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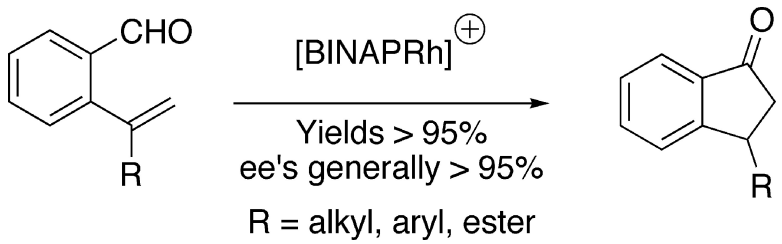

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Hydroacylation of 2-Vinyl Benzaldehyde Systems: An Efficient Method for the Synthesis of Chiral 3-Substituted Indanones

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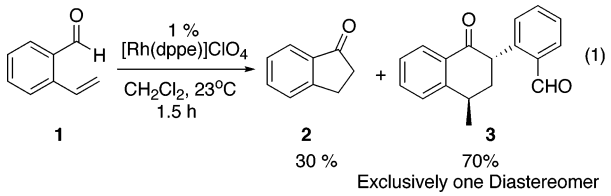
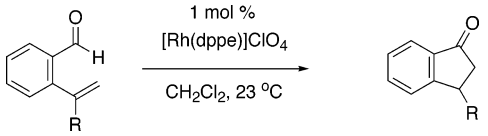
Indan ring frameworks are ubiquitous in a large number of bioactive and pharmaceutically interesting molecules.[1] Chiral 3-substituted indanones therefore are very useful molecules as starting chiral building blocks for the synthesis of biologically active compounds and thus are of tremendous industrial interest.[2] General approaches toward introducing chirality in the indanone framework include Friedel−Crafts cyclization of chiral aryl carboxylic acids synthesized either by resolution or asymmetric synthesis[3] and the kinetic resolution of racemic substrates recently reported by Buchwald[4] and Fu.[5] The Friedel−Crafts reaction calls for high temperature or highly acidic conditions, while the kinetic resolution approach[4] utilizes air-sensitive imines as the substrates. Catalytic enantioselective Negishi reaction of racemic indanones requires multistep synthesis of the 3-substituted indanones and suffers from high catalyst loading.[5] Rhodium(I)-catalyzed intramolecular hydroacylation[6] has emerged as a very efficient method for the synthesis of various carbocycles mainly via the elegant works of Bosnich,[7a,b] Jun,[7c,d] Fu,[7e] and Shair.[7f] However, utilization of this wonderful methodology in synthesis of chiral indanones has not been previously reported. Herein, we report our study of the utility of asymmetric hydroacylation in the synthesis of chiral 3-substituted indanones and some unexpected mechanistic details.

Our study of rhodium-catalyzed hydroacylation was initiated with investigation of the results reported for 2-vinyl benzaldehyde (**1**),[8] wherein the authors reported obtaining a 30% yield of the desired 1-indanone product (**2**) along with unidentified material they believed was a polymer. When we reproduced the experiment, we also obtained 30% of the desired product as previously reported. However, the side product was determined to be a dimer (**3**) and not a polymer, as suggested by previous authors. The dimer was obtained in 70% yield with exclusive selectivity for the trans-isomer.



The proposed mechanistic pathway for formation of the dimeric product is shown in Scheme 1, with the branch point coming after the initial oxidative addition. The migratory insertion then can occur in either a 1,2- or 2,1-sense. Migratory 1,2-insertion will lead to 1-indanone as the product after the reductive elimination of the metallocycle **B**. Migratory insertion in the 2,1-sense will lead to the intermediate **C**, which in the presence of excess 2-vinyl benzaldehyde can bind with another molecule of the substrate. The second insertion will form the intermediate **D**, which upon reductive elimination leads to the dimeric product (Scheme 2). Fu has reported a [4 + 2] cycloaddition of 4-pentynals that likely proceeds via a similar mechanism.[9]

Table 1. Hydroacylation of 2-Formyl Styrenes[a]



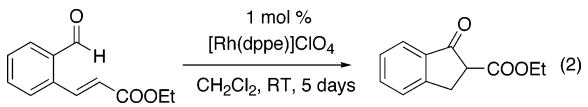
entry	substrate (R=)	yield (%)[b]
1	Me	97
2	Et	97
3	Ph	98
4	2-Naph	88
5	CH_2CH_2OH	97
6	$SiMe_3$	93
7	CF_3	90
8	COOEt	88

[a] [Rh(dppe)(NBD)]ClO_4 (1 mol %) was weighed and dissolved in dry and degassed dichloromethane (1 mL). Hydrogen gas was then passed through the solution for 5 min, followed by flushing with nitrogen to remove the hydrogen gas. The substrate (3 mmol in 1 mL of CH_2Cl_2) was added dropwise to the above catalyst solution via syringe. The reaction mixture was stirred for 2 h at ambient temperature under nitrogen. The product was isolated by flash column chromatography on silica gel using 9:1 hexane and ethyl acetate. [b] Isolated yield.

In accordance with the proposed mechanism, the concentration of the substrate should play an important role. As we expected, 95% of the 1-indanone product was obtained when the substrate was added slowly by a syringe pump over 18 h. (Scheme 2).

We postulated that for steric reasons substitution at the α-position of the 2-vinyl benzaldehyde might shut down the 2,1-insertion pathway, leading exclusively to 3-substituted indanone products. As we hoped, the indanone products were obtained in very high yields without the formation of any side products. Simple aliphatic (entries 1, 2, and 5) and aromatic (entries 3 and 4) substituents were found to be well suited for this reaction. Electron-withdrawing (entries 7 and 8) as well as electron-donating groups (entry 6) were also found to be compatible with the reaction conditions. These additions proceeded efficiently (≥90% conversion) using only 1 mol % of the rhodium(I) catalyst (Table 1).

β-Substituted 2-vinyl benzaldehydes were found to be extremely sluggish as hydroacylation substrates. For example, (*E*)-3-(2-formylphenyl)ethyl acrylate required 5 days to proceed to 90% conversion (eq 2).



After the encouraging results from the hydroacylation of α-substituted 2-formyl styrenes, we concentrated on an asymmetric

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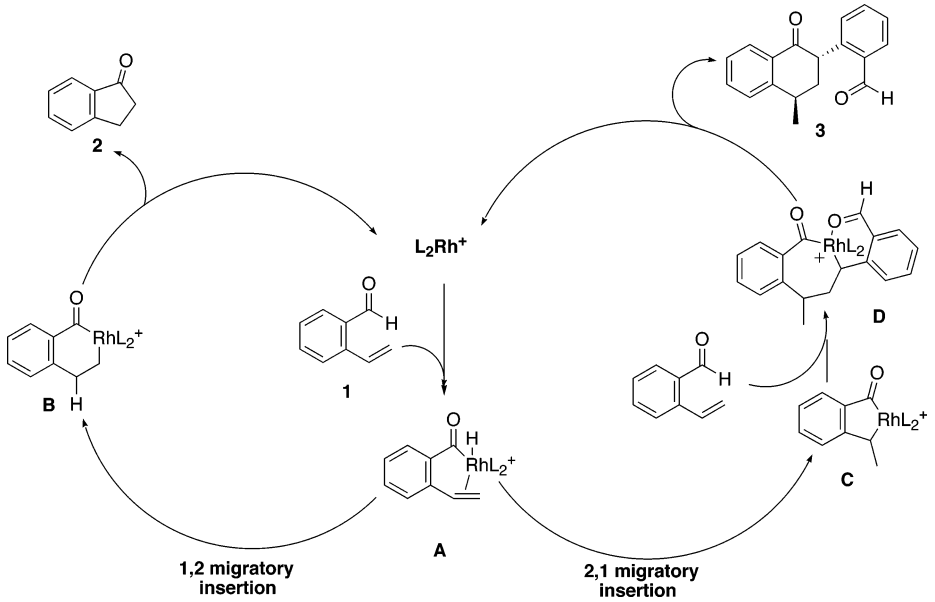
Scheme 1. Mechanistic Rationale for the Formation of the Dimer



Scheme 2. Concentration Dependence of the Hydroacylation of **1**

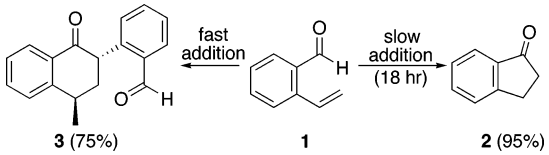


Table 2. Asymmetric Hydroacylation of 2-Formyl Styrenes[a]

entry	substrate (R=)	yield (%)[b]	ee (%)[c]
1	Me	97	99
2	Et	97	99
3	Ph	98	98
4	2-Naph	88	96
5	CH_2CH_2OH	97	96
6	$SiMe_3$	93	70
7	CF_3	90	99
8	COOEt	89	96

[a] [Rh(*R*-BINAP)(NBD)]ClO_4 (1 mol %) was weighed and dissolved in dry and degassed dichloromethane (1 mL). Hydrogen gas was then passed through the solution for 5 min and then flushed with nitrogen to remove hydrogen gas. The substrate (3 mmol in 1 mL of CH_2Cl_2) was added dropwise to the above catalyst solution via syringe. The reaction mixture was stirred for 2 h at ambient temperature under nitrogen. The product was isolated by flash column chromatography on silica gel using 9:1 hexane and ethyl acetate. [b] Isolated yield. [c] Enantiomeric excess is obtained by Chiral GC.

version. Cationic [Rh(*R*-BINAP)]$^+$ was found to be an excellent catalyst in terms of both yields and enantiocontrol. Both alkyl (entries 1, 2, 5, and 7 in Table 2) and aromatic (entries 3 and 4) substituents in the substrates were observed to be very effective. Enantioselectivity was also found to be exceptional in substrates with electron-withdrawing substituents (entries 7 and 8), with only the trimethylsilyl substituent (entry 6) resulting in poor enantiocontrol.

In conclusion, we have utilized our understanding of the mechanism to successfully carry out the hydroacylation of 2-vinyl benzaldehydes to synthesize indanones with high conversions and enantioselectivity. The mechanistic and kinetic details of the dimer formation and its application toward the development of a novel formal [4 + 2] cycloaddition are currently under investigation.

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Supporting Information Available: Experimental details and the spectral data of all the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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