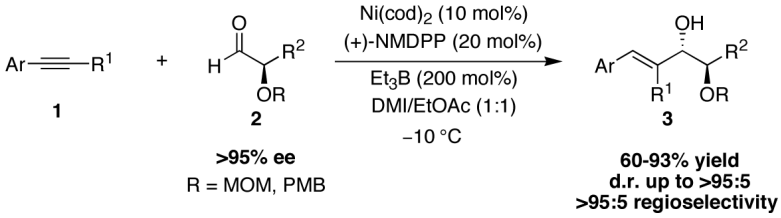
Published in final edited form as:
Org Lett. 2005 July 7; 7(14): 2937–2940. doi:10.1021/ol050881k.

Anti-1,2-Diols *via* Ni-Catalyzed Reductive Coupling of Alkynes and α-Oxyaldehydes

Torsak Luanphaisarnnont, **Chudi O. Ndubaku**, and **Timothy F. Jamison**
Department of Chemistry, Massachusetts Institute of Technology, 77 Massachusetts Ave., Cambridge, Massachusetts 02139

Abstract



Ni-catalyzed reductive coupling of aryl alkynes (1) and enantiomerically enriched α-oxyaldehydes (2) afford differentiated *anti*-1,2-diols (3) with high diastereoselectivity and regioselectivity, despite the fact that the methoxymethyl (MOM) and *para*-methoxybenzyl (PMB) protective groups typically favor *syn*-1,2-diol formation in carbonyl addition reactions of this family of aldehydes.

Enantiomerically pure 1,2-diols are important and commonly occuring functional group patterns in natural products such as carbohydrates and polyketides and in chiral ligands used in asymmetric catalysis. Consequently, much effort has been invested in the development of stereoselective methods for 1,2-diol synthesis. A very powerful one for preparing *syn*-1,2-diols is the Sharpless asymmetric dihydroxylation of *trans*-disubstituted olefins.[1] However, the diastereomeric *anti*-1,2-diols are not as easily accessed using this transformation because the corresponding dihydroxylations of *cis*-disubstituted olefins typically proceed with diminished enantioselectivity.[1c]

Auxiliary-based, *anti*-selective glycolate aldol addition reactions have been developed to address this limitation.[2] Nevertheless, these methods are much less common than those for analogous, *syn*-selective addition, and this area continues to be actively investigated. Recently, MacMillan and List reported catalytic asymmetric aldol reactions that afford the *anti*-1,2-diol architecture.[3] Aldolases,[4] catalytic antibodies,[5] and a heteropolymetallic catalyst[6] also have been used to favor *anti* addition in related reactions.

A contrasting approach to the synthesis of 1,2-diols involves nucleophilic addition to aldehydes bearing protected hydroxyl groups adjacent to the carbonyl.[7] Cram's rule, after over fifty years, remains a good predictor of the stereochemical outcome of additions to these chiral α-oxyaldehydes (Fig 1).[8]

tfj@mit.edu.

Supporting Information Available. Experimental procedures and data for all new compounds. These materials are available free of charge via the Internet at http://pubs.acs.org.

For α-alkoxy groups that have the ability to coordinate (such as MeO—, MOMO—, BnO— or PMBO—, among others), the "*Cram-chelate*" model typically applies, and *syn*-1,2-diols are favored (Fig 1, **A**).[8b,9] When larger groups (such as *t*BuMe$_2$SiO— or Ph$_3$CO—) are employed, the "*dipolar*" model is invoked to account for the general preference for *anti*-1,2-diol products (Fig 1, **B**). However, due to the greater degree of flexibility in the latter process (σ—bond rotation), nucleophilic additions of this type usually proceed with moderate selectivity and therefore are not always viable means to access *anti*-1,2-diols.

In rare instances, α-oxyaldehydes bearing chelating groups adjacent to the carbonyl afford *anti*-1,2-diols with >95:5 diastereoselectivity.[10] This unusual preference is particularly interesting from a mechanistic point-of-view because it suggests that even in the presence of highly coordinating groups such as MOMO— or BnO—, the nucleophilic addition occurs instead *via* the "*dipolar*" model. This phenomenon may be observed when reagents lacking the ability to chelate are utilized,[10a,10c] or when a reagent that imparts complete stereocontrol is employed.[10d]

We have previously reported that nickel-catalyzed reductive coupling reactions of aryl-substituted alkynes and aldehydes proceed with high regioselectivity and enantioselectivity when a chiral phosphine such as neomenthyldiphenylphosphine (NMDPP) is utilized (Scheme 1).[11,12] We now disclose that the corresponding reaction with chiral α-oxyaldehydes preferentially affords 1,2-diol products of the *anti* relative configuration.

We began our studies by investigating the role of the ligand in catalytic reductive coupling reactions of 1-phenyl-1-propyne (**1a**) and the known aldehyde **2a**[13] (eq 1).

A high level of substrate control was observed with both (+)- and (—)-NMDPP providing the coupling product **3a** as predominantly the *anti* diastereomer (Table 1, entries 1 and 2).[14] (+)-NMDPP was selected for further studies because it provided the *anti* product in higher yield and selectivity (Table 1, entry 1). The diastereoselectivity and yield were further improved by careful examination of reaction temperature. At —10 °C, near 9:1 diastereoselectivity was obtained without compromising the reaction yield (Table 1, entry 3). On further cooling, however, the yield diminished severely and no appreciable improvement in diastereoselectivity was observed (Table 1, entry 4).[15] On the other hand, by increasing the amount of the aldehyde and extending the reaction time, a balance of yield and selectivity for the reductive coupling of **1a** and **2a** was achieved (Table 1, entry 6).

The relative stereochemistry of **3a** was determined by removal of the MOM protective group and conversion to the corresponding cyclic carbonate **4** (Scheme 2). A large nOe was observed between the carbinol protons, suggesting a *cis* relationship between them in **4**, i.e. of the *anti*configuration in **3a**. Further confirmation of the relative configuration involved conversion of **3a** to ketodiol **5** whose data were consistent with those previously reported (Scheme 2).[3a]

The scope of this novel, *anti*-selective reductive coupling is shown in Table 2. Placing a larger substituent on the side of the alkyne where C-C bond formation occurs (e.g. Me to Et or cyclopropyl, Table 2, entries 1, 3 and 4), dramatically improved the selectivity, albeit with depreciation in yield. Notably, heteroatom-substituted alkynes are tolerated and do not affect the *anti* selectivity (Table 2, entry 5). Also changing the protective group on the aldehyde to PMB improves the chemical yield while maintaining excellent diastereoselectivity (Table 2, entry 6 vs. entry 3). However, changing the cyclohexyl substituent on the aldehyde to either a phenyl group (Table 2, entry 7) or an *n*-hexyl group (Table 2, entry 8) resulted in lowered selectivity, likely due to a reduced conformational bias in the aldehyde.

The simplest interpretation of the observed sense of induction is that, due to the absence of any chelating metal in the reaction, the preferred mode of addition can be rationalized by the "*dipolar*" model (Fig 2, **B**).

In conclusion, a nickel-catalyzed reductive coupling of alkynes and easily accessible, enantiomerically enriched α-oxyaldehydes has been developed. These coupling reactions provide efficient access to a variety of differentially-protected *anti*-1,2-diols, despite the fact that additions to methoxymethyl- (MOM) and *p*-methoxybenzyl-protected (PMB) 2-hydroxyaldehydes typically display a preference for *syn*-1,2-diols. Currently we are investigating the utility of this novel method for preparing these useful intermediates as a catalytic, stereoselective fragment coupling reaction in target-oriented synthesis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgment

Support for this work was provided by the National Institute of General Medical Sciences (GM-063755). T. L. thanks the MIT Undergraduate Research Opportunities Program, and C. O. N. thanks the Pfizer Diversity in Organic Chemistry Program for fellowship support. We also thank the NIGMS (GM-072566), NSF (CAREER CHE-0134704), the Sloan Foundation, Amgen, Boehringer-Ingelheim, Bristol Myers-Squibb, GlaxoSmithKline, Johnson & Johnson, Merck Research Laboratories, Wyeth, and the Deshpande Center (MIT) for generous financial support of our program. We are grateful to Dr. Li Li for obtaining mass spectrometric data for all compounds (MIT Department of Chemistry Instrumentation Facility, which is supported in part by the NSF (CHE-9809061 and DBI-9729592) and the NIH (1S10RR13886-01)).

References

(1) (a). Jacobsen EN, Marko I, Mungall WS, Schröder G, Sharpless KB. J. Am. Chem. Soc 1988;110:1968–1970. (b) Kolb HC, VanNieuwenhze MS, Sharpless KB. Chem. Rev 1994;94:2483–2547.Johnson, RA.; Sharpless, KB. Catalytic Asymmetric Synthesis. 2nd. Ojima, I., editor. VCH; New York: 2000. p. 357-398.

(2) (a). Mukaiyama T, Iwasawa N. Chem. Lett 1984:753–756. (b) Evans DA, Gage JR, Leighton JL, Kim AS. J. Org. Chem 1992;57:1961–1963. (c) Crimmins MT, McDougall PJ. Org. Lett 2003;5:591–594. [PubMed: 12583777]

(3) (a). Notz W, List B. J. Am. Chem. Soc 2000;122:7386–7387. (b) Northrup AB, Mangion IK, Hettche F, MacMillan DWC. Angew. Chem., Int. Ed 2004;43:2152–2154. (c) Northrup AB, MacMillan DWC. Science 2004;305:1752–1755. [PubMed: 15308765]

(4) (a). Bednarski MD, Simon ES, Bishofberger N, Fessner W-D, Kim M-J, Lees W, Saito T, Waldmann H, Whitesides GM. J. Am. Chem. Soc 1989;111:627–635. (b) Fessner W-D, Sinerius G, Schneider A, Dreyer M, Schulz GE, Badia J, Aguilar J. Angew. Chem., Int. Ed 1991;30:555–558.

(5) (a). List B, Shabat D, Barbas CF III, Lerner RA. Chem. Eur. J 1998;4:881–885. (b) Hoffmann T, Zhong G, List B, Shabat D, Anderson J, Gramatikova S, Lerner RA, Barbas CF III. J. Am. Chem. Soc 1998;120:2768–2779.

(6). Yoshikawa N, Suzuki T, Shibasaki M. J. Org. Chem 2002;67:2556–2565. [PubMed: 11950301]

(7) (a). Reviews:Reetz MT. Angew. Chem., Int. Ed 1984;23:556–569. (b) Reetz MT. Acc. Chem. Res 1993;26:462–468.(c)ElielELMorrisonJDAsymmetric Synthesis19832Part A125155AcademicNew York

(8) (a). Cram DJ, Abd Elhafez RA. J. Am. Chem. Soc 1952;74:5828–5835.Gawley, RE.; Aube, J. Principles of Asymmetric Synthesis; Tetrahedron Organic Chemistry Series. 14. Pergamon Press, Elsevier; Oxford: 1996. p. 121-160.

(9). Of particular interest is the NMR observation of a chelate as an intermediate in the addition of dimethylmagnesium to α-alkoxy aldehydes:Chen X, Hortelano ER, Eliel EL, Frye SV. J. Am. Chem. Soc 1992;114:1778–1784.

(10) (a). Banfi L, Bernardi A, Colombo L, Gennari C, Scolastico C. J. Org. Chem 1984;49:3784–3790. (b) Tio H, Mizobuchi T, Tsukamoto M, Tokoroyama T. Tetrahedron Lett 1986;27:6373–6376. (c) Marumoto S, Kogen H, Naruto S. Chem. Commun 1998:2253–2254.An example of highly reagent-controlled nucleophilic addition to a MOMO— aldehyde: (d) Corey EJ, Yu C-M, Kim SS. J. Am. Chem. Soc 1989;111:5495–5496.

(11) (a). Miller KM, Huang W-S, Jamison TF. J. Am. Chem. Soc 2003;125:3442–3443. [PubMed: 12643701]See also: (b) Huang W-S, Chan J, Jamison TF. Org. Lett 2000;2:4221–4223. [PubMed: 11150204] (c) Colby EA, Jamison TF. J. Org. Chem 2003;68:156–166. [PubMed: 12515474]

(12) (a). Reviews of Ni-catalyzed reductive couplings:Miller KM, Molinaro C, Jamison TF. Tetrahedron: Asymmetry 2003;14:3619–3625. (b) Ikeda, S.-i. Angew. Chem., Int. Ed 2003;42:5120–5122. (c) Montgomery J. Angew. Chem., Int. Ed 2004;43:3890–3908.

(13). Racemic 2a:Paquette LA, Mitzel TM. J. Am. Chem. Soc 1996;118:1931–1937.

(14). We found no achiral phosphine that was as efficient as NMDPP, thus preventing a meaningful estimation of the “inherent selectivity” of these aldehydes in these catalytic coupling reactions:Masamune S, Choy W, Peterson JS, Sita LR. Angew Chem., Int. Ed 1985;24:1–30.

(15). Further cooling to —40 °C resulted in improved diastereoselectivity (>95:5) but also severely reduced conversion (<10%).

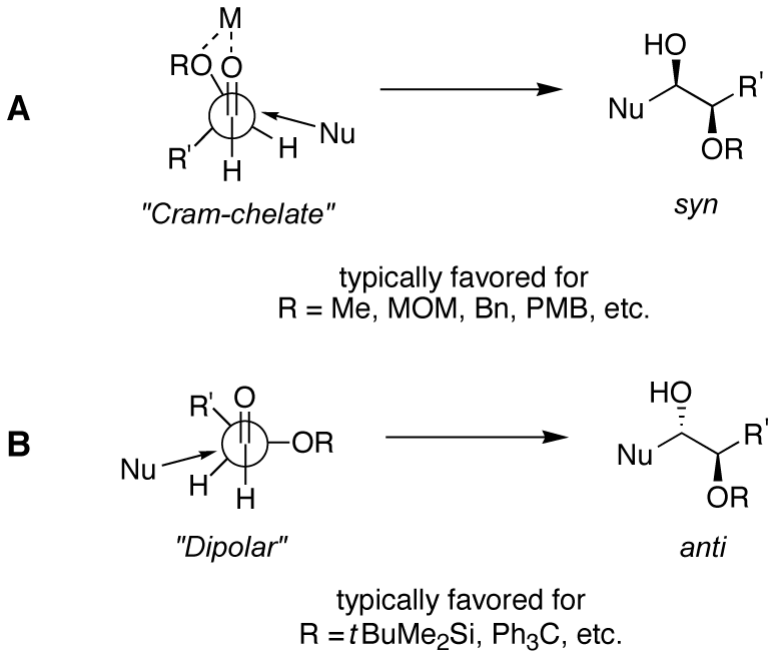
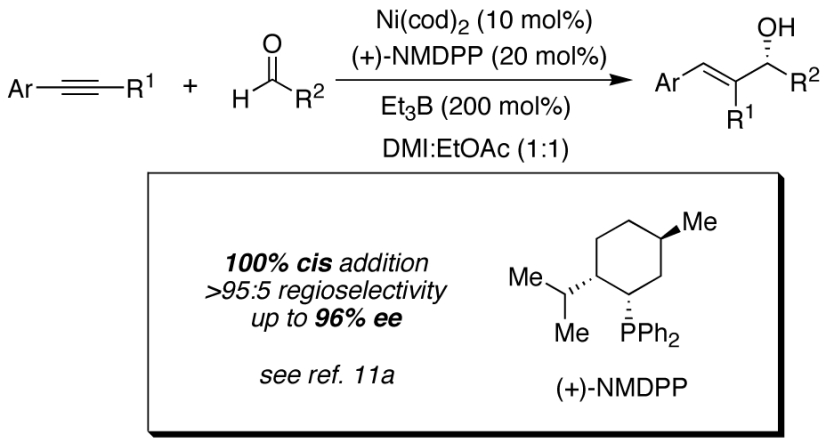
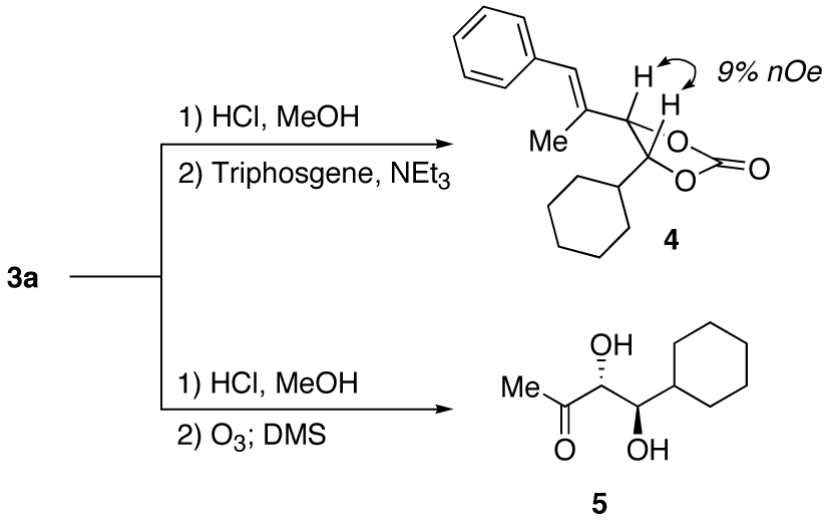


Figure 1.
Models for stereoselective nucleophilic additions to α-oxyaldehydes. (A) The cyclic "*Cram-chelate*" model predicts *syn*-1,2-diols. (B) The "*dipolar*" model predicts *anti*-1,2-diols.



Scheme 1.
Catalytic Asymmetric Reductive Coupling of Alkynes and Aldehydes



Scheme 2.
Assignment of the Relative Configuration of **3a**

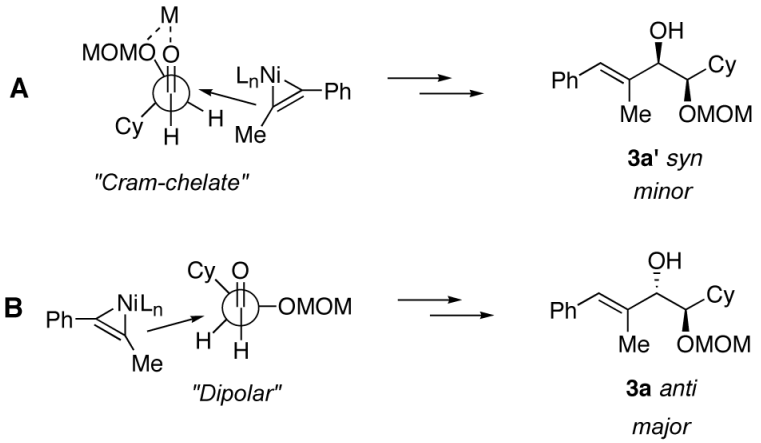
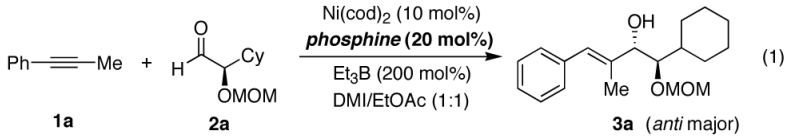


Figure 2.
Schematic representation of divergent pathways leading to *syn*- and *anti*-1,2-diols.

Table 1

Ni/NMDPP-Catalyzed Reductive Coupling of 1-Phenyl-1-propyne (**1a**) and MOM-Protected α-Oxyaldehyde **2a**



1a **2a** **3a** (*anti* major)

entry[a]	**phosphine**	**time(h)**	**temp (°C)**	**d.r**[b]	**yield (%)*(d.r.)*[c]**
1	(+)-NMDPP	6	0	84:16	61 *90:10)*
1	(-)-NMDPP	6	0	77:23	32 *(80:20)*
3	(+)-NMDPP	6	-10	89:11	62 *(90:10)*
4	(+)-NMDPP	6	-20	90:10	37 *(90:10)*
5[d]	(+)-NMDPP	6	-10	89:11	77 *(90:10)*
6[d]	(+)-NMDPP	20	-10	88:12	87 *(90:10)*

[a] See Supporting Information for experimental procedures. 100 mol% of alkyne and 100 mol% of aldehyde were used, unless otherwise noted. All reactions proceeded with >95:5 regioselectivity.

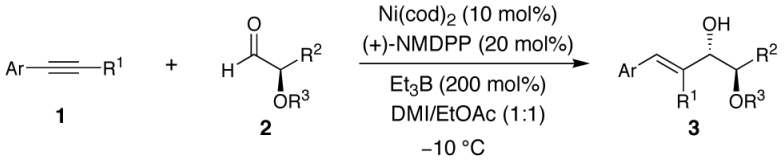
[b] Ratio of *anti:syn* determined by ^{1}H NMR analysis of crude reaction mixtures.

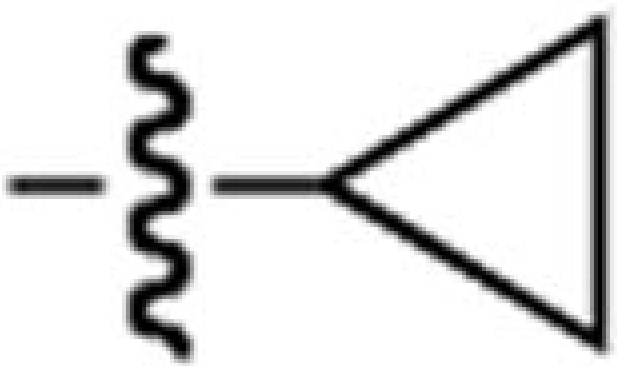
[c] Yield and d.r. of the isolated reaction product.

[d] Conducted using 150 mol% of aldehyde.

Table 2

Extension of the *Anti*-Selective Reductive Coupling to a Variety of Aryl Alkynes and α-Oxyaldehydes[a]



entry	Ar	R[1]	R[2]	R[3]	d.r.[b]	yield (%) (d.r.)[c]
1	Ph	Me	Cy	MOM	88:12	87 *(90:10)*
2	1-Naphthyl	Me	Cy	MOM	83:17	93 *(83:17)*
3	Ph	Et	Cy	MOM	>95:5	54 (*>95:5*)
4	Ph		Cy	MOM	>95:5	62 (*>95:5*)
5	Ph	CH_2NHBoc	Cy	MOM	90:10	60 *(95:5)*
6	Ph	Et	Cy	PMB	>95:5	74 (*>95:5*)
7	Ph	Et	Ph	MOM	68:32	39 (*>95:5*)[d]
8	Ph	Et	*n*-hexyl	MOM	75:25	86 *(80:20)*

[a] All reactions were conducted with 100 mol% of alkyne and 150 mol% of aldehyde. All reactions proceeded with >95:5 regioselectivity.

[b] Ratio of *anti:syn* determined by ^{1}H NMR analysis ofcrude reaction mixtures.

[c] Yield and diastereoselectivity of the isolated reaction product.

[d] The *syn* product was also isolated in 18% yield (>95:5 d.r.).