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3,3′-Dipyridyl BINOL Ligands. Synthesis and Application in Enantioselective Addition of Et_2Zn to Aldehydes[#]

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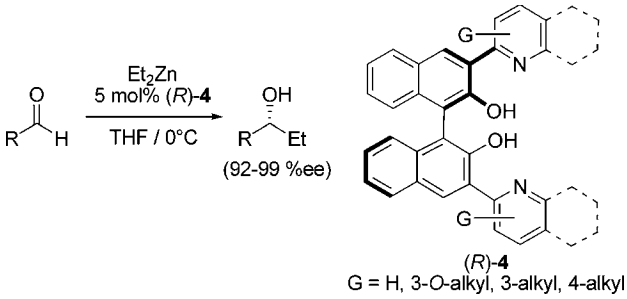
ABSTRACT



3,3′-Di(2-pyridyl) BINOLs (4), prepared in three steps from commercial substances by a combined directed ortho metalation–Negishi cross-coupling protocol, constitute new members of the BINOL ligand family. They are among the most selective, general ligands, providing equal or greater stereoselectivities in the Et_2Zn addition to benzaldehydes and cinnamaldehydes (Table 3) than any single BINOL ligand reported to date.

We report on the convenient synthesis of new 3,3′-di(2-pyridyl) BINOL ligands **4a**−**h** by the directed *ortho* metalation (D*o*M)−cross-coupling protocol developed in our laboratories[1] and demonstrate their application to the highly enantioselective addition of Et_2Zn to benzaldehydes and cinnamaldehydes. Since the pioneering studies of Cram,[2] the BINOL motif has enjoyed widespread use as a chiral element/ligand scaffold in asymmetric synthesis.[3] Although structural variations of the BINOL 3,3′-substituents have mainly been concerned with steric effects,[4] an increasing number of reports deal with systems capable of metal coordination for application in a range of reactions[5] among which, most prominently, are the diorganozinc additions to aldehydes.[6] Our new family of dipyridyl BINOL ligands **4a**−**h** show enantioinductions in this reaction which are comparable to or higher than those previously observed for the 3,3′-diamide BINOL **1** by Katsuki[6b,h,i] and the 3,3′-bisaryl BINOL **2** by Pu[6a,e−g] (Scheme 1).

Of the two categories of 3,3′-substituted BINOLs which are capable of coordination (Scheme 2), simple Lewis acid (**A**)[7] or bifunctional (**B**),[8] we propose that the dipyridyl BINOLs act as bifunctional catalysts[9] and that the reported

[#] Dedicated to Hisashi Yamamoto for lasting contributions to our armamentarium of synthetic methods, particularly in Lewis acid catalysis, for thoughtful service to high standards of our literature, and for warm friendship.

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(1) Cox, P. J.; Wang, W.; Snieckus, V. *Tetrahedron Lett.* **1992**, *33*, 2253. For application of the combined DoM−cross-coupling method, see ref 10.

(2) This work deals with the incorporation of 3,3′-disubstituted BINOLs into crown ethers: Lingenfelter, D. S.; Helgeson, R. C.; Cram, D. J. *J. Org. Chem.* **1981**, *46*, 393.

(3) Reviews: (a) Brunel, J. M. *Chem. Rev.* **2005**, *105*, 857. (b) Chen, Y.; Yekta, S.; Yudin, A. K. *Chem. Rev.* **2003**, *103*, 3155. (c) Pu, L.; Yu, H.-B. *Chem. Rev.* **2001**, *101*, 757.

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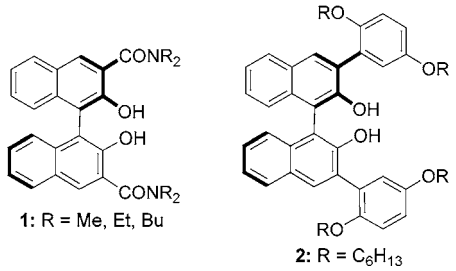
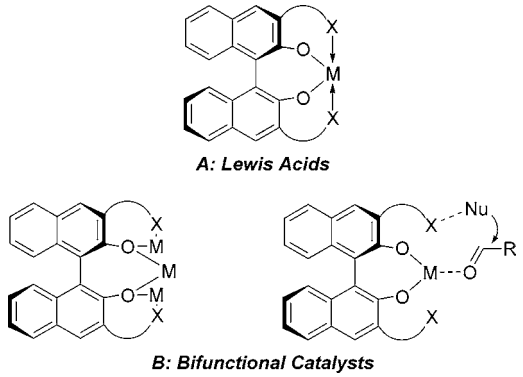
Scheme 1



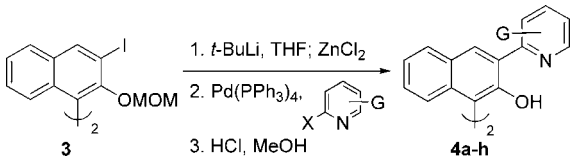
Scheme 2



results convey knowledge for the design and development of new robust BINOL ligands for asymmetric catalysis.

The combined DoM−cross-coupling sequence to chiral 3,3′-disubstituted BINOLs using exchangeable 3,3′-dihalo and dimetalo 2,2′-di-DMG-bearing partners (DMG = directed metalation group: OMOM, OCONEt$_2$, OSEM) is a particularly flexible, rapid, and convergent route to optically pure ligands.[10,11] After experimentation with combinations of cross coupling partners,[12] the Negishi regimen involving reaction of the 3,3′-di-ZnCl BINOLs with 2-halopyridines under Pd(PPh$_3$)$_4$ catalysis provided optimal conditions to afford coupled products which, for efficiency and ease of handling, were directly deprotected to give the 3,3′-di(2-pyridyl) BINOLs **4** in acceptable yields along with modest yields of the monocoupled products (Table 1). Use of

Table 1. Synthesis of 3,3′-Di(2-pyridyl) BINOL Ligands **4a**−**h**



3 **4a-h**

entry	X, G	ligand	yield, %	entry	X, G	ligand	yield, %
1	Br, H	**4a**	75	5	Br, Me	**4e**	41
2	I, 3-OC$_4$H$_9$	**4b**	45	6	I, 3-F	**4f**	60
3	I, 3-OC$_6$H$_{13}$	**4c**	42	7	I, 4-*t*-Bu	**4g**	68
4	I, 3-OCH$_2$Ph	**4d**	49	8	2-Br, quinoline	**4h**	66

π-acidic ligands (P(furyl)$_3$) did not result in improved yields. Although the intermediate 3,3′-di-ZnCl BINOL may be prepared directly through DoM to form 3,3′-di-Li BINOL then transmetalation with ZnCl$_2$ and the 3,3′-di-ZnCl BINOL

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(6) For the application of coordinating 3,3′-disubstituted BINOLs in the diorganozinc addition to aldehydes, see ref 3c and references cited therein: (a) Qin, Y.; Liu, L.; Sabat, M.; Pu, L. *Tetrahedron* **2006**, *62*, 9335 and references cited therein. (b) Ito, K.; Tomita, Y.; Katsuki, T. *Tetrahedron Lett.* **2005**, *46*, 6083. (c) Guo, Q.; Liu, B.; Lu, Y.; Jiang, F.; Song, H.; Li, J. *Tetrahedron: Asymmetry* **2005**, *16*, 3667. (d) Hatano, M.; Miyamoto, T.; Ishihara, K. *Adv. Synth. Catal.* **2005**, *347*, 1561. (e) Li, Z.-B.; Pu, L. *Org. Lett.* **2004**, *6*, 1065 and references cited therein. (f) Xu, M.-H.; Pu, L. *Org. Lett.* **2002**, *4*, 4555 and refernences cited therein. (g) Huang, W.-S.; Pu, L. *J. Org. Chem.* **1999**, *64*, 4222. (h) Kitajima, H.; Ito, K.; Katsuki, T. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 207. (i) Kitajima, H.; Ito, K.; Katsuki, T. *Chem. Lett.* **1996**, 343.

(7) See, for example: Ishihara, K.; Kurihara, H.; Matsumoto, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1998**, *120*, 6920.

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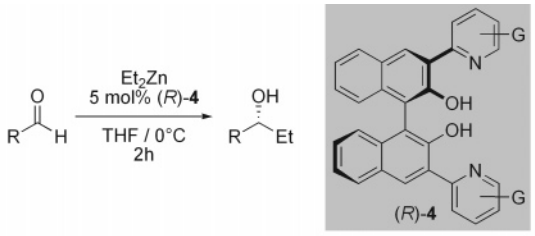
(9) Additional classes (furyl, thiephenyl, quinolyl) of 3,3′-diheteraromatic BINOLs have been synthesized; see: Milburn, R. R. M.Sc. Thesis, University of Waterloo, 1998.

(10) For the name reaction coupling of 3,3′-dihalo BINOLs, see: Kumada: (a) Dolman, S. J.; Hultzsch, K. C.; Pezet, F.; Teng, X.; Hoveyda, A.; Schrock, R. R. *J. Am. Chem. Soc.* **2004**, *126*, 10945. (b) Wipf, P.; Jung, J. K. *J. Org. Chem.* **2000**, *65*, 6319. Suzuki: (c) Wu, T. R.; Shen, L.; Chong, J. M. *Org. Lett.* **2004**, *6*, 2701. Stille: (d) Fujita, M.; Oka, H.; Ogura, K. *Tetrahedron Lett.* **1995**, *36*, 5247. Negishi: (e) Gribkov, D. V.; Hultzsch, K. C.; Hampel, F. *Chem. Eur. J.* **2003**, *9*, 4796. Heck: (f) Cui, Y.; Ngo, H. L.; Lin, W. *Chem. Commun.* **2003**, 1388. Sonogashira: (g) Bahr, A.; Felber, B.; Schneider, K.; Diederich, F. *Helv. Chim. Acta* **2000**, *83*, 1346. For the coupling of 3,3′-dimetallo BINOLs, see ref 10b and: (h) Simonsen, K. B.; Gothelf, K. V.; Jorgensen, K. A. *J. Org. Chem.* **1998**, *63*, 7536.

thus generated readily participates in Negishi cross coupling, significant monocoupled products result due to incomplete BINOL lithiation. We therefore found it advantageous to apply a two-step sequence, *via* intermediate iodide **3**, which allows for rejection of the monolithiated products formed during the DoM step, facilitates clean formation of 3,3′-di-ZnCl BINOL, and significantly reduces the amount of monocoupled product.

For our studies, we employed the enantioselective addition of Et_2Zn to aldehydes, a thoroughly explored reaction,[13] which has become recognized as a standard assay in guiding new ligand development.[14] The results (Table 2) demonstrate

Table 2. Asymmetric Et_2Zn Addition to Benzaldehyde and Cinnamaldehyde Catalyzed by 3,3′-Di(2-pyridyl) BINOL Ligands **4a**−**h**



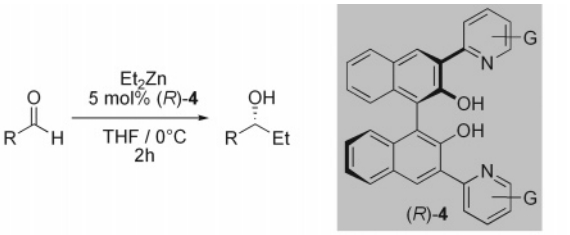
Entry	Ligand	G	R = Ph Yld, %[a]	R = Ph % ee[b]	R = Ph Yld, %[a]	R = Ph % ee[b]
1	**4a**	H	91	98	77	93
2	**4b**	3-OC_4H_9	71	99	78	92
3	**4c**	3-OC_6H_{13}	96	98	92	96
4	**4d**	3-OCH_2Ph	81	97	83	90
5	**4e**	3-Me	63	97	74	89
6	**4f**	3-F	56	97	52	92
7	**4g**	4-*t*-Bu	86	96	85	89
8	**4h**	2-quinoline	56	94	72	88

[a] Determined by GC analysis using undecane as an external standard. [b] Determined via chiral GC analysis using β-cyclodextrin stationary phase. (See the Supporting Information.)

that the series of 3,3′-di(2-pyridyl) BINOLs **4a**−**h** are very effective ligands for the catalytic asymmetric addition of Et_2Zn to benzaldehyde (the reaction standard) and cinnamaldehyde (the reaction benchmark, see below). Thus, compared to the unsubstituted pyridyl ligand **4a** (entry 1), 3-oxygenated pyridyl derivatives **4b**−**d** impart similar (entries 2 and 4) or improved (entry 3) enantioselectivities, while 4-substitution (entry 7) and aromatic ring annelation (2-quinolinyl, **4h**, entry 8) result in similar or decreased enantioselectivities.

Substrate scope was then examined using the most promising ligands: **4a** and **4c** (Table 3). Ligand **4a** showed

Table 3. Asymmetric Et_2Zn Addition to Aldehydes Catalyzed by 3,3′-Di(2-pyridyl) BINOL Ligands **4a** and **4c**



Entry	RCHO		Ligand (*R*)-**4a** Yld, %[a]	Ligand (*R*)-**4a** % ee[b]	Ligands (*R*)-**4c** Yld, %[a]	Ligands (*R*)-**4c** % ee[b]
1	PhCHO		91	98 (*R*)[c]	96	98 (*R*)[c]
2	Ph–CH=CH–CHO		77	93 (*R*)[c]	92	96 (*R*)[c]
3	MeO–C6H4–CHO	2-OMe	97	95	99	97
4	MeO–C6H4–CHO	4-OMe	31	97	40	98
5	Me–C6H4–CHO		37	96	25	97

[a] Determined by GC analysis using undecane as an external standard. [b] Determined by chiral GC analysis using β-cyclodextrin stationary phase. [c] Assessed by comparison of the measured optical rotation with known values. (See the Supporting Information.)

excellent enantioinduction for a range of aldehydes albeit, in some cases (entries 4 and 5), with decreased yields while ligand **4c** displayed significantly improved selectivity (>97% ee) for both *ortho*-substituted aryl (entry 3) and α,β-unsaturated (entry 2) aldehydes. In comparison with the Katsuki diamide **1**[6b,h,i] and Pu bis aryl **2**[6a,e−g] ligands, the following features of the dipyridyl ligands **4a** and **4c** are noted: (1) Ligand **4a** displays stereoselectivities of similar magnitude as **1** and **2**, while the selectivity of ligand **4c** is consistently higher; (2) catalytic activities of **4a** and **4c** appear to be lower than that of **2** since the aliphatic aldehydes did not undergo ethylation and less reactive aldehydes (entries 4 and 5) required extended reaction times for complete conversion; (3) prominent solvent effects were noted (THF > PhMe > CH_2Cl_2), which are consistent with those observed for ligands **1**[6b,h,i] and **2**[6f] but opposite to those of

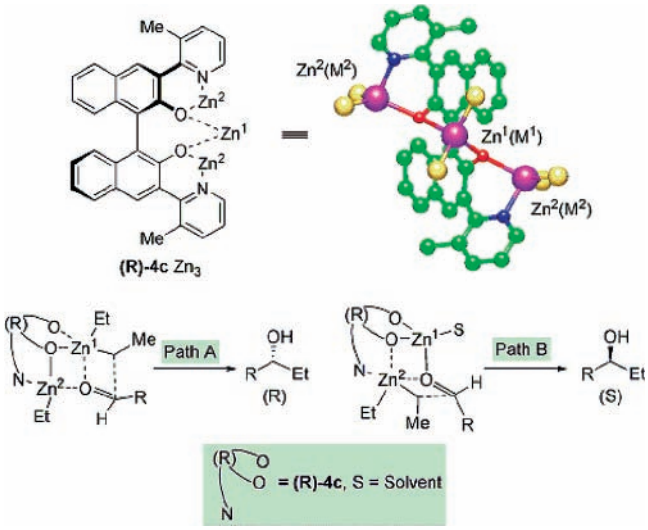
(11) Cram first demonstrated the DoM−cross-coupling route for the synthesis of 3,3′-substituted BINOLs from 2,2′-diOMe BINOLs; see ref 2. The limitations placed on this route by the harsh conditions required for OMe deprotection to the corresponding BINOLs have been alleviated by the application of other DMGs which may be cleaved under mild conditions, see ref 1.

(12) Based on our experience, cross coupling of heteroaryls is best achieved using the heteroaryl halide and the corresponding Suzuki, Stille, or Negishi organometallic partners which takes advantage of the stability and availability of the former and avoids the problematic formation and instability of the latter.

(13) (a) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994. (b) Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833.

(14) For representative work on the screening of new ligands monitored by organozinc addition to aldehydes, see: (a) Richmond, M. L.; Seto, C. T. *J. Org. Chem.* **2003**, *68*, 7505. (b) Yus, M.; Ramon, D. J.; Prieto, O. *Tetrahedron: Asymmetry* **2003**, *14*, 1103. (c) Bauer, R.; Tarasiuk, J. *Tetrahedron Lett.* **2002**, *43*, 687. (d) Page, P. C. B.; Allin, S. M.; Maddocks, S. J.; Elsegood, M. R. J. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2827. (e) Priego, J.; Farcia, O.; Cabrera, S.; Carretero, J. C. *Chem. Commun.* **2001**, 2026. (f) Kostova, K.; Genov, M.; Philipova, I.; Dimitrov, V. *Tetrahedron: Asymmetry* **2000**, *11*, 3253. (g) Chen, Y.-X.; Yang, L.-W.; Zhou, Z. Y.; Lam, K.-H.; Chan, A. S. C.; Kwong, H.-L. *Chirality* **2000**, *12*, 510. (h) Bae, S. J.; Kim, W.-W.; Hyeon, T.; Kum, B. M. *Chem. Commun.* **2000**, 31.

Scheme 3



the amino alcohol class of ligands;[15] and (4) the *R* ligand consistently gives the *R* alcohol; hence, the sense of stereoinduction is consistent with the other 3,3′-disubstituted BINOL ligands.

For the purpose of mechanistic rationalization, two models are considered (Scheme 2): simple Lewis acid type (**A**)[7] in which the 3,3′-substituents coordinate the central metal of the complexes, imparting further rigidity and propagating the stereochemical environment around the metal, and a complex capable of bifunctional catalysis (**B**)[8] by formation of aggregates or coordination of the reactant to direct it toward the substrate bound to the Lewis acidic central metal. The matching stereoselectivity profiles, direction of enantioinduction, generality, and solvent effects displayed by **1**,[6b,h,i] **2**,[6f] and **4a**−**h** suggest the participation of all ligands *via* a common mechanism. There is, however, a limited amount of physical and theoretical data accumulated on these metal−ligand complexes and the mechanisms thus far proposed, involving dimeric complexes (**A**) or bifunctional catalysis (**B**), are largely speculative. In the absence of such data, we are forced to rely largely on analogy with the β-amino alcohol catalyzed reaction[16] to formulate a working hypothesis for the mode in which these ligands function in enantioselective catalysis. The studies (^{1}H NMR and X-ray structure) of the zinc complex of **1** disclosed by Katsuki[6b,h,i] suggest that all 3,3′-disubstituted BINOL ligands **1**, **2**, and **4a**−**h** catalyze the Et_2Zn addition to aldehydes *via* complexes of type (**B**) (Scheme 2). Although assignment of M^1 or M^2 to Lewis acidic or nucleophilic roles in the catalyst complex is premature at present, application of a geometry-optimized model (generated *via* PM3 calculations) of (*R*)-**4c** Zn_3 complex (Scheme 3) and invoking the accepted transition state for the Et_2Zn addition to aldehydes[16] suggests the assignment of M^2 to a Lewis acidic role and M^1 to the nucleophilic role in the reaction, and this is in accord with the observed direction of stereoinduction (path A). The alternative configuration (path B), in which the aldehyde is bound to the central M^1 and the ethyl is delivered by M^2, leads to the incorrect prediction of stereoinduction. Based on this argument, we further surmise that the improved stereoselectivity observed using 3,3′-dipyridyl BINOLs is the result of angle alternation of the pyridine-biaryl axis which is dependent on the 3,3′-substituents with the benzyloxy and methyl substitution being too large while the alkoxy substituent being optimal to allow geometrically proper coordination.

In summary, the unsubstituted 3,3′-dipyridyl BINOL ligand **4a**, readily prepared in two steps from commercially available starting materials, delivers ee's in Et_2Zn addition to aryl and cinnamyl aldehydes equal to those observed for the more complex ligands **1** and **2**. The more elaborate ligand **4c** delivers ee's superior to any of the BINOL-type ligands thus far reported, and both **4a** and **4c** maintain the unique generality displayed by the family of BINOL ligands for Et_2Zn addition to both aromatic and α,β-unsaturated aldehydes. A model is proposed which is in agreement with the sense of the observed enantioinduction. Our mechanistic understanding of the enantiodiscrimination in the Et_2Zn addition to aldehydes catalyzed by 3,3′-disubstituted BINOL ligands may be further enhanced from the investigation of a wider range of 3,3′-disubstituted ligands incorporating donor substituents which promote bifunctional catalytic behavior in conjunction with computational studies.

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Supporting Information Available: Detailed experimental procedures and spectroscopic data for compounds **3** and **4a**−**h**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Yang, X.; Shen, J.; Da, C.; Wang, R.; Chio, M. C. K.; Yang, L.; Wong, K.-Y. *Tetrahedron: Asymmetry* **1999**, *10*, 133.

(16) Rudolph, J.; Bolm, C.; Norrby, P.-O. *J. Am. Chem. Soc.* **2005**, *127*, 1548 and references cited therein.