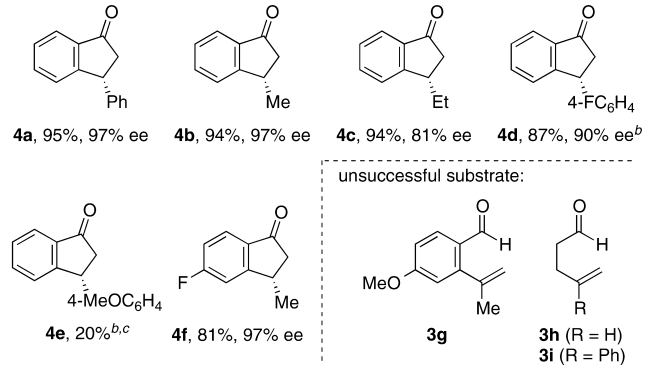
dark brown over several hours. Furthermore, manganese and indium powders did not promote the reaction at all, where the color remained green (entries 9 and 10). These observations suggest that the reduction of the Co(II)–BDPP precatalyst is much slower than that of the Co(II)–Ph–BPE precatalyst, occurring along with the reaction progress.

The present olefin hydroacylation turned out rather sensitive to substituents on the olefinic and aromatic moieties, thus offering a narrower scope compared with that of the ketone hydroacylation (Scheme 3). While the substrates bearing 1-phenylvinyl or 1-methylvinyl groups underwent the cyclization reaction with excellent enantioselectivities (see **4a** and **4b**), a significant decrease in the enantioselectivity (81% ee) was observed with the one bearing a 1-ethylvinyl group (see **4c**). The reaction of the substrate bearing a 1-(4-fluorophenyl)vinyl group proceeded at an elevated temperature of 80 °C (see **4d**), while the one bearing a 1-(4-methoxyphenyl)vinyl group reacted sluggishly even at this temperature (see **4e**). In contrast to the ketone hydroacylation (see **2b** in Scheme 2), a methoxy group on the *para* position of the formyl group completely shut down the reaction (see **3g**). Note that linear substrates such as 4-pentenal (**3h**) and 4-phenyl-4-pentenal (**3i**) failed to participate in the reaction.

In order to gain mechanistic insight into the present intramolecular hydroacylation reactions, we performed experiments using substrates bearing a deuterated formyl group (**1a**-*d* and **3b**-*d*; Schemes 4 and S1). The reaction of a mixture of **1a**-*d* and **1b** under the Co–Ph–BPE catalysis cleanly produced a mixture of deuterated phthalide **2a**-*d* and nondeuterated phthalide **2b** without any H/D crossover, demonstrating the intramolecularity of the hydroacylation process and excluding a Tishchenko-type mechanism involving a free cobalt hydride

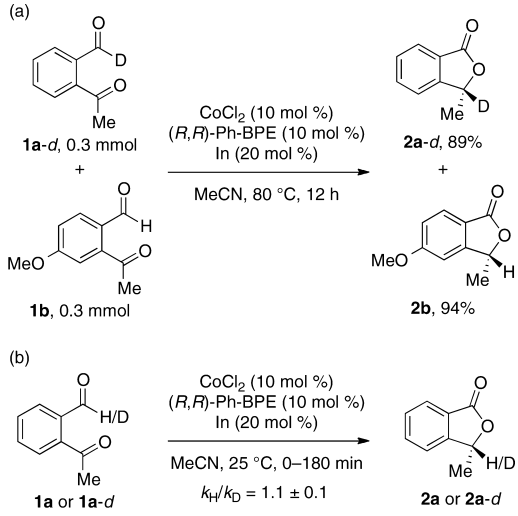
Scheme 3. Intramolecular Hydroacylation of 2-Alkenylbenzaldehydes[a]





[a]The reaction was performed on a 0.3 mmol scale. Isolated yields are shown. The ee's were determined by chiral HPLC analysis. [b]The reaction was performed at 80 °C. [c]^{1}H NMR yield. Ee value was not determined.

Scheme 4. Deuterium-Labeling Experiments



species (Scheme 4a).[16] Comparison of initial rates of individual reactions of **1a** and **1a**-*d* at 25 °C (up to ca. 25% conversion) gave a kinetic isotope effect (KIE) of 1.1 ± 0.1, suggesting that the C–H activation is not involved in the rate-limiting step (Scheme 4b). We surmise that reductive elimination rather than ketone insertion is the rate-limiting step, because the latter step would also exhibit a certain (if not substantial) magnitude of KIE (see the SI for further discussion).[12b] On the other hand, the reaction of **3b**-*d* gave highly fluctuating yields even with the same batch of substrate and catalyst (Scheme S1). We speculate that the fluctuation comes from the slow and heterogeneous nature of the precatalyst reduction (vide infra), the efficiency of which would be susceptible to subtle changes of the reaction conditions. The search for a protocol suitable for kinetic analysis is currently underway.[17]

In summary, we have demonstrated that cobalt–chiral diphosphine catalytic systems are capable of promoting the

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enantioselective intramolecular hydroacylation of ketones and olefins. While these reactions appear to involve, as in the case of rhodium-catalyzed hydroacylations, catalytic cycles consisting of C−H oxidative addition, insertion of the C═X bond into the Co−H bond, and C−X reductive elimination, the relative rates of the elementary steps deserve further investigation. Efforts to expand the scope of cobalt-catalyzed hydroacylation of unsaturated bonds are also underway.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures and compound characterization. This material 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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■ REFERENCES

(1) For reviews, see: (a) Jun, C.-H.; Jo, E.-A.; Park, J.-W. *Eur. J. Org. Chem.* **2007**, 1869. (b) Willis, M. C. *Chem. Rev.* **2010**, *110*, 725. (c) Leung, J. C.; Krische, M. J. *Chem. Sci.* **2012**, *3*, 2202. (d) Trost, B. M.; Krische, M. J. *Synlett* **1998**, 1. (e) Murphy, S. K.; Dong, V. M. *Chem. Commun.* **2014**, *50*, 13645.

(2) For recent examples, see: (a) Gonzaléz-Rodríguez, C.; Pawley, R. J.; Chaplin, A. B.; Thompson, A. L.; Weller, A. S.; Willis, M. C. *Angew. Chem., Int. Ed.* **2011**, *50*, 5134. (b) Hoffman, T. J.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 10670. (c) Lenden, P.; Entwistle, D. A.; Willis, M. C. *Angew. Chem., Int. Ed.* **2011**, *50*, 10657. (d) Murphy, S. K.; Coulter, M. M.; Dong, V. M. *Chem. Sci.* **2012**, *3*, 355. (e) Chaplin, A. B.; Hooper, J. F.; Weller, A. S.; Willis, M. C. *J. Am. Chem. Soc.* **2012**, *134*, 4885. (f) von Delius, M.; Le, C. M.; Dong, V. M. *J. Am. Chem. Soc.* **2012**, *134*, 15022. (g) Hooper, J. F.; Young, R. D.; Weller, A. S.; Willis, M. C. *Chem.—Eur. J.* **2013**, *19*, 3125. (h) Castaing, M.; Wason, S. L.; Estepa, B.; Hooper, J. F.; Willis, M. C. *Angew. Chem., Int. Ed.* **2013**, *52*, 13280. (i) Murphy, S. K.; Bruch, A.; Dong, V. M. *Angew. Chem., Int. Ed.* **2014**, *53*, 2455. (j) Ghosh, A.; Stanley, L. M. *Chem. Commun.* **2014**, *50*, 2765. (k) Arnold, J. S.; Mwenda, E. T.; Nguyen, H. M. *Angew. Chem., Int. Ed.* **2014**, *53*, 3688. (l) Kou, K. G. M.; Le, D. N.; Dong, V. M. *J. Am. Chem. Soc.* **2014**, *136*, 9471.

(3) Gao, K.; Yoshikai, N. *Acc. Chem. Res.* **2014**, *47*, 1208.

(4) For selected recent reports and review articles, see: (a) Obligacion, J. V.; Semproni, S. P.; Chirik, P. J. *J. Am. Chem. Soc.* **2014**, *136*, 4133. (b) Santhoshkumar, R.; Mannathan, S.; Cheng, C.-H. *Org. Lett.* **2014**, *16*, 4208. (c) Tan, B.-H.; Yoshikai, N. *Org. Lett.* **2014**, *16*, 3392. (d) Friedfeld, M. R.; Shevlin, M.; Hoyt, J. M.; Krska, S. W.; Tudge, M. T.; Chirik, P. J. *Science* **2013**, *342*, 1076. (e) Yoshino, T.; Ikemoto, H.; Matsunaga, S.; Kanai, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 2207. (f) Karthikeyan, J.; Masilamani, J.; Cheng, C.-H. *Chem.—Eur. J.* **2010**, *16*, 8989. (g) Hess, W.; Treutwein, J.; Hilt, G. *Synthesis* **2008**, 3537. (h) Chopade, P. R.; Louie, J. *Adv. Synth. Catal.* **2006**, *348*, 2307. (i) Varela, J. A.; Saá, C. *Chem. Rev.* **2003**, *103*, 3787. (j) Beller, M.; Cornils, B.; Frohning, C. D.; Kohlpaintner, C. W. *J. Mol. Catal. A* **1995**, *104*, 17.

(5) (a) Lenges, C. P.; Brookhart, M. *J. Am. Chem. Soc.* **1997**, *119*, 3165. (b) Lenges, C. P.; White, P. S.; Brookhart, M. *J. Am. Chem. Soc.* **1998**, *120*, 6965.

(6) Chen, Q.-A.; Kim, D. K.; Dong, V. M. *J. Am. Chem. Soc.* **2014**, *136*, 3772.

(7) Vinogradov, M. G.; Tuzikov, A. B.; Nikishin, G. I.; Shelimov, B. N.; Kazansky, V. B. *J. Organomet. Chem.* **1988**, *348*, 123.

(8) For a review of cobalt-catalyzed enantioselective reactions, see: Pellissier, H.; Clavier, H. *Chem. Rev.* **2014**, *114*, 2775.

(9) For examples of enantioselective reactions using cobalt−chiral diphosphine catalysts, see refs 4d and 4f, and the following: (a) Sawano, T.; Ashouri, A.; Nishimura, T.; Hayashi, T. *J. Am. Chem. Soc.* **2012**, *134*, 18936. (b) Wei, C.-H.; Mannathan, S.; Cheng, C.-H. *Angew. Chem., Int. Ed.* **2012**, *51*, 10592. (c) Wei, C.-H.; Mannathan, S.; Cheng, C.-H. *J. Am. Chem. Soc.* **2011**, *133*, 6942. (d) Sharma, R. K.; RajanBabu, T. V. *J. Am. Chem. Soc.* **2010**, *132*, 3295.

(10) Phan, D. H. T.; Kim, B.; Dong, V. M. *J. Am. Chem. Soc.* **2009**, *131*, 15608.

(11) Kundu, K.; McCullagh, J. V.; Morehead, A. T., Jr. *J. Am. Chem. Soc.* **2005**, *127*, 16042.

(12) For other examples of enantioselective Rh-catalyzed hydroacylation of C═O bonds, see ref 2l and the following: (a) Khan, H. A.; Kou, K. G. M.; Dong, V. M. *Chem. Sci.* **2011**, *2*, 407. (b) Shen, Z.; Dornan, P. K.; Khan, H. A.; Woo, T. K.; Dong, V. M. *J. Am. Chem. Soc.* **2009**, *131*, 1077. (c) Shen, Z.; Khan, H. A.; Dong, V. M. *J. Am. Chem. Soc.* **2008**, *130*, 2916.

(13) For other examples of enantioselective Rh-catalyzed hydroacylation of C═C bonds, see refs 2b, 2j, 2k, and the following: (a) Phan, D. H.; Kou, K. G. M.; Dong, V. M. *J. Am. Chem. Soc.* **2010**, *132*, 16354. (b) Coulter, M. M.; Kou, K. G. M.; Galligan, B.; Dong, V. M. *J. Am. Chem. Soc.* **2010**, *132*, 16330. (c) Shibata, Y.; Tanaka, K. *J. Am. Chem. Soc.* **2009**, *131*, 12552. (d) Coulter, M. M.; Dornan, P. K.; Dong, V. M. *J. Am. Chem. Soc.* **2009**, *131*, 6932. (e) Osborne, J. D.; Randell-Sly, H. E.; Currie, G. S.; Cowley, A. R.; Willis, M. C. *J. Am. Chem. Soc.* **2008**, *130*, 17232. (f) Barnhart, R. W.; Wang, X.; Noheda, P.; Bergens, S. H.; Whelan, J.; Bosnich, B. *J. Am. Chem. Soc.* **1994**, *116*, 1821. (g) Taura, Y.; Tanaka, M.; Wu, X.-M.; Funakoshi, K.; Sakai, K. *Tetrahedron* **1991**, *47*, 4879.

(14) Fiebig, L.; Kuttner, J.; Hilt, G.; Schwarzer, M. C.; Frenking, G.; Schmalz, H.-G.; Schäfer, M. *J. Org. Chem.* **2013**, *78*, 10485.

(15) The addition of 1 equiv of $PhNEt_2$ to the reaction of **1a** did not interfere with the formation of **2a** (86%, 95% ee). This suggests that the lack of reactivity of **1t** is not due to coordination of the amino group to the catalyst.

(16) (a) Omura, S.; Fukuyama, T.; Murakami, Y.; Okamoto, H.; Ryu, I. *Chem. Commun.* **2009**, 6741. (b) Murphy, S. K.; Dong, V. M. *J. Am. Chem. Soc.* **2013**, *135*, 5553.

(17) For previous kinetic studies on rhodium- and cobalt-catalyzed olefin hydroacylation, see refs 2e and 5b, and the following: (a) Fairlie, D. P.; Bosnich, B. *Organometallics* **1988**, *7*, 946. (b) Barnhart, R. W.; Bosnich, B. *Organometallics* **1995**, *14*, 4343. (c) Roy, A. H.; Lenges, C. P.; Brookhart, M. *J. Am. Chem. Soc.* **2007**, *129*, 2082. (d) Hyatt, I. F. D.; Anderson, H. K.; Morehead, A. T., Jr.; Sargent, A. L. *Organometallics* **2008**, *27*, 135.