# Catalytic Diastereoselective Reductive Aldol Reaction: Optimization of Interdependent Reaction Variables by Arrayed Catalyst Evaluation

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Introduction of mild, stereoselective, and catalytic processes for the synthesis of polypropionates is a topic of current interest. While most approaches to such bond formation employ silyl enol ethers and Lewis acid catalysts,[1] reports of Co-, Rh-, Pt-, and Pd-catalyzed condensation between acrylate esters, aldehydes, and silanes (eq 1) have also shown promise for the synthesis of aldol
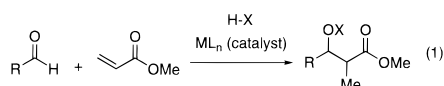
adducts.[2–4] One advantage of such a reductive aldol reaction is that stoichiometric preformation of an activated enolate is not required. While there is only scant literature precedent describing the reductive aldol coupling of α,β-unsaturated esters and aldehydes, it is apparent from these reports that a variety of late transition metal catalysts may be used. Although useful product yields are often realized for these reactions, diastereoselection remains challenging (maximum 4:1 syn:anti selectivity). No efforts have been made in regards to asymmetric catalysis and little is known about the reaction mechanism. Herein, we disclose the discovery of an effective catalyst system for the stereoselective reductive aldol reaction obtained from high-throughput evaluation of 192 independent catalytic systems.[5,6] In addition to revealing a catalyst with synthetic utility, these studies illustrate a remark-

able interdependence of reaction variables and thereby presuppose arrayed catalyst evaluation for future catalyst development.[7]

From the outset, we expected that the transition metal salt, ligand, and hydride source would affect reactivity and selectivity in the catalytic reductive aldol reaction. We also expected that, in the absence of substantial mechanistic data, proper choice of each variable would be challenging. Therefore, we chose to evaluate a number of different combinations of these reaction components (Figure 1). To examine the effect of the above-mentioned reaction variables, we performed an array of experiments in glass 96-well plates. In our initial array, we employed four transition metal salts, seven ligands (plus a blank), and six hydride sources. The metals and hydrides included those known for catalytic alkene reduction.[8] Ligands[9] were chosen to achieve the greatest functional group diversity. In the experiment, the metals and ligands were premixed at 50 °C in dichloroethane for 1 h. After incubating each catalyst with the hydride reagent for 30 min at room temperature, benzaldehyde and methyl acrylate (20:1 substrate:catalyst) were added and the reaction was allowed to proceed at room temperature for 16 h. After acidic workup, each reaction was analyzed by chiral GC versus an internal standard. In this manner, relative conversion and stereoisomer ratios were determined for every experiment.

Figure 1 shows the relative yield for each of the 192 independent experiments described above[10] and reveals a number of noteworthy relationships between reaction conditions and yield. First, catechol borane tends to give reaction with the largest number of catalysts whereas Cl_3SiH is effective only with [(allyl)-PdCl]$_2$ in the presence of MOP ligand. Second, reactivity characteristics are often opposed when substituting one hydride source for another: [(cod)IrCl]$_2$ is poisoned by the addition of Ph-semicorrin ligand when Et_2MeSiH is used (78% relative yield without ligand, 0% relative yield with ligand) although the same metal salt is activated by Ph-semicorrin when $PhSiH_3$ is used (2% relative yield without ligand, 24% relative yield with ligand). This interdependence of reaction variables is reflected in the observation that none of the three most active catalyst systems ([(cod)-RhCl]$_2$-DuPhos-Cl$_2$MeSiH, Co(acac)$_2$-MOP-PhSiH$_3$, and [(cod)-RhCl]$_2$-binap-catechol borane) are related by the permutation of a single reaction component. Last, it should be noted that reactivity and selectivity (data not shown) have no correlation; the three most active catalyst systems, [(cod)RhCl]$_2$-binap-catechol borane (100% relative yield), Co(acac)$_2$-MOP-PhSiH$_3$ (94% relative yield), and [(cod)RhCl]$_2$-DuPhos-Cl$_2$MeSiH (94% relative yield), show syn:anti selectivity of 7:1, 2:1, and 23:1, respectively.

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(9) Abbreviations: ^{i}Pr-pybox, 2,6-bis(4-isopropyl-2-ozazolin-2-yl)pyridine-binap; tBu-box, 2,2′-isopropylidenebis(4-*tert*-butyl-2-oxazoline); Ph-semicorrin, 4-phenyl-α-[4-phenyloxazolidin-2-ylidene]-2-oxazoline-2-acetonitrile; MOP, 2-(diphenylphosphino-2′methoxy-1,1′-binaphthyl; BINAP, 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl; DUPHOS, 1,2-bis(2,5)-dimethylpholano)-benzene; QUINAP, 1-(2-diphenylphospino-1-naphthyl)isoquinoline.

(10) Most catalytic reactions showed low diastereoselection (<5:1 syn: anti). Other than those mentioned in the text, catalyst systems exhibiting notable selectivity are as follows: [(allyl)PdCl]$_2$, quinap, Ph$_2$SiH$_2$ (10.9:1 syn:anti); [(cod)RhCl]$_2$, quinap, Ph$_2$SiH$_2$ (8.6:1 syn:anti); [(allyl)PdCl]$_2$, MOP, Cl$_3$SiH (5.8:1 syn:anti). See Supporting Information for selectivity of all reactions.
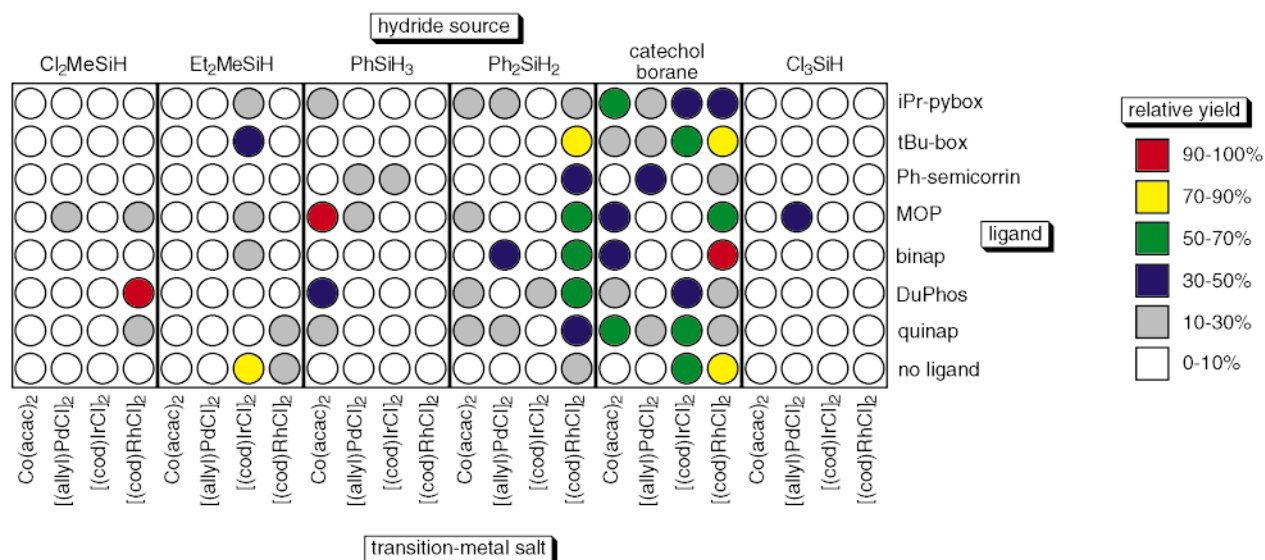
Figure 1. Relative yield for each of 192 independent catalytic reductive aldol reactions.

Table 1. Catalytic Stereoselective Reductive Aldol Reaction

entry	RCHO	Product[a]	% yield[b]	syn:anti[c]
1			69 %	23 : 1
2			82 %	10 : 1
3			38 %	21 : 1
4			15 %	15 : 1
5			41%	>20 : 1

[a] Stereochemistry determined by comparison to authentic syn and anti stereoisomers (entry 1 and 3−5) or analysis of coupling constants (entry 2). [b] Yield of isolated material after chromatography. Adequate elemental analysis was obtained for all reaction products. [c] Stereochemical ratios determined by GC (entries 1, 3, and 4) or ^{1}H NMR (entry 2 and 5).

Of the catalysts examined, we chose to explore the synthetic utility of the catalyst system derived from the combination of [(cod)RhCl]$_2$, DuPhos, and Cl$_2$MeSiH (94% relative yield, 23:1 syn:anti selectivity, 0% ee). As shown in Table 1, moderate yields and useful levels of diastereoselectivity may be achieved in reactions that employ aromatic aldehydes as reaction substrates (entries 1 and 2). While reported reductive aldol reactions[2a,b] involving nonaromatic aldehydes and either RhCl$_3$-Me$_3$SiH or Co-(dpm)$_2$-PhSiH$_3$ proceed in good yield but with no diastereoselection, we have found that analogous reactions with [(cod)RhCl]$_2$-DuPhos-Cl$_2$MeSiH (entries 3−5) provide diminished product yields but high syn stereoselection.[11] Entry 5 indicates that

unsaturated aldehydes can participate in the reaction without interference from competitive conjugate reduction (^{1}H NMR analysis of unpurified reaction mixture shows product, unchanged starting materials, and ∼5% side-product). It is important to note that, when larger scale reactions (1.5 mmol substrate) were performed using the same conditions as in the microscale assay ([substrate] = 0.2 M), good conversion was observed although the reaction proceeded with low diastereoselection (3:1 syn:anti). As reaction concentration was increased ([substrate] = 1.5 M), diastereoselection increased to 23:1 syn:anti.[12] We made no other attempts to optimize product yields or diastereoselection.

In conclusion, we have uncovered an effective catalyst for the diastereoselective reductive aldol reaction discovered with the aid of an arrayed catalyst evaluation protocol. This approach has revealed a significant interdependence of metal, ligand, and hydride source for reactivity and selectivity. Due to this interdependence of reaction parameters, it is reasonable to expect that an empirical catalyst development approach, wherein reaction variables are independently optimized, would not have revealed all highly active catalysts. Further experiments in regards to reaction optimization, synthesis utility, mechanism, and enantioselective catalysis[13] involving reductive aldol reactions are in progress.

Supporting Information Available: Characterization data for all compounds (Table 1), tabular numerical relative yields and diastereomer ratios (Figure 1), and experimental details (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) While we have no experimental evidence in regards to reaction mechanism, it is plausible that insertion of the acrylate alkene into a metal hydride provides a metal enolate. It is known that similar rhodium enolates will add to nonenolizable aldehydes in an aldol fashion but are protonated by aldehydes bearing an α-hydrogen (ref 3c). This may offer an explanation for diminished product yield with isobutyraldehyde.

(12) This surprising discrepancy between large-scale and microscale reactions is not general. Other scaled-up reactions perform as in the 96-well plate. Further, the reaction with [(cod)RhCl]$_2$, DuPhos, and Cl$_2$MeSiH reproducibly provides 23:1 syn:anti selectivity in a 96-well plate at 0.2 M substrate concentration. In general, reactions in the 96-well plate format proceed without noticeable loss in reaction volume over the course of the experiment.

(13) Enantioselective transformation was observed with a few of the catalyst systems described in Figure 1. Further discussion at this point is unwarranted as ee values were lower than 30%.