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Enantio- and Diastereoselective Reductive Aldol Reactions with Iridium-Pybox Catalysts

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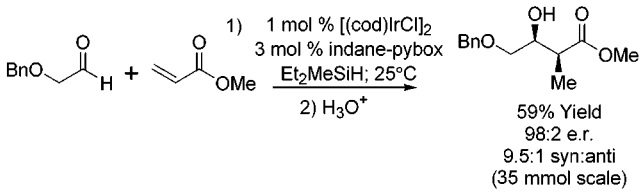
ABSTRACT



A catalytic amount of $[(cod)IrCl]_2$ and indane-pybox converts diethylmethylsilane, methyl acrylate, and certain aldehydes to the derived reductive aldol adduct with good enantio- and diastereocontrol.

Although the 2,6-bis(oxazolinyl)pyridine (pybox) ligands introduced by Nishiyama[1] are used for a number of late transition metal catalyzed enantioselective reactions,[2] they have not proven to be highly effective for asymmetric reactions when complexed to iridium salts. In the context of catalytic reductive aldol reactions,[3] we presumed that pybox ligands (i.e., **1**−**5**) would be ineffective with group 9 metals containing coordinating counterions. Suspecting the initial step in this reaction to be oxidative addition of silane to the M(I) center,[4] we reasoned that insertion reactions in the resulting 18-electron octahedral complex would occur with diminished rate since no coordination site would be available for substrate preassociation. Consistent with this conjecture, we have found that in the reductive aldol reaction with $[(cod)RhCl]_2$-binap catalyst,[5] addition of 1 equiv of triphenylphosphine is sufficient to suppress the catalytic transformation.[6] Additionally, in all previous reports concerning hydrosilation of carbonyls with Rh(I) pybox complexes[1] and Ir(I)-PNP[7] complexes, addition of $AgBF_4$ or $NaClO_4$ is required to generate an effective catalyst. Considering this, it was particularly exciting that an arrayed catalyst evaluation revealed *i*-Pr-pybox (**2**) and $[(cod)IrCl]_2$ as one metal−ligand combination able to effect enantioselective reductive aldol reaction (1:1 *syn*:*anti*, 24% ee *anti*, 12% ee *syn*).[8] With respect to catalyst development, this metal−ligand combination is attractive because a variety of pybox ligands may be accessed through efficient synthesis routes from commercially available materials.[9] In this

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(4) For the oxidative addition of silanes to Ir(I), see: Corey, J. Y.; Braddock-Wilking, J. *Chem. Rev.* **1999**, *99*, 175.

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communication we report that Ir(I) salts, when complexed to an appropriate pybox ligand, are able to catalyze reductive aldol reactions and that, with certain substrates, the reaction provides the highest level of enantio- and diastereoselectivity yet reported.

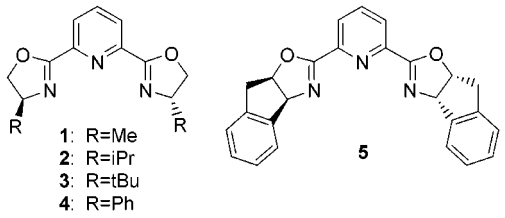
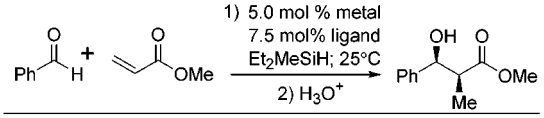


Figure 1.

An initial survey of the impact of ligand architecture revealed that the nature of the pybox ligand substitution has a significant impact on stereoselectivity in the iridium-catalyzed reductive aldol reaction. As might be expected, the more bulky ligands tend to give higher enantioselection, although this does not necessarily translate to higher diastereoselection (compare entries 2 and 3, Table 1). It is also

Table 1. Ir-Pybox Catalyzed Asymmetric Reductive Aldol Reaction[a]



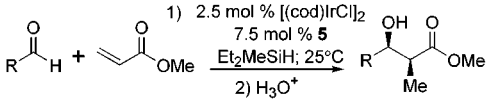
entry	ligand	metal salt	*syn:anti*[b]	% yield	e.r. (syn)[c]
1	**1**	$[(cod)IrCl]_2$	1.7:1	<10	75:25
2	**2**	$[(cod)IrCl]_2$	1:1.3	46	50:50
3	**3**	$[(cod)IrCl]_2$	2.0:1	32	90:10
4	**4**	$[(cod)IrCl]_2$	1.5:1	30	85:15
5	**5**	$[(cod)IrCl]_2$	3.9:1	48	96:4
6	**5**	$[(coe)_2IrCl]_2$	4.4:1	53	96:4
7[d]	**5**	$[(coe)_2IrCl]_2$	6.6:1	68	97:3
8	**5**	$(cod)IrBF_4$	4.0:1	35	93:7
9	**5**	$(CO)_2Ir(acac)$	4.0:1	56	91:9
10	**5**	$[(cod)RhCl]_2$	2.0:1	9	55:45

[a] All reactions were carried out at room temperature for 24 h in dichloroethane. [b] Ratios determined by GC analysis of the unpurified esters. [c] Absolute configuration established by optical rotation. Enantiomer ratio determined by chiral GC analysis. [d] In this experiment ethyl acrylate and $[(coe)_2IrCl]_2$ were used and the reaction was allowed to proceed 45 h.

apparent that there is a nonlinear correlation between the size of the ligand substituent and reaction enantioselection (see entries 1−3). The best ligand in regards to both enantio- and diastereoselectivity is the aminoindanol-derived indane-pybox (**5**).[10] Notably, there is not a substantial variation in selectivity when various iridium salts are used with the indane-pybox ligand. This observation suggests that the Ir(I) precatalysts may be converted to a common catalytic intermediate in the presence of the silane and pybox ligand.

The reductive aldol reaction catalyzed by $[(cod)IrCl]_2$-indane-pybox shows remarkable enantioselectivity with benzaldehyde and α-alkoxy aldehydes;[11] however, it is a poor reaction with simple aldehydes. Comparison of entries 2−4 in Table 2 indicates that oxygenation adjacent to the aldehyde

Table 2. Ir-Pybox Catalyzed Asymmetric Reductive Aldol Reaction[a]



entry	RCHO	% yield[b]	*syn:anti*[c]	e.r. (syn) [d]
1[e]	Ph, H	68	6.6:1	97:3
2	BnO, H	49 59	9.9:1 9.5:1	98:2 98:2[f]
3	TBSO, H	47	8.2:1	98:2
4	Me, H	<5	na	na
5	BnO, H	65	2.7:1	91:9
6	Ph, H	-no reaction-		

[a] All reactions were carried out at room temperature for 24. See Supporting Information for experimental procedures. [b] Percent yield is of isolated material. Satisfactory elemental analysis was obtained for all products. [c] Ratios determined by GC or HPLC analysis, see Supporting Information. [d] Configuration determined by comparison to authentic enantiomers. [e] Ethyl acrylate and $[(coe)_2IrCl]_2$ were used. [f] Reaction carried out on 35 mmol scale with 1 mol % $[(cod)IrCl]_2$ and 3 mol % ligand at 0.45 M substrate concentration for 48 h.

enhances reactivity relative to non-oxygenated aliphatic substrates, although it seems unlikely that the function of the heteroatom is to associate with the metal when one considers the lower coordinating ability of silyl ethers relative to benzyl ethers[12] (cf. entries 2 and 3, Table 2). While simple inductive effects may provide an explanation for enhanced reactivity with α-alkoxy aldehydes, it is difficult to imagine that they play a role in the pronounced reactivity of *β*-benzyloxypropionaldehyde (entry 5) where such field effects would have to operate over three *σ*-bonds.

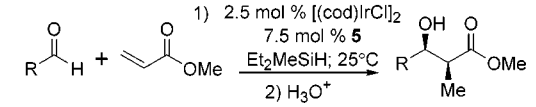
(10) Davies, I. W.; Gerena, L.; Lu, N.; Larsen, R. D.; Reider, P. J. *J. Org. Chem.* **1996**, *61*, 9629. Marked differences between reactions catalyzed by metal complexes of Ph-pybox and in-pybox have been observed previously; see: Schaus, S. E.; Jacobsen, E. N. *Org. Lett.* **2000**, *2*, 1001−1004.

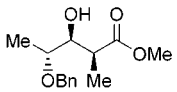
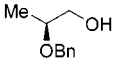
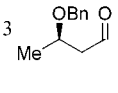
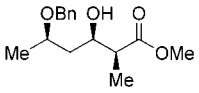
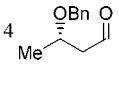
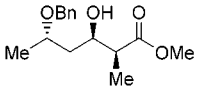
(11) For highly stereoselective asymmetric Mukaiyama aldol reactions where benzyloxyacetaldehyde binds in a bidentate fashion, see: Evans, D. A.; Kozlowski, M. C.; Murry, J. A.; Burgey, C. S.; Campos, K. R.; Connell, B. T.; Staples, R. J. *J. Am. Chem. Soc.* **1999**, *121*, 669−685 and references therein.

(12) (a) Keck, G. E.; Castellino, S. *Tetrahedron Lett.* **1987**, *28*, 281−284. (b) Chen, X.; Hortelano, E. R.; Eliel, E. L.; Frye, S. V. *J. Am. Chem. Soc.* **1992**, *114*, 1778−1784.

The influence of preexisting substrate chirality was analyzed with reactions utilizing chiral nonracemic alkoxy aldehydes. Although β-alkoxyaldehydes exhibit little double stereodifferentiation (entries 3 and 4, Table 3) and therefore

Table 3. Double Stereodifferentiation in the Ir-Pybox Catalyzed Asymmetric Reductive Aldol Reaction[a]



entry	RCHO	product	%yield[b]	syn_a:syn_b[c]	syn:anti[d]
1			50	>95:5	>95:5
2			<5	na	na
3			65	89:11	2.7:1
4			57	88:12	3.0:1

[a] All reactions were carried out at room temperature for 24 h in dichloroethane solvent. [b] Yield is of purified reductive aldol adduct. Satisfactory elemental analysis was obtained for all products. [c] syn_a:syn_b refers to the ratio of major syn diastereomer (shown) to minor syn diastereomer. [d] Refers to collective *syn* diastereomers:collective *anti* diastereomers.

may be useful substrates in double asymmetric synthesis, as shown in entries 1 and 2 (Table 3), there is a significant level of double stereodifferentiation in reductive aldol reactions with α-alkoxyaldehydes. Notably, the matched substrate enantiomer is one where catalyst control and Felkin stereoselection (entry 1) (OBn = large group) act in concert, and in this case, the reductive aldol adduct is furnished with high 1,2- and 2,3-stereocontrol. In contrast, reductive aldol reaction with the mismatched α-alkoxyaldehyde enantiomer (entry 2) provides only carbonyl reduction; the reductive aldol adduct could not be detected. While the double stereodifferentiation observed with α-alkoxyaldehydes is substantial, we have not been able to transform this observation into a useful kinetic resolution process.

Considering that reductive elimination reactions to form C−C, C−H, C−Si, O−Si, and Si−Cl bonds (among others) are known for iridium(III) complexes,[13] overly detailed speculation into the reaction mechanism is unwarranted. We do suspect that oxidative addition of silane to the Ir-X (X = Cl, O) center, followed by elimination of Si-X, may generate a common iridium hydride intermediate, and this is consistent with our observation that many of the iridium salts exhibit similar reactivity.[14] While we have not been able to crystallize any metal−ligand complexes, we suspect that the pybox ligand binds in a three coordinate fashion,[15] since reaction with ligand **6** (Figure 2) provides no selectivity and reaction with **7** provides only carbonyl reduction.

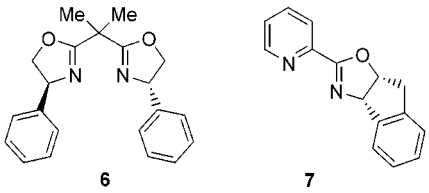


Figure 2.

In conclusion, we have reported a highly enantio- and diastereoselective reductive aldol reaction albeit with limited substrate scope. Experiments in regards to elucidating the reaction mechanism, expanding the useful substrate scope, and exploring the utility of these reactions in the context of complex natural products synthesis are in progress and will be reported in due course.

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

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(14) Formation of a C-bound Ir(I) enolate was proposed to occur by reaction of an Ir(I) hydride with methyl acrylate; see: Drouin, M.; Harrod, J. F. *Can. J. Chem.* **1985**, *63*, 353.

(15) For 2,6-pyridyl-bisimines that bind in a bidentate fashion, see: (a) Orrell, K. G.; Osborne, A. G.; Sik, V.; de Silva, M. W.; Hursthouse, M. B.; Hibbs, D. E.; Malik, K. M. A.; Vassilev, N. G. *J. Organomet. Chem.* **1997**, *538*, 171. (b) Haarman, H. F.; Ernsting, J. M.; Kranenburg, M.; Kooijman, H.; Veldman, N.; Spek, A. L.; van Leeuwen, P. W. N. M.; Vrieze, K. *Organometallics* **1997**, *16*, 887. (c) Albon, J. M.; Edwards, D. A.; Moore, P. J. *Inorg. Chim. Acta* **1989**, *159*, 19. See also: Creber, M. L.; Orrell, K. G.; Osborne, A. G.; Sik, V.; Coles, S. J.; Hibbs, D. E.; Hursthouse, M. B. *Inorg. Chim. Acta* **2000**, *299*, 209.