Diastereoselection in the Conjugate Additions of Organocopper Reagents to N-Enoyloxazolidinones

David R. Williams,* William S. Kissel, and Jie Jack Li
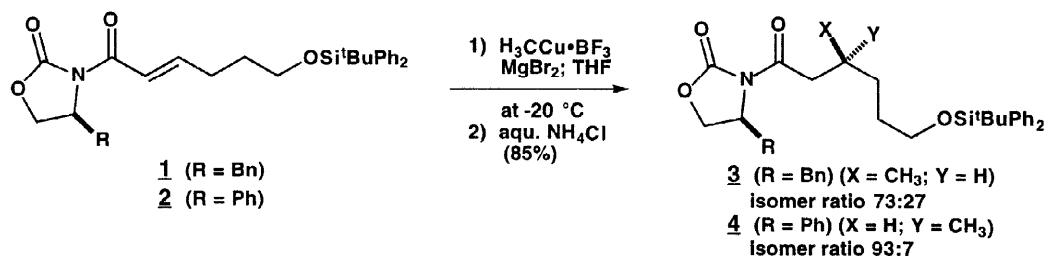
Department of Chemistry, Indiana University
Bloomington, Indiana 47405 U.S.A.

Abstract: A survey of conjugate additions of Yamamoto organocopper reagents to N-enoyl-4-substituted oxazolidinones is reported. Diastereofacial selectivity is reversed for 4-phenyl and 4-benzyloxazolidinones of the same relative configuration. Alkenylcopper reagents demonstrate superior results in asymmetric additions using the 4-phenyloxazolidinone auxiliary. © 1998 Elsevier Science Ltd. All rights reserved.

The asymmetric conjugate addition reaction has been a central topic for development of carbon-carbon bond formation in organic synthesis.[1] Covalently attached chiral auxiliaries have been devised to effect *si-* or *re-* face selectivity at the distal end of the α,β-unsaturated carbonyl system. Oppolzer published the use of 8-phenylmenthol esters,[2a] and subsequently incorporated camphor-based esters[2b] for the stereoselective additions of organocopper reagents. In 1986, Kogo first reported the glutamic acid-based, O-tritylprolinol as an amide auxiliary,[3] and Pourcelot described the first examples for asymmetric conjugate additions using chiral oxazolidinones and the corresponding imidazolidinones.[4a,4b] Recently, Hruby and coworkers have documented asymmetric cuprate additions to crotonoyl and cinnamoyl-derived imides of chiral 4-phenyl oxazolidinones.[5] Since 1990, our early studies toward myxovirescin A_1,[6] as well as subsequent efforts for natural product synthesis,[7] have led to the accumulation of a body of results for the asymmetric 1,4-addition of Yamamoto-based[8] organocopper reagents to N-enoyloxazolidinones. Herein, we have provided a comparison survey of diastereoselectivity for reactions of alkyl, alkenyl, and allyl organocopper reagents as influenced by chiral 4-benzyl- and 4-phenyloxazolidinone auxiliaries.

The commercial availability of optically pure oxazolidinones, and the ease of removal and recovery of these auxiliaries are valued characteristics in asymmetric synthesis. Our experiments have utilized the organocopper species RCu•BF$_3$(MgBr$_2$) as prescribed by addition of Grignard reagent (1 equiv) into a suspension of recrystallized CuBr•DMS (1 equiv, THF at -40 °C). Freshly distilled BF$_3$•Et$_2$O (1 equiv) was introduced after one hour (-78 °C) followed by dropwise addition of N-enoyloxazolidinone in THF. Reactions generally proceeded to completion by stirring at -78 °C (3 hr), and slowly warming and maintaining reactions at -20 °C over 18 hours. In this fashion, the reactions of homochiral 4-benzyl- and 4-phenyloxazolidinones

1) H$_3$CCu•BF$_3$
   MgBr$_2$; THF

at -20 °C
2) aqu. NH$_4$Cl
(85%)

1 (R = Bn)
2 (R = Ph)

3 (R = Bn) (X = CH$_3$; Y = H)
isomer ratio 73:27
4 (R = Ph) (X = H; Y = CH$_3$)
isomer ratio 93:7

1 and **2** exhibited divergent results. Although product yields were comparable for the two cases, the 4(*S*)-phenyloxazolidinone (**2**) afforded superior diastereoselectivity (85% de). On the other hand, the

4(*S*)-benzyl auxiliary led to modest facial selectivity in the opposite sense (47% de), as demonstrated by the separation and characterization of the major products **3** and **4**.[9] This reversal in stereoselectivity was observed for the series of alkyl and phenyl conjugate additions as summarized in the Table (entries 1, 2, and 3) for the starting N-enoyloxazolidinones **5** and **6**. In fact, increasing steric requirements of the nucleophile afforded some improvement in diastereomeric ratios (*i*Pr > Et > Me) in the case of the 4-benzyl imides **5**. Reactions of allyl and methallyl Yamamoto reagents (entry 4) provided solely the C-3' (*S*)-isomer. However, these reagents were clearly different, and displayed exceptional reactivity with rapid conjugate addition at -78 °C. Outstanding diastereoselectivity was achieved in the reactions of alkenyl reagents with the Hruby auxiliary of **6** (entries 6, 7, and 8),[10] whereas the 4-benzyloxazolidinone **5** showed substantial erosion of facial selectivity.
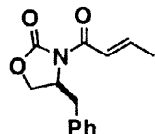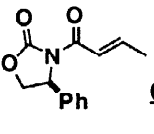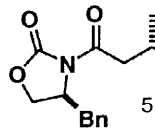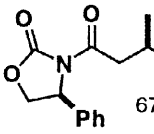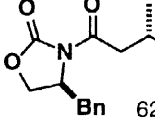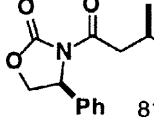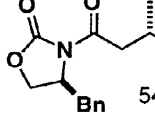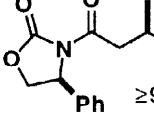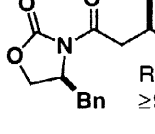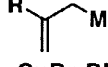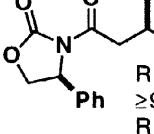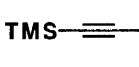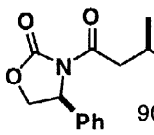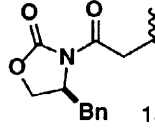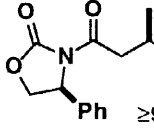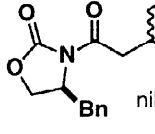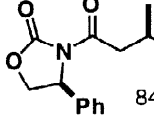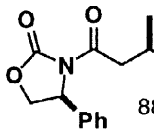
We have postulated that these results may reflect the reactivity of populations of conformers for Lewis acid complexes of the starting imides. Low temperature NMR studies have concluded that the rigid *syn*-s-cis structure **7** is exclusively formed with 2 equivalents of Et_2AlCl.[11] This accounts for the high selectivity in the 4-phenyloxazolidinone series with *re*-face attack in the chelated **8**. Nilsson[12] has recently shown that alkylcopper reagent, activated with trimethylsilyl iodide (RCu•LiI•TMSI), provides a reversal of diastereofacial additions compared with analogous reactions of dialkylcuprates reported by Koga.[3,13] These results support nucleophilic *si*-face addition to the *anti*-s-cis conformer **9**, which may gain greater significance in our complexed 4-benzyloxazolidinones **10**. A *mono*- or *bis*-chelated **11** also provides a rationale for *si*-face conjugate addition. However, calculations reveal that *syn*-s-trans conformer **11** suffers unfavorable steric interactions, which perturb the N-enoylimide from planarity. Interestingly, the observation of exceptional stereocontrol in the allylic reagent (Table, entry 4) would suggest exclusive involvement of **8** compared to much less reactive alkyl and alkenylcopper species. In one experiment (entry 9), reactions of the preformed aluminum chelate **7** (2 equivs; Et_2AlCl at -78 °C)[11] with subsequent addition of the ethylcopper species led to greater stereoselectivity for imide **6**, and reduced % de for the product of the 4-benzyl imide **5** compared to entry 1 (Table). Results suggest that less stable conformers **10/11** are important contributors to the reactions of **5** at -20 °C.

7 (M = Al; X = Et)
8 (M = Mg; X = Br)

9 (MX_2 = TMS)
10 (MX_2 = $MgBr_2$)
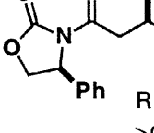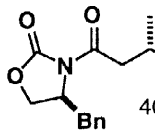
11 (MX_2 = $MgBr_2$)
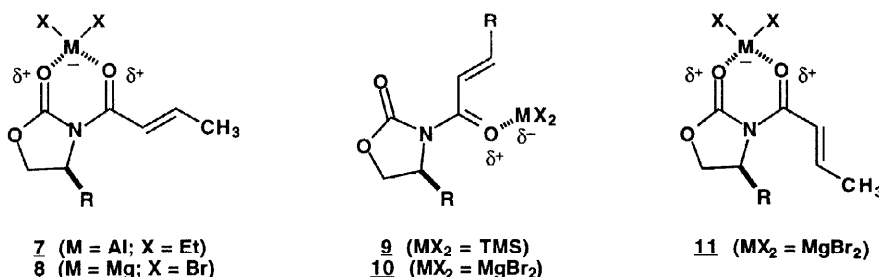
Overall, stereocontrol in conjugate additions to N-enoyloxazolidinones is complicated by the availability of several activated conformers, by the nature of the Lewis acid, and by the structure and mechanism associated with the organocopper species itself. In spite of these substantial issues, the 4-phenyloxazolidinone auxiliary, introduced by Hruby and coworkers, offers predictable, and in some cases, outstanding stereoselectivity for 1,4-conjugate addition reactions.

TABLE: **Comparison Results of Conjugate Additions of Organocopper Reagents to 4-Benzyl and 4-Phenyl-N-Enoyl-Oxazolidinones.**

Structures **5** (4-benzyl-N-enoyl-oxazolidinone, Ph via Bn) and **6** (4-phenyl-N-enoyl-oxazolidinone, Ph).

Entry	Major Product [de (yield)]	Reagent	Major Product [de (yield)]
1.	Bn 53% (78%)	EtMgBr CuBr•DMS BF₃•OEt₂	Ph 67% (89%)
2.	Bn 62% (99%)	(isopropyl) MgCl CuBr•DMS BF₃•OEt₂	Ph 81% (99%)
3.	Ph Bn 54% (66%)	PhMgBr CuBr•DMS BF₃•OEt₂	Ph Ph ≥97% (65%)[5a]
4.	R = H Bn ≥97% (74%)	R ⎯ MgCl CuBr•DMS BF₃•OEt₂	R = H Ph ≥97% (85%) R = Me ≥97% (86%)
5.	—	TMS⎯≡⎯ MgCl CuBr•DMS BF₃•OEt₂	TMS Ph 90% (92%)
6.	Bn 15% (90%)	(isopropenyl) MgBr CuBr•DMS BF₃•OEt₂	Ph ≥97% (95%)
7.	Bn nil (75%)	⟍⟍MgBr CuBr•DMS Me₂AlCl (2 equivs) at -78 °C	Ph 84% (67%)[10]
8.	—	⟍⟍⟍OSiᵗBuPh₂ MgBr CuBr•DMS BF₃•OEt₂	OR Ph R = SiᵗBuPh₂ ≥99% (95%)
9.	Bn 40% (80%)	EtMgBr CuBr•DMS Me₂AlCl (2 equivs) at -78 °C	Ph 88% (88%)

References:

1. For a review: Rossiter, B.E.; Swingle, N.M. *Chem. Rev.* **1992**, *92*, 771.

2. a) Oppolzer, W.; Löher, H.J. *Helv. Chim. Acta, 1981, 64*, 2808. b) Oppolzer, W.; Stevenson, T. *Tetrahedron Lett.* **1986**, *27*, 1139.

3. Tomioka, K.; Suenaga, T.; Koga, K. *Tetrahedron Lett.* **1986**, *27*, 369.

4. a) For cuprate additions: Pourcelot, G.; Aubouet, J.; Caspar, A.; Cresson, P. *J. Organomet. Chem.* **1987**, *328*, C43. Melnyk, O.; Stephan, E.; Pourcelot, G.; Cresson, P. *Tetrahdron*, **1992**, *48*, 841. b) For *mono*-organocopper additions: Van Heerden, P.S.; Bezuidenhoudt, B.C.B.; Ferreira, D. *Tetrahedron Lett.* **1997**, *38*, 1821.

5. a) For aryl cuprate additions: Nicolàs, E.; Russell, K.C.; Hruby, V.J. *J. Org. Chem.* **1993**, *58* 766. b) For CuBr-catalyzed aryl Grignard additions: Li, G.; Jarosinski, M.A.; Hruby, V.J. *Tetrahedron Lett.* **1993**, *34*, 2561. Liao, S.; Han, Y.; Qui, W.; Bruck, M.; Hruby, V.J. *Tetrahedron Lett.* **1996**, *37*, 7917.

6. Williams, D.R.; Li, J. *Tetrahedron Lett.* **1994**, *35*, 5113.

7. These results have been discussed in our presentation of the total synthesis of amphidinolide J. See: Williams, D.R.; Kissel, W.S. American Chemical Society 214th National Meeting; Las Vegas, NV; Sept. 10, 1997; Abstr. 279. Also: Rzasa, R.M.; Shea, H.A.; Romo, D. *J. Am. Chem. Soc.* **1998**, *120*, 591.

8. Yamamoto, Y. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 947.

9. Isomer ratios (% de) are based upon ^{1}H NMR (400 MHz, CDCl$_3$) data of crude product mixtures, and yields are for purified material. The stereoassignments of major products were ascertained by chemical conversions and direct comparisons with known optically pure compounds. Characterization data for major isomers of the Table: **Entry 1 (C$_4$-Bn)**, $[\alpha]_D^{24}$ + 48.4 (2.26, CHCl$_3$; ^{1}H NMR δ 7.36-7.21 (m, 5H), 4.68 (m, 1H), 4.17 (m, 2H), 3.31 (dd, J = 13.3, 3.3 Hz, 1H), 2.86 (AB of ABX, J_{AB} = 16.4 Hz, J_{AX} = 8.4 Hz, J_{BX} = 5.5 Hz, Δv_{AB} = 30.1 Hz, 2H), 2.75 (dd, J = 13.2, 9.4 Hz, 1H), 2.01 (m, 1H), 1.44 (m, 1H), 1.27 (m, 1H), 0.99 (d, J = 6.9 Hz, 3H), 0.92 (t, J = 7.4, 3H); **(C$_4$-Ph)**, $[\alpha]_D^{24}$ +49.0 (c 1.29, CHCl$_3$); ^{1}H NMR δ 7.32 (m, 5H), 5.43 (dd, J = 8.8, 4.0 Hz, 1H), 4.67 (t, J = 8.8 Hz, 1H), 4.25 (dd, J = 8.8, 3.6 Hz, 1H), 3.83 (AB of ABX, J_{AB} = 16.0 Hz, J_{AX} = 9.8 Hz, J_{BX} = 4.2 Hz, Δv_{AB} = 245.5 Hz, 2H), 1.92 (m, 1H), 1.31 (m, 1H), 1.22 (m, 1H), 0.86 (m, 6H). **Entry 2 (C$_4$-Br)**, $[\alpha]_D^{22}$ +30.3 (c 1.92, CHCl$_3$); ^{1}H NMR δ 7.27 (m, 5H), 4.68 (m, 1H), 4.17 (m, 2H), 3.32 (dd, J = 13.5, 3.3 Hz, 1H), 2.87 (AB of ABX, J_{AB} = 16.1 Hz, J_{AX} = 8.7 Hz, J_{BX} = 4.8 Hz, Δv_{AB} = 50.0 Hz, 2H), 2.75 (dd, J = 13.2, 9.8 Hz, 1H), 2.02 (m, 1H), 1.66 (m, 1H), 0.93 (d, J = 6.9 Hz, 3H), 0.92 (d, J = 6.6 Hz, 3H), 0.87 (d, J = 6.9 Hz, 3H); **(C$_4$-Ph)**, $[\alpha]_D^{24}$ +59.8 (c 1.25, CHCl$_3$); ^{1}H NMR δ 7.34 (m, 5H), 5.43 (dd, J = 8.8, 3.8 Hz, 1H), 4.67 (t, J = 8.8 Hz, 1H), 4.25 (dd, J = 8.8, 3.6 Hz, 1H), 2.83 (AB of ABX, J_{AB} = 15.8 Hz, J_{AX} = 11.6 Hz, J_{BX} = 2.2 Hz, Δv_{AB} = 267.1 Hz, 2H), 1.93 (m, 1H), 1.55 (m, 1H), 0.85 (d, J = 7.2 Hz, 3H), 0.83 (d, J = 7.2 Hz, 3H), 0.77 (d, J = 6.6 Hz, 3H). **Entry 3 (C$_4$-Bn)**, $[\alpha]_D^{24}$ +76.1 (c 2.03, CHCl$_3$); ^{1}H NMR δ 7.29 (m, 8H), 7.20 (m, 2H), 4.55 (m, 1H), 4.07 (AB of ABX, J_{AB} = 8.5 Hz, J_{AX} = 8.3 Hz, J_{BX} = 2.9 Hz, Δv_{AB} = 22.6 Hz, 2H), 3.39 (m, 2H), 3.24 (dd, J = 13.4, 3.3 Hz, 1H), 3.18 (m, 1H), 2.70 (dd, J = 13.4, 9.9 Hz, 1H), 1.37 (d, J = 7.2 Hz, 3H). **Entry 4 (C$_4$-Bn; R = H)**, $[\alpha]_D^{24}$ +55.2 (c 2.22, CHCl$_3$; ^{1}H NMR δ 7.28 (m, 5H), 5.81 (m, 1H), 5.05 (m, 2H), 4.68 (m, 1H), 4.17 (m, 2H), 3.32 (dd, J = 13.2, 3.1 Hz, 1H), 3.01 (dd, J = 16.5, 5.5 Hz, 1H), 2.73 (dd, J = 13.5, 10.1 Hz, 1H), 2.73 (dd, J = 16.0, 7.6 Hz, 1H), 2.24-2.05 (m, 3H), 1.00 (d, J = 6.8 Hz, 3H); **(C$_4$-Ph; R = H)**, $[\alpha]_D^{23}$ +53.9 (c, 2.12, CHCl$_3$); ^{1}H NMR δ 7.31 (m, 5H), 5.71 (m, 1H), 5.43 (dd, J = 8.6, 3.6 Hz, 1H), 4.98 (m, 1H), 4.95 (m, 1H), 4.68 (t, J = 9.0 Hz, 1H), 4.27 (dd, J = 9.1, 3.8 Hz, 1H), 2.99 (dd, J = 16.5, 5.2 Hz, 1H), 2.71 (dd, J = 16.4, 8.2 Hz, 1H), 2.55 (m, 1H), 2.01 (m, 2H), 0.88 (d, J = 6.6 Hz, 1H). **Entry 5 (C$_4$-Ph)**, $[\alpha]_D^{24}$ +31.0 (c 2.40, CHCl$_3$); ^{1}H NMR δ 7.35 (m, 5H), 5.43 (dd, J = 3.8, 8.8 Hz, 1H), 4.69 (t, J = 8.8 Hz, 1H), 4.26 (dd, J = 4.1, 8.8 Hz, 1H), 3.11 (dd, J = 5.7, 16.9 Hz, 1H), 2.83 (dd, J = 7.2, 16.9 Hz, 1H), 2.20 (m, 3H), 0.99 (d, J = 6.6 Hz, 3H), 0.15 (s, 9H) ppm. **Entry 6 (C$_4$-Ph)**, $[\alpha]_D^{24}$ +73.0 (c 1.23, CHCl$_3$); ^{1}H NMR δ 7.32 (m, 5H), 5.42 (dd, J = 8.4, 3.6 Hz, 1H), 4.66 (m, 3H), 4.25 (dd, 8.8, 3.6 Hz, 1H), 3.14 (dd, J = 15.6, 6.4 Hz, 1H), 2.86 (dd, J = 16.0, 8.0 Hz, 1H), 2.69 (m, 2H), 1.69 (s, 3H), 1.01 (d, J = 6.8 Hz, 3H). **Entry 7 (C$_4$-Ph)**, $[\alpha]_D^{23}$ +63.7 (c 1.40, CHCl$_3$); ^{1}H NMR δ 7.30 (m, 5H), 5.76 (ddd, J = 17.3, 10.4, 7.2 Hz, 1H), 5.43 (dd, J = 8.8, 3.8 Hz, 1H), 4.94 (dt, J = 17.2, 1.4 Hz, 1H), 4.89 (dt, J = 10.4, 1.2 Hz, 1H), 4.69 (t, J = 8.8 Hz, 1H), 4.28 (dd, J = 9.2, 4.0 Hz, 1H), 3.08 (dd, J = 15.7, 6.6 Hz, 1H), 2.84 (dd, J = 16.0, 7.6 Hz, 1H), 2.71 (m, 1H), 1.55 (s, 3H), 1.01 (d, J = 6.8 Hz, 3H). **Entry 8 (C$_4$-Ph)**, $[\alpha]_D^{24}$ +31.1 (c 7.75, CHCl$_3$); ^{1}H NMR δ 7.65 (d, J = 8.0 Hz, 4H), 7.43-7.24 (m, 11H), 5.40 (dd, J = 8.6, 3.7 Hz, 1H), 4.78 (s, 1H), 4.66 (s, 1H), 4.66 (t, J = 8.8 Hz, 1H), 4.26 (dd, J = 8.9, 3.7 Hz, 1H), 3.70 (m, 2H), 3.12 (dd, J = 16.3, 5.5 Hz, 1H), 2.82 (dd, J = 16.0, 9.0 Hz, 1H), 2.62 (m, 1H), 2.25 (t, J = 7.0 Hz, 2H), 1.03 (s, 9H), 0.97 (d, J = 7.0 Hz, 3H).

10. Dimerization in the case of vinyl copper (entry 7) was a significant problem when reactions were conducted with BF$_3$•OEt$_2$ at -20 °C. When Et$_2$AlCl (2 equivs) was premixed with oxazolidinone 5 or 6, addition of vinylcopper occurred at -78 °C in 4 hours. Recently a related study of TMSCl promoted conjugate addition of vinyl Grignard has appeared. See: Han, Y.; Hruby, V.J. *Tetrahedron Lett.* **1997**, *38*, 7317.

11. Castellino, S.; Dwight, W.J. *J. Am. Chem. Soc.* **1993**, *115*, 2986.

12. Bergdahl, M.; Iliefski, T.; Nilsson, M.; Olsson, T. *Tetrahedron Lett.* **1995**, *36*, 3227.

13. Additionally, a reversal of stereoselection has been reported for related Michael reactions promoted by Et$_2$AlCl vs. TiCl$_4$. Amoroso, R.; Cardillo, G.; Sabatino, P.; Tomasini, C.; Trerè, A. *J. Org. Chem.* **1993**, *58*, 5615.