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Stereoselective synthesis of *syn*- and *anti*-1,3- and 1,2-dimethyl arrays via asymmetric conjugate additions

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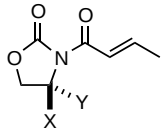
Abstract—Asymmetric conjugate additions have been investigated with enantiopure *N*-enoyloxazolidinones for efficient construction of *syn* and *anti*-1,3-dimethyl arrays on an acyclic carbon backbone. Reactions of Yamamoto organocopper species exhibit characteristics of double asymmetric induction resulting from influences of the 4-substituted chiral auxiliary and features of side chain stereochemistry. © 2002 Published by Elsevier Science Ltd.

Processes of asymmetric conjugate addition to α,β-unsaturated carbonyl moieties are of crucial importance in synthesis endeavors.[1] This is particularly significant as applied to problems of formation of new carbon–carbon bonds.[2] The 1,4-addition of organocopper reagents to conjugated enoyl systems which incorporate chiral auxiliaries has received much attention.[3]

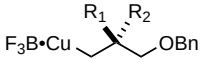
Over the past decade, our goals in natural product synthesis have periodically focused on aspects of conjugate addition which would prove effective for the direct installation of 1,3-*syn*- and 1,3-*anti*-dimethyl stereoarrangements along an acyclic backbone. Our syntheses of myxovirescin A_1,[4] sambutoxin[5] and *O*,*O*-dimethylfuniculosin[6] are illustrative of these efforts. Although solutions to this problem are not general, the hydroxyl-directed reduction of acyclic homoallylic alcohols provides access to 1,3-*syn*-dimethyl constructions via homogeneous catalysis.[7] Additionally, investigators have also developed successful strategies to this end in the course of natural product syntheses.[8]

Hoffman has provided significant insights for conformational organization of flexible molecules bearing 1,3-dimethyl substitution, which may contribute to the understanding of molecular recognition and biochemical properties.[9] This body of work underscores the need for adaptable and effective methodology as a fundamental tool in the proactive design of molecular architecture.[10] Herein we communicate our studies of asymmetric conjugate additions for the stereoselective construction of 1,3-*syn*- and 1,3-*anti*-dimethyl arrays. These efforts also briefly examine the implications for 1,2-dimethyl arrangements.

Initially our experiments examined reactions of the 4-benzyl-*N*-enoyl-1,3-oxazolidin-2-one **1** with enantiopure Yamamoto organocopper species **3a** and **3b**.[11] While the addition of **3a** (Table 1; entry A) proceeded to give **4** in high yield and with good stereoselectivity, use of the enantiomer **3b** led to an interesting reversal of facial selectivity, albeit with reduced stereocontrol, in the production of **5** (entry B). Based on the report of Hruby,[3g] our utilization of 4-phenyl-1,3-oxazolidin-2-one **2a** in reactions with **3a** proved highly successful for synthesis of the 1,3-*anti*-dimethyl array in **6** (entry C), whereas 1,3-*syn* diastereomer **7** (entry D) was available from **2b** in diminished yield and stereoselectivity.[12]



1 X = Bn, Y = H
2a X = Ph, Y = H
2b X = H, Y = Ph



3a R_1 = H, R_2 = CH_3
3b R_1 = CH_3, R_2 = H

Based on these results, a general strategy to provide *anti*- and *syn*-1,3-dimethyl constructions was examined. Efforts explored the differences in selectivity as promoted by the 4-phenyl- and 4-benzyloxazolidinone chiral auxiliaries. In contrast to the addition of the asymmetric organocopper reagents **3a** and **3b**, the addition of a methylcopper species to chiral imides permit-

Keywords: asymmetric organocopper additions; 1,3-stereocontrol.

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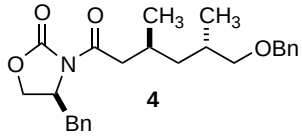
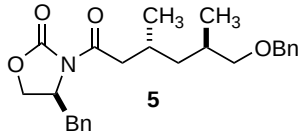
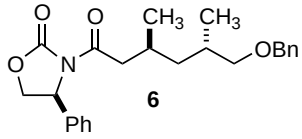
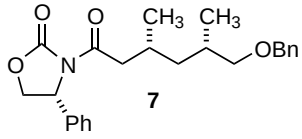
Table 1. Double asymmetric induction reactions of *N*-enoyl-oxazolidinones and organocopper reagent 3[a]

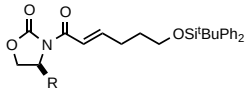
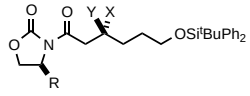
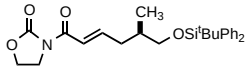
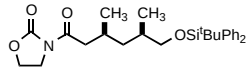
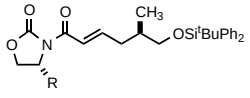
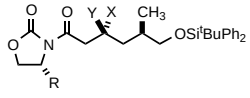
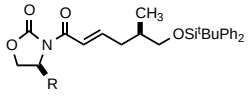
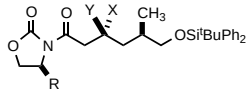
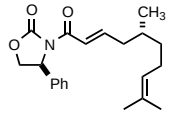
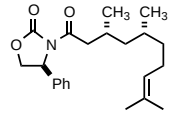
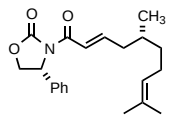
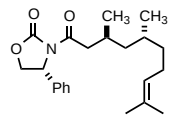
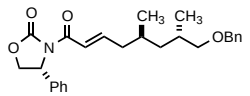
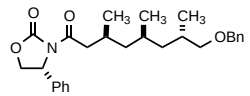
Entry	Imide	R-Cu	Major Product	de (yield)
A	**1**	**3a**	 **4**	87 (96%)
B	**1**	**3b**	 **5**	51 (83%)
C	**2a**	**3a**	 **6**	99 (96%)
D	**2b**	**3a**	 **7**	72 (77%)

(a) All reactions were carried out with Yamamoto organocopper reagent in THF at −78°C.

ted more detailed explorations of the effects of preexisting proximate asymmetry in the conjugate acceptor.

To evaluate the inherent contributions of the individual elements of chirality, initial reactions examined the diastereofacial selectivity in the addition of methylcopper reagent for the 4(*S*)-phenyl, the 4(*S*)-benzyl, and the 4-unsubstituted oxazolidinones of entries A, B and C of Table 2. While comparable product yields were obtained in each of these reactions, evidence for good diastereoselectivity prevailed only in the case of the 4-phenyl auxiliary.[13,14]

Table 2. Double asymmetric induction from chiral auxiliary and homoallylic methyl[a]

Entry	Substrate	Major Product	de (Yield)
A (R = Ph, X = CH_3, Y = H) B (R = Bn, X = H, Y = CH_3)			85% (85%) 47% (86%)
C			59% (83%)
D (R = Ph, X = H, Y = CH_3) E (R = Bn, X = CH_3, Y = H)			>97% (84%) 0% (99%)
F (R = Ph, X = CH_3, Y = H) G (R = Bn, X = H, Y = CH_3) H (R = ^{i}Bu, X = H, Y = CH_3)			84% (75%) 74% (96%) 74% (96%)
I			85% (78%) 83% (77%)[b]
J			67% (87%) 67% (89%)[b]
K			88% (78%)

(a) Reactions performed with $CH_3Cu{\cdot}BF_3(MgBr_2)$ in THF warming from −78 to −20°C. (b) $(Et_2AlCl)_2{\cdot}$oxazolidinone complex added to CH_3Cu.

Surprisingly, the homochiral 4(*S*)-benzyloxazolidinone (entry B) led to a reversal of facial selectivity, albeit with modest diastereocontrol. The presence of chirality at the homoallylic site in entry C also yielded results of moderate diastereofacial selectivity.[15]

Throughout our studies, methylcopper reagent[16] was prepared via the addition of methylmagnesium bromide in ether to a suspension of 1 equiv. of CuBr·DMS complex, followed by 1 equiv. of freshly distilled boron trifluoride etherate at −78°C. Subsequently, the starting *N*-enoyloxazolidinones were added at −78°C in THF with careful warming to −20°C. The increase in reaction temperature, compared to efforts of Table 1, reflects the reduced reactivity of the methyl reagent as compared to related alkyl, alkenyl or allylic species.[3i]

We and others have postulated that the reactivity of populations of Lewis acid complexes of the starting imides may be reflected in the overall observations of diastereoselectivity for these reactions. Low temperature NMR studies have indicated that the six-membered chelation complex of the *syn-s-cis* oxazolidinone conformer is formed exclusively upon addition of 2 equiv. of Et_2AlCl.[17] Monocoordination of a Lewis acid provides the *anti-s-cis* conformer which minimizes carbonyl dipoles and nonbonded interactions, while other possibilities are clearly of higher energy.

The results of Table 2 have demonstrated products which are consistent with nucleophilic addition to the bis-chelated *syn-s-cis* enoyl system via *anti*-facial selectivity with respect to the 4-phenyl substituent. As a test of this hypothesis, we have examined the reactions of preformed $(Et_2AlCl)_2$/oxazolidinone complexes (entries I and J) at −78°C. These results were nearly identical to examples featuring the 4-phenyl auxiliary using Yamamoto conditions. However, gaps in this simplified view are evident from modeling, which clearly shows that the 4-phenyl cannot sterically impede nucleophilic attack at the β-carbon of the Michael acceptor. Additionally, growing evidence suggests that the rate-determining step of 1,4-cuprate addition to enones involves reductive elimination of a β-cuprio(III) intermediate.[18] Thus, unfavorable interactions of the 4-phenyl substituent and a carbon-bound copper species arising from the *syn* four-centered addition of methylcopper may explain our stereochemical results. These rationalizations are also incomplete as evidenced by the reversal of diastereoselectivity found in the corresponding 4-benzyl examples of Table 2 (compare entries A versus B; entries D versus E; entries F versus G). The latter observations cannot be explained by favorable directive π-complexation effects with the organocopper species in reactions of a *syn-s-cis* chelation complex (R = benzyl) since the analogous isobutyl derivative (entry H) gave identical results.[19,20]

An additional element of chirality is introduced with the incorporation of the homoallylic methyl substituent in the *N*-enoyl side chain. This leads to reinforcing and opposing factors for asymmetric conjugate additions. Thus, reactions of the 4(*R*)-phenyl auxiliary of entry D yielded the 1,3-*syn*-dimethyl array with greater than 97% diastereoselectivity. Throughout our investigations, the 4-phenyl-2-oxazolidinone auxiliary was the dominant contributor for asymmetric induction leading to the efficient assembly of the 1,3-*syn*-dimethyl arrangements in matched cases (entries D, I and K). Mismatched substrates (entries F and J) exhibited erosion of diastereofacial selectivity. Overall, the technique was highly effective for acyclic synthesis as illustrated by formation of the 1,3,5-stereotriad of entry K.

A rationalization for the role of the preexisting γ-stereogenic site is based upon 1,4-steric arguments (Fig. 1). For example, the matched scenario of entry D (Table 2) suggests that conformer **A** would minimize nonbonded interactions with a staggered butane geometry (alkenyl/methyl). As a result, vinylic H_a and H_b define a plane whereby the remaining acyclic chain impedes nucleophilic attack to the α-face of the enoyl unit, enhancing the role of the chiral auxiliary. Conformer **B** is a less stable rotamer introducing the gauche butane interaction of the homoallylic methyl group and the β-carbon of the enone. In conformer **B**, the siloxymethylene of the acyclic chain is projected above a plane defined by the 1,3-interaction of H_a and the methyl group.[21] In fact, *tert*-butyldiphenylsilyl ethers ($R = t\text{-}C_4H_9Ph_2Si$) provided for higher levels of stereocontrol than we recorded in earlier experiments using the corresponding benzyl ethers.

We have also investigated the effects of γ-methyl substitution for asymmetric conjugate addition in the preparation of 1,2-dimethyl arrays. In Scheme 1, reactions provided 1,2-*syn*- and 1,2-*anti*-dimethyl arrays with moderate to good asymmetric induction, offering promise for adaptation in the stereocontrolled synthesis of acyclic systems.[22]

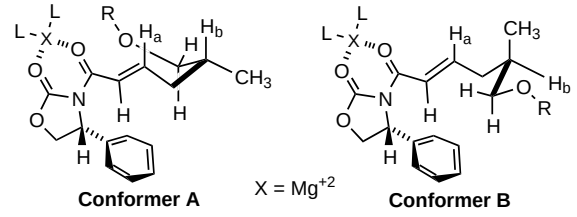
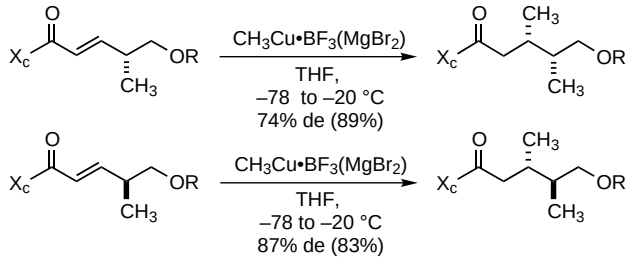


Figure 1. Conformations of γ-methyl substitution.



X_c = 4(*S*)-phenyl-1,3-oxazolidin-2-one; R = Si^tBuPh_2

Scheme 1. Preparation of 1,2-dimethyl array.

Indeed, subsequent to our experiments,[23] Gerwick and co-workers have effectively utilized this strategy for *anti*-1,2-dimethyl stereoselection in the course of total synthesis of (+)-kalkitoxin, a novel marine toxin.[24]

In conclusion, asymmetric conjugate addition reactions have been demonstrated for construction of 1,3-*syn*- and 1,3-*anti*-dimethyl arrays on an acyclic framework utilizing 4-phenyl-1,3-oxazolidin-2-ones as chiral auxiliaries. Limitations have been explored, and the concept has been extended to also provide 1,2-*anti*- and 1,2-*syn*-dimethyl arrangements. The generality of the methodology provides an advance for the synthesis of acyclic compounds via organocopper-mediated addition processes.

Acknowledgements

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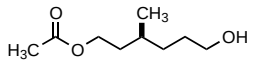
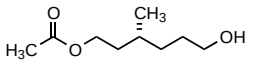
12. For stereochemical assignments of products of Table 1, transformations leading to individual diastereomers permitted correlations with isomers derived from asymmetric crotylations using Roush boronate methodology: Roush, W. R.; Palkowitz, A. D.; Palmer M. A. *J. Org. Chem*. **1987**, *52*, 316. See also Refs. 4 and 5.
13. Diastereomeric excesses (% de) are based upon ^1H NMR (400 MHz) data of crude products, and yields are for purified materials.
14. The stereoassignments of entries A and B were proven following separation of the diastereomers, reduction ($LiBH_4$), acetylation (AcCl; DMAP; CH_2Cl_2), and silyl ether cleavage (TBAF) to give the enantiomeric alcohols ***i*** and ***ii*** for comparison with the literature: Thijs, L.; Stokkingreef, E. H. M.; Lemmons, J. M.; Zwanenburg, B. *Tetrahedron* **1985**, *41*, 2949.

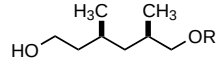


i

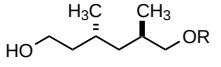


ii

15. *syn*- and *anti*-Diastereomeric products of entries C through H (Table 2) were clearly distinguished by proton and carbon NMR data. Separation of isomers by flash silica gel chromatography followed by reduction ($LiBH_4$; MeOH, ether at 0°C) gave pure *syn*- and *anti*-3,5-dimethyl-hexane-1,6-diol derivatives ***iii*** and ***iv***, respectively. Confirmation of our stereochemistry was feasible via comparisons with data previously reported for ***iii***: Evans, D. A.; Dow, R. L.; Shih, T. L.; Takacs, J. M.; Zahler, R. *J. Am. Chem. Soc*. **1990**, *112*, 5290.



iii (R = Si^tBuPh_2)



iv (R = Si^tBuPh_2)

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