Asymmetric Catalysis

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Cobalt-Catalyzed Enantio- and Diastereoselective Intramolecular Hydroacylation of Trisubstituted Alkenes

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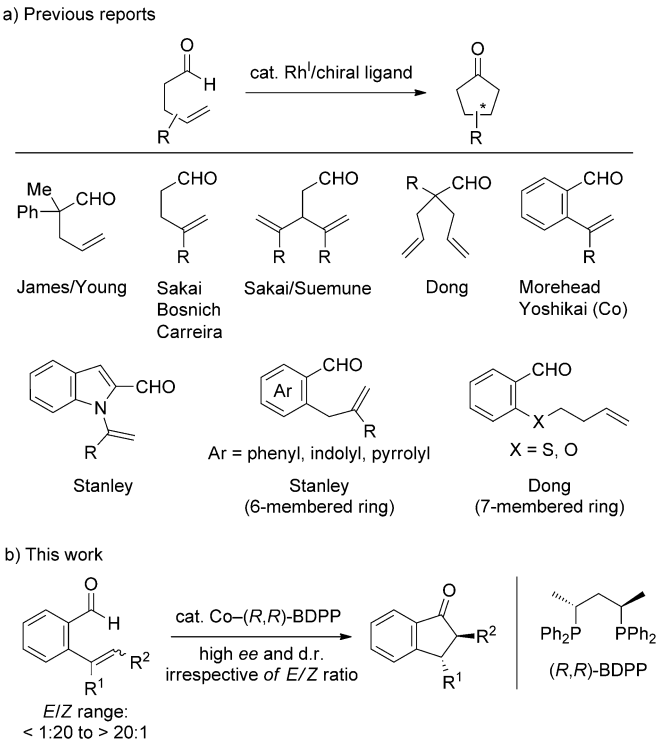
Abstract: *Enantio- and diastereoselective synthesis of trans-2,3-disubstituted indanones is achieved by intramolecular hydroacylation of 2-alkenylbenzaldehydes bearing trisubstituted alkenyl groups under cobalt-chiral diphosphine catalysis. Notably, a high level of enantioselectivity is induced regardless of the stereochemistry (E/Z ratio) of the alkenyl group of the starting material. Deuterium-labeling experiments shed light on the productive reaction pathways of the E- and Z-isomers.*

Hydroacylation of alkenes represents an atom-economical approach for the synthesis of ketones.[1] The development of intramolecular and enantioselective variants of this transformation is attractive in light of the abundance of chiral cyclic ketones in natural products and synthetic pharmaceuticals,[2] as well as the utility of such ketones as building blocks.[3] Since the seminal work of James and Young on the kinetic resolution of 2,2-disubstituted 4-pentenal as the first example,[4] major progress in intramolecular enantioselective hydroacylation has been made using chiral rhodium complexes as catalysts (Scheme 1 a).[5,6] In particular, the use of cationic rhodium-chiral phosphine complexes, initially introduced by the groups of Sakai and Bosnich,[7] has enabled cyclizations leading to chiral cyclopentanones,[8] including those involving desymmetrization[9] or kinetic resolution processes.[10] The rhodium catalysis has been extended to benzene- and indole-tethered substrates,[11] and also to substrates leading to six-[12] and seven-membered cycles.[13–15] These successful examples, however, are limited to substrates bearing either mono- or disubstituted (particularly 1,1-disubstituted) alkenyl groups. Intramolecular hydroacylation of trisubstituted alkenes, enantioselective as well as racemic variants, remains largely unexplored.[16] Herein, we report on the development of an intramolecular enantio- and diastereoselective hydroacylation of 2-alkenylbenzaldehydes bearing trisubstituted alkenyl groups, a reaction which is promoted by a cobalt/chiral diphosphine catalyst (Scheme 1 b). Notably, good to high enantioselectivity is achieved regardless of the *E*/*Z* ratio of the alkenyl group. The reaction allows facile preparation of a variety of enantiomerically enriched *trans*-2,3-disubstituted indanones, for which existing synthetic methods have been limited in number and scope.[17]



Scheme 1. Intramolecular enantioselective hydroacylation of alkenes.

Recently, we reported on the use of a cobalt/chiral disphosphine catalytic system for the enantioselective intramolecular hydroacylation of 2-alkenylbenzaldehydes bearing 1,1-disubstituted alkene moieties.[18] The present study began with our attempt to extend the scope of this catalytic system to substrates bearing trisubstituted alkenes. To this end, we chose (*E*)-2-(dec-5-en-5-yl)benzaldehyde (**1a**) as the model substrate, which was readily prepared with exclusive *E* stereochemistry by cobalt-catalyzed migratory arylzincation of 5-decyne (see the Supporting Information for details).[19] The reaction under our original reaction conditions, employing $CoCl_2$ (10 mol%), (*R*,*R*)-BDPP (10 mol%), and Zn (50 mol%) in MeCN,[18] was rather sluggish, thus affording the indanone product **2a** in only 9% yield at 80°C after 12 hours (Table 1, entry 1). The following experiments revealed significant effects of the solvent, the cobalt precatalyst, and the reductant on the reaction efficiency. By using

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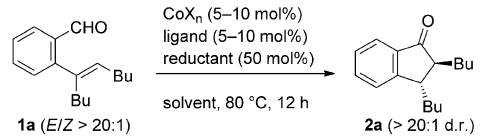
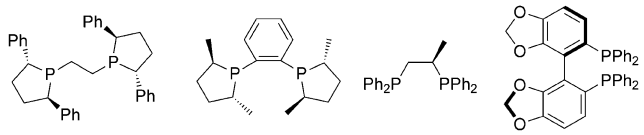
Table 1: Effect of reaction conditions.[a]





Entry	Catalytic system	Yield [%][b]	*ee* [%][c]
1	$CoCl_2$/(*R*,*R*)-BDPP (10%), Zn, MeCN	9	n.d.
2	$CoCl_2$/(*R*,*R*)-BDPP (5%), Zn, DMF	49	92
3	$CoBr_2$/(*R*,*R*)-BDPP (5%), Zn, DMF	75	92
4	$CoBr_2$/(*R*,*R*)-BDPP (5%), Mn, DMF	95 (92)	92
5	CoI_2/(*R*,*R*)-BDPP (5%), Mn, DMF	75	92
6	$CoBr_2$/(*R*,*R*)-BDPP (5%), Mn, MeCN	12	n.d.
7	$CoBr_2$/(*R*,*R*)-Ph-BPE (5%), Mn, DMF	85	85
8	$CoBr_2$/(*R*,*R*)-Me-Duphos (5%), Mn, DMF	66	46
9	$CoBr_2$/(*R*)-Prophos (5%), Mn, DMF	42	7
10	$CoBr_2$/(*R*)-Segphos (5%), Mn, DMF	16	75

[a] The reaction was performed on a 0.1 mmol scale at a concentration of 0.3 M. [b] Determined by GC using mesitylene as an internal standard. Yield of isolated product (for a 0.3 mmol scale reaction) is shown within the parentheses. [c] Determined by HPLC using a chiral stationary phase. DMF = *N*,*N*-dimethylformamide, n.d. = not determined.

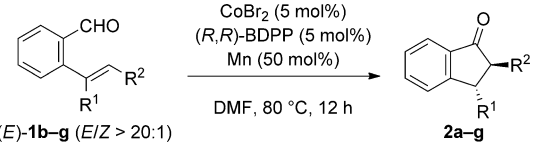
DMF as the solvent, the same catalytic system (with 5 mol% loading) promoted the reaction to a considerable extent to afford **2a** in 49% yield with 92% *ee* and greater than 20:1 d.r. (entry 2). The yield was further improved by changing the precatalyst and the reductant to $CoBr_2$ and Mn, respectively. Thus, **2a** was obtained in 92% yield upon isolation without change of the enantio- and diastereoselectivties (entry 4), while replacement of $CoBr_2$ with CoI_2 led to a slight decrease in the yield (entry 5). Regardless of the precatalyst and the reductant, the reaction proved sluggish in MeCN (entry 6), and no product formation was observed in other solvents such as THF and toluene (data not shown). Among the chiral diphosphines tested, (*R*,*R*)-Ph-BPE induced a good level of efficiency and enantioselectivity (entry 7), while the rest showed unsatisfactory performances (entries 8–10).

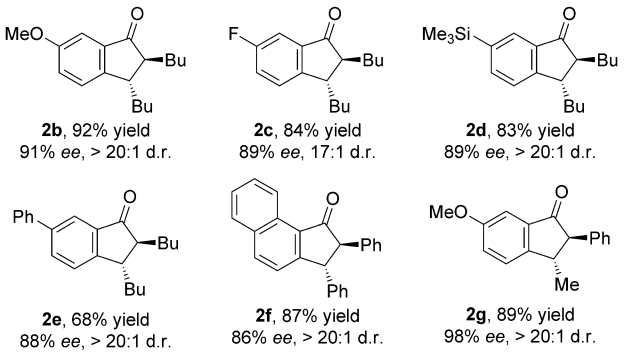
With the new optimized catalytic system in hand, we explored the scope with respect to the 2-alkenylbenzaldehydes for the present 2,3-disubstituted indanone synthesis. First, we focused on a small set of substrates [(*E*)-**1b**–**g**] which could be prepared with high *E* selectivity (> 20:1) by either the cobalt-catalyzed migratory arylzincation[19] or cobalt-catalyzed, aldimine-directed alkyne hydroarylation (Table 2).[20] As a result, indanone derivatives bearing 2,3-dibutyl (**2b**–**e**), 2,3-diphenyl (**2f**), or 2-phenyl-3-methyl (**2g**) groups, and different substituents on the benzo moiety, were synthesized in good yields with *ee* values around or higher than 90% and d.r. values around or higher than 20:1.

In the next set of experiments, we examined reactions of the 2-alkenylbenzaldehydes **1g**–**x** prepared by Wittig olefination (Table 3). Except for a few cases, these starting materials were either moderately or substantially rich in the *Z* isomer, with typical *E*/*Z* ratios ranging from 1:2 to 1:7. We were intrigued to find that the 2-phenyl-3-methylindanone derivative **2g** could be obtained from **1g**, having a modest *E*/*Z* ratio (1:2.5), with high enantio- and diastereoselectivities (96% *ee*, 20:1 d.r.), which were comparable to that of **2g** obtained from (*E*)-**1g** (see Table 2). Likewise, a series of 2-aryl-3-methyl (or ethyl) indanones (**2h**–**n**) were obtained in good yields with high enantio- and diastereoselectivities regardless of the *E*/*Z* ratio of the starting material, while a modest diastereoselectivity was observed for **2k** bearing a 4-trifluoromethyl group. 2-Butyl-3-methylindanone (**2o**) was also obtained in a highly enantio- and diastereoselective manner from the corresponding substrate with an *E*/*Z* ratio of 1:7. Furthermore, a series of substrates bearing aryl and methyl groups at the R^1 and R^2 positions, respectively, underwent enantioselective cyclization to give the corresponding 2-methyl-3-arylindanones **2p**–**w**, albeit with somewhat lower diastereoselectivities (< 10:1). Here, 4-dimethylamino and 4-trifluoromethyl groups on the aryl ring lowered the enantioselectivity (**2t** and **2u**), and the substrate bearing a 2-thienyl group exhibited a sharp drop in the enantio- and diastereoselectivities (**2w**). Last but not least, 2-butyl-3-phenylindanone (**2x**) was obtained in a good yield with moderate enantioselectivity. Note that an attempt on cyclization of a substrate analogous to **1p**, which contains an alkyl (CH_2CH_2) tether instead of the benzene tether, failed to produce the desired cyclopentanone derivative.

Having clarified the scope of the 2,3-disubstituted indanone synthesis, we became interested in the reaction pathway of the present cyclization and the origin of the low sensitivity of the enantioselectivity to the *E*/*Z* ratio of the starting material. To gain insight into these issues, experiments using deuterium-labeled substrates were performed (Scheme 2). The stereochemically pure substrate bearing a deuterated

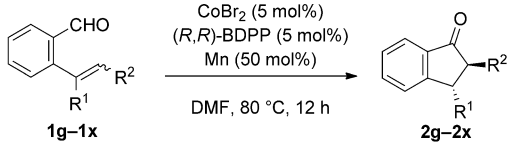
Table 2: Cyclization of 2-alkenylbenzaldehydes with high *E*/*Z* ratios (> 20:1).[a]

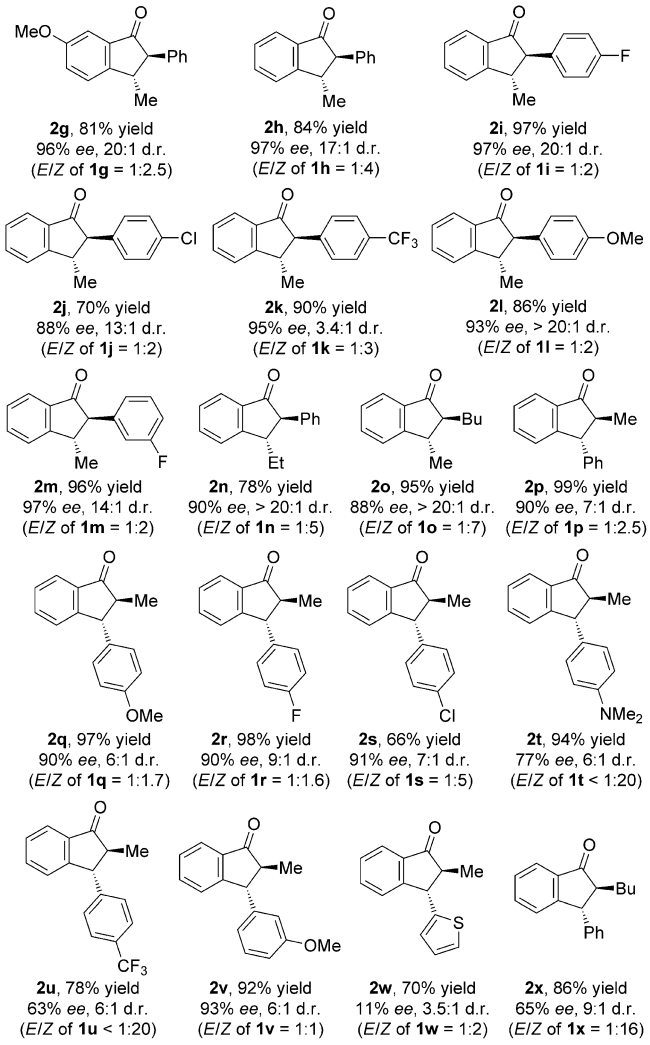




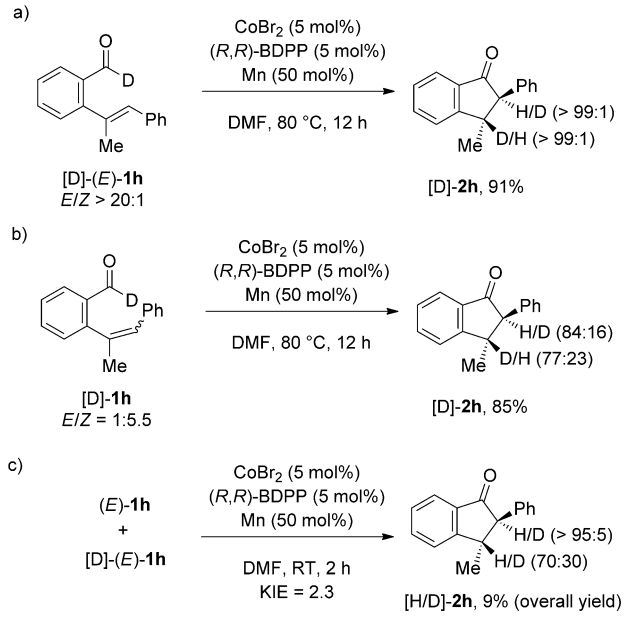
[a] The reaction was performed on a 0.3 mmol scale under the reaction conditions in Table 1, entry 4. Diastereomer ratio (d.r.) was determined by GC analysis of the crude reaction mixture.

Table 3: Cyclization of 2-alkenylbenzaldehydes with low to moderate *E*/*Z* ratios.[a]





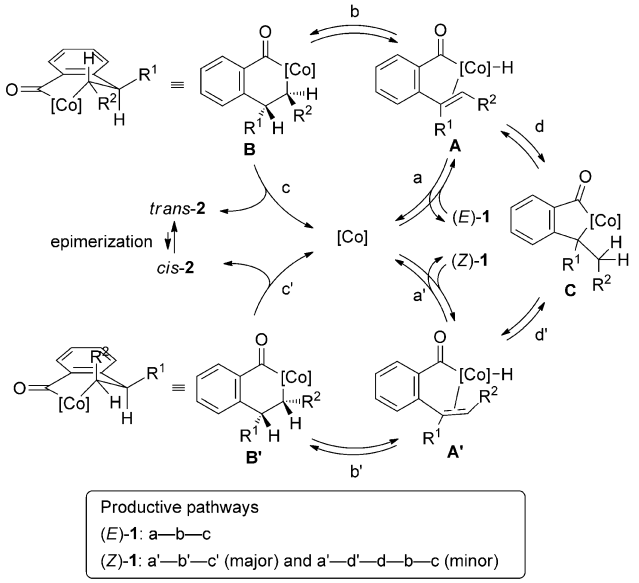
[a] The reaction was performed on a 0.3 mmol scale under the conditions in Table 1, entry 4. Diastereomer ratio (d.r.) was determined by GC analysis of the crude reaction mixture.



Scheme 2. Deuterium-labeling experiments.

formyl group, [D]-(*E*)-**1h**, underwent cyclization to give the indanone [D]-**2h** with a clean transfer of the deuterium atom to the 3-position (Scheme 2a). On the other hand, the reaction of the *Z*-rich deuterated substrate [D]-**1h** (*E*/*Z* = 1:5.5) resulted in substantial deuterium incorporation into the 3-position (77%) accompanied by slight deuteration of the 2-position (16%; Scheme 2b). In addition, the reaction of a 1:1 mixture of (*E*)-**1h** and [D]-(*E*)-**1h**, when performed at room temperature and quenched at the early stage, afforded the product **2h** with a H/D ratio of 70:30 at the 3-position (Scheme 2c), thus corresponding to a KIE value of 2.3.

Building on the above experiments and assuming mechanistic analogy of the cobalt- and rhodium-catalyzed hydroacylation,[21] we propose the catalytic cycle illustrated in Scheme 3. The reduction of the Co^{II} precatalyst in the presence of the chiral diphosphine would give rise to a catalytically active Co^{I}/diphosphine species.[22] Oxidative addition of the aldehyde C–H bond of the substrate, either (*E*)- or (*Z*)-**1**, to this species, which may be assisted by the coordination of the alkenyl group, leads to the acyl(hydrido)cobalt intermediates **A** and **A′**, respectively. Intramolecular migratory insertion of **A** and **A′** gives diastereomeric six-membered cobaltacycles, **B** and **B′**, respectively, or the common five-membered cobaltacycle **C**. The intermediate **B** features a di-equatorial arrangement of the substituents R^1 and R^2, and its reductive elimination results in the indanone product *trans*-**2**.[23] In contrast, reductive elimination of **B′** produces *cis*-**2**, which is then epimerized to the major diastereomer, that is, *trans*-**2**, while this process may be less favored because of the axial orientation of the R^2 group. Meanwhile, **C** may serve as a channel for the interconversion between **A** and **A′** (i.e., *E*/*Z* isomerization) by migratory insertion/β-hydride elimination. Note that this interconversion causes exchange of the cobalt-bound hydrogen and the olefinic hydrogen. The reaction of [D]-(*E*)-**1h** (Scheme 2a) indicates its exclusive cyclization via **A** and **B** without *E*/*Z* isomerization. On the other hand, the deuterium distribution in the reaction of *Z*-rich [D]-**1h** (Scheme 2b) suggests that some of the *Z*-isomers undergo *E*/*Z* isomerization via **C** and then afford *trans*-**2** via **A** and **B**, while the rest would initially produce *cis*-**2** via **A′** and **B′**. Additional control experiments confirmed the feasibility of the product epimerization under the reaction conditions, and also excluded the possibility of rapid equilibration between the *E*/*Z* isomers prior to hydroacylation (see Scheme S1 in the Supporting Information). The competitive isotope effect (Scheme 2c) may reflect either the

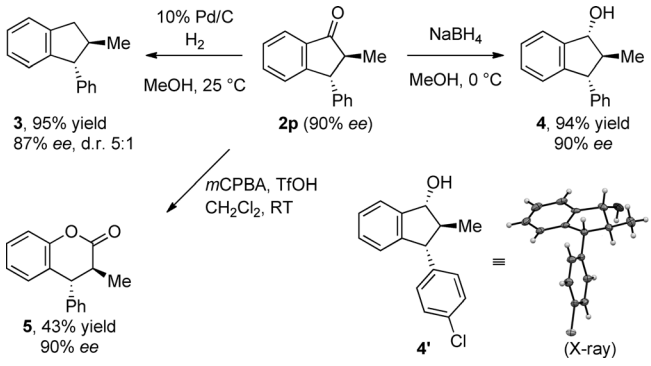


Scheme 3. Proposed catalytic cycle and rationale for the *E*/*Z*-insensitive enantioselectivity.

C–H activation or the migratory insertion as the first irreversible step.[24,25]

The enantioenriched 2,3-*trans*-substituted indanones would serve as valuable building blocks for further synthetic manipulations. To illustrate this point, 2-methyl-3-phenylindanone (**2p**) was subjected to deoxygenation under Pd/C and H_2, reduction with $NaBH_4$, and Baeyer–Villiger oxidation to afford the indane **3**, indanol **4**, and dihydrocoumarin **5**, respectively, with retention of the enantiomeric purity (Scheme 4). Note that the $NaBH_4$ reduction was also performed on 2-methyl-3-(4-chlorophenyl)indanone (**2s**), and X-ray crystallographic analysis of the corresponding indanol product **4′** allowed determination of the absolute configurations of the stereocenters generated by the hydroacylation.[26]

In summary, we have achieved enantio- and diastereoselective synthesis of 2,3-disubstituted indanones by intramolecular hydroacylation of 2-alkenylbenzaldehydes catalyzed by a cobalt-chiral diphosphine complex. The reaction represents a rare example of enantioselective intramolecular hydroacylation of trisubstituted alkenes, and is notable for its ability to convert starting materials of modest alkene *E*/*Z* ratios into cyclization products with high enantio- and diastereoselectivities. Further synthetic and mechanistic investigations into hydroacylation and related C–H transformations catalyzed by cobalt complexes[27,28] are in progress in our laboratory.



Scheme 4. Selected product transformations. *m*CPBA = *m*-chloroperbenzoic acid, Tf = trifluoromethanesulfonyl.

Acknowledgments

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Conflict of interest

The authors declare no conflict of interest.

Keywords: asymmetric synthesis · C–H activation · cobalt · cyclizations · hydroacylation

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[23] Alternatively, **B** (**B′**) may undergo decarbonylation, re-insertion of CO into the cobalt-alkyl bond, and reductive elimination to produce *trans*-**2** (*cis*-**2**). See Ref. [21] for a relevant mechanistic discussion on rhodium-catalyzed intramolecular hydroacylation.
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[25] The individual kinetics of (*E*)-**1h** and [D]-(*E*)-**1h** were difficult to study because of a fluctuating induction period for the reaction (see Ref. [18]).
[26] CCDC 1518421 (**4′**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.
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Communications

Asymmetric Catalysis

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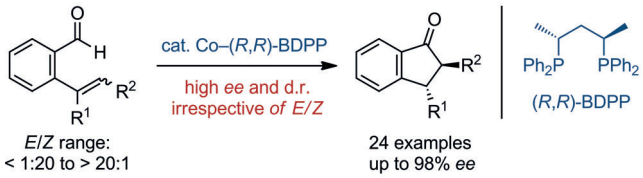
Cobalt-Catalyzed Enantio- and Diastereoselective Intramolecular Hydroacylation of Trisubstituted Alkenes



EZ: Enantio- and diastereoselective synthesis of *trans*-2,3-disubstituted indanones is achieved by intramolecular hydroacylation of 2-alkenylbenzaldehydes containing trisubstituted alkenyl groups under cobalt-chiral diphosphine catalysis. High level of enantioselectivity is induced regardless of the stereochemistry (*E*/*Z* ratio) of the alkenyl group of the starting material.

