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A Stereoselective Approach to γ-Functionalized Carbonyls Exploiting the Cu-Promoted S_N2' Reaction

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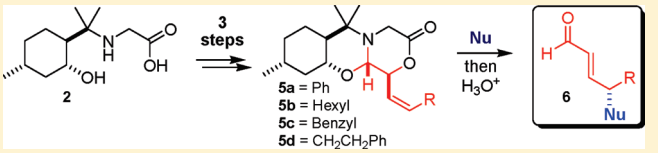
Supporting Information

ABSTRACT: While several efficient processes exist to effect the stereoselective creation of carbon−carbon bonds in the α- and β-position of carbonyls, functionalization of the γ-position is much more challenging. We disclose an alternative methodology exploiting the Cu-promoted S_N2' reaction to achieve the addition of various nucleophiles upon the allylic lactones **5a**−**d** which lead to the generation of the desired γ-functionalized α,β-unsaturated aldehydes **6** following in situ hydrolysis.



INTRODUCTION

The stereoselective formation of carbon−carbon bonds ranks as one of the most important reactions of organic chemistry. Among the various chemical handles utilized to perform this reaction the carbonyl remains among the most powerful functionalities. Stereoselective introduction of substituents either at the α- or β-positions (Figure 1) can be readily achieved respectively via stereoselective alkylation[1] and Michael addition.[2] Achieving similar results at the γ-position is inherently more difficult[3] as it is too far removed from the carbonyl to allow direct functionalization, especially in a stereoselective manner.

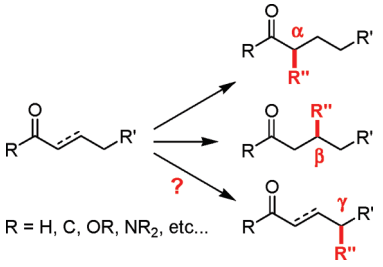


Figure 1. Stereoselective functionalization utilizing the carbonyl group.

Despite these challenges, a growing number of methodologies have been developed to address this gap and allow for the synthesis of various O-,[4] S-,[5] N-,[6] and C-substituted[7] γ-functionalized carbonyls. In our efforts to broaden the scope of these technologies, we have devised a complementary stereoselective approach that exploits the versatility of the Cu-promoted S_N2' reaction.[8]

Inspired by Nakai's work[7b] that utilizes Evans' oxazolidinone imide chemistry to prepare chiral allylic carbonates which undergo Pd(0)-catalyzed allylic substitution to afford the γ-functionalized products, our strategy (Figure 2) analogously generates the electrophilic center in the γ-position by removing the double bond from conjugation and activating it with a leaving group at the α-position. Our auxiliary, however, must serve the triple purpose of (1) masking the sensitive carbonyl, (2) tethering the leaving group in the α-position, and (3) providing the required chiral bias for high stereoselectivity.

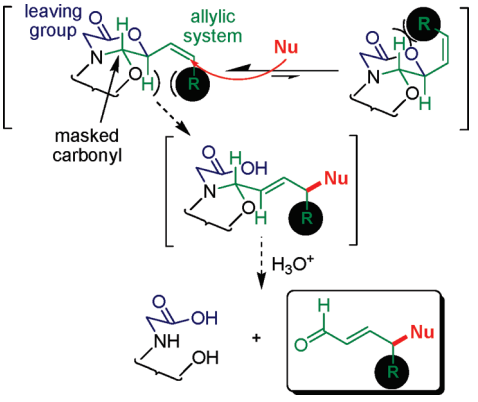


Figure 2. The design of a system exploiting the Cu-promoted S_N2' reaction to carry out stereoselective γ-functionalization.

Further refinement of our model led to the inclusion of another key component. While the Cu-promoted S_N2' reaction proceeds via an anti attack,[9] free rotation around the allylic bond exposes both faces of the alkene, thereby precluding high stereoselectivity. Trost,[10] however, demonstrated that in systems where the leaving group was locked within a ring, very high stereoselectivity could be achieved only if the reactive double bond, outside the ring, was of *Z* geometry. These results can be rationalized by virtue of $A^{1,3}$-strain[11] in one of the two reactive conformers, thereby selectively exposing only one face to attack.

Incorporation of all of the requisite aforementioned elements within our strategy led to the design of the system depicted in Figure 2. Nucleophilic attack upon such a chiral allylic system would perform a stereoselective S_N2' reaction generating, after

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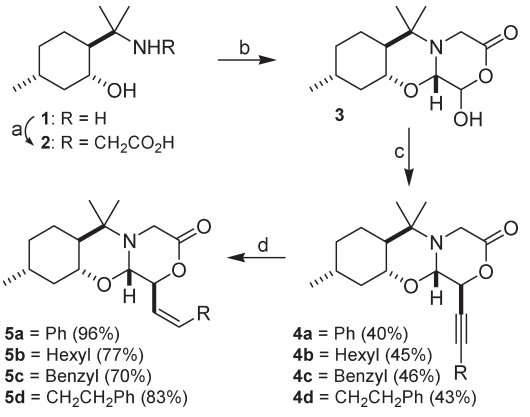
unmasking of the carbonyl group, the desired γ-substituted product. Of further interest is the fact that the final product bears a versatile α,β-unsaturated system that is poised for further chemical transformations.

RESULTS AND DISCUSSION

Our synthesis (Scheme 1) begins with commercially available amino-menthol **1**,[12] which was alkylated with bromoacetic acid to afford the zwitterion **2** in 73% yield. Condensation of amino-acid **2** with glyoxal in 1,4-dioxane afforded the carboxy-lactol **3** in 82% yield.[13] Deprotonation of **3** with sodium hydride followed by addition of the appropriately substituted organo-cerium reagents produced the desired lactones **4a**−**d** with yields ranging between 40% and 46%. Upon workup of these reactions, the crude ^{1}H NMR indicated partial lactonization that was driven to completion by stripping down the crude product several times with MePh and a small amount of AcOH. The diastereomeric ratio of these additions varied between 4:1 to 5:1 in favor of the indicated stereochemistry.[14] Semihydrogenation of these alkynes (**4a**−**d**) using Brown's P-2 Ni method[15] afforded the corresponding *cis* alkenes **5a**−**d** (with $Z/E > 99:1$)[16] in yields ranging between 70% and 96%. The structural assignment of **5a** was rigorously ascertained with the help of NMR experiments (see the Supporting Information). With these key intermediates in our hands, we then turned our attention to performing the crucial Cu-promoted S_N2' reaction using a variety of nucleophiles.

Scheme 1. Synthesis of the Key Precursors 5a−d[a]

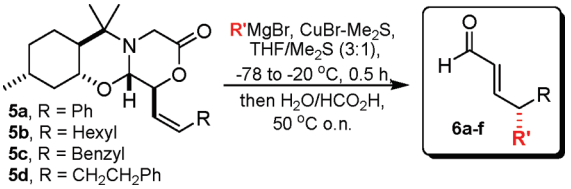


[a] Reagents and conditionsy: (a) $BrCH_2CO_2H$, NaOH, H_2O/EtOH, rt−80 °C, 73%; (b) Glyoxal, 1,4-dioxane, 70 °C, 1 h, 82%; (c) NaH, THF, 0 °C, then Cl_2CeCCR, −78 °C, then AcOH/MePH; (d) H_2, $NaBH_4$, $Ni(OAc)_2$, TMEDA, EtOH, 0 °C to rt.

Treatment of these differentially substituted allylic lactones **5a**−**d** (Table 1) with 2.5 equiv of primary (entries 1−4), secondary (entry 5), and tertiary (entry 6) monoalkyl copper reagents effected the desired S_N2' reaction, which afforded, following in situ hydrolysis using aqueous formic acid, the desired γ-functionalized aldehydes **6a**−**f**.[17] Reaction yields varied between 52% and 72% along with stereoselectivities ranging between 85% and 98% ee. An authentic standard of compound **6a** was synthesized (data not shown) which confirmed that the stereochemical outcome of the S_N2' reaction was as predicted and served as validation for our model.

It was found that extending this methodology to include aryl copper nucleophiles was only possible by utilizing a large excess

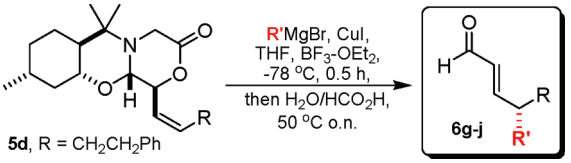
Table 1. Stereoselective Synthesis of γ-Alkylated Aldehydes 6a−f via the Cu-Promoted S_N2' Reaction



entry	product	R	R'	Yield (%)	e.e.[a] (%)
1	**6a**	Ph	Me	55	98[b]
2	**6b**	5Me	Me	67	92[c]
3	**6c**	Ph	Me	72	85
4	**6d**	2Ph	Me	72	98
5	**6e**	2Ph		52	95
6	**6f**	2Ph		68	94

[a] ee determinations were established by using chiral HPLC conditions developed to resolve the racemates. [b] ee was determined by using the saturated alcohol. [c] ee was determined by using chiral HPLC conditions to resolve the Mosher's ester of the allylic alcohol.

Table 2. Stereoselective Synthesis of γ-Arylated and γ-Alkenylated Aldehydes 6g−j via the Cu-Promoted S_N2' Reaction



entry	product	R'	Yield (%)	e.e.[a] (%)
1	**6g**		56	98
2	**6h**	OMe	51	96[b]
3	**6i**	F	75	92
4	**6j**	Me	43	95

[a] ee determinations were established by using chiral HPLC conditions developed to resolve the racemates.

of nucleophile along with higher reaction temperature and time. Aware that the lesser reactivity of the aryl-copper species was likely the source of the problem, we turned our attention to Lewis acid activation of the reaction. After screening a variety of Lewis

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acids, copper sources, and reaction conditions (data not shown), we discovered that the combination of a substoichiometric amount of $BF_3 \cdot OEt_2$ along with a higher order cuprate (Table 2) afforded results comparable to those obtained with the alkyl nucleophiles.

Thus, treatment of the allylic lactone **5d** with 2.0 equiv of various higher order aryl cuprates (entries 1−3) in the presence of 0.5 equiv of $BF_3 \cdot OEt_2$ afforded, again following hydrolysis with aqueous formic acid, the desired γ-functionalized aldehydes **6g**−**i**. Chemical yields varied between 51% and 75% along with stereoselectivities ranging from 92% to 98% ee. The utilization of a vinylic nucleophile (entry 4) also proved possible, furnishing the desired γ-functionalized aldehyde **6j** in 43% yield and 95% ee.

CONCLUSION

In summary, we have established a general stereoselective approach that allows the preparation of γ-functionalized aldehydes via a 5-step sequence beginning from commercially available amino-menthol **1**. This methodology exploits the potential of the Cu-promoted S_N2' reaction allowing the stereoselective introduction of substituents upon our scaffolds **5a**−**d**. Further efforts are currently underway to expand the scope of this methodology to include transition metal catalysis as well as extending the range of nucleophiles to include various heteroatoms.

EXPERIMENTAL SECTION

({2-[(1*S*,2*R*,4*R*)-2-Hydroxy-4-methylcyclohexyl]propan-2-yl}amino)acetic acid (2): To α-bromoacetic acid (5.75 g, 43.86 mmol, 1.5 equiv) in water (10 mL) at 0 °C was added 10 N NaOH until the pH was approximately 12. The *l*-8-amino-menthol **1** (5.0 g, 29.24 mmol) was dissolved in a minimal amount of EtOH and added to the reaction, which was gradually warmed to 80 °C. After 1 h another 0.5 equiv of α-bromoacetic acid (again dissolved in a minimal amount of water and basified with 10 N NaOH) was added to the reaction mixture, which was then stirred at 90 °C for another hour. The reaction was then cooled to rt and concentrated in vacuo to remove all of the EtOH. The crude product was directly purified by flash chromatography over SiO_2 (NH_4OH/MeOH/DCM, 1:9:90, then 2:18:80) to afford the desired amino-acid auxiliary **2** as a white solid (4.86 g, 73% yield). Alternatively, compound **2** could also be purified by reverse-phase flash chromatography over C_{18} Lichroprep (column loaded using MeCN/H_2O, 2:8 + 0.1% HCO_2H, then washed and eluted with MeCN/H_2O 5:95 + 0.1% HCO_2H, then 1:9 + 0.1% HCO_2H, then 2:8 + 0.1% HCO_2H). The fractions were concentrated to remove most of the MeCN and lyophilized to afford the desired product as the HCO_2H salt as a white solid. ^{1}H NMR (500 MHz, D_2O) δ 3.66 (dt, J = 4.0, 10.7 Hz, 1H), 3.49 (d, J = 16.1 Hz, 1H), 3.41 (d, J = 16.1 Hz, 1H), 1.82−1.79 (m, 1H), 1.68−1.64 (m, 1H), 1.62−1.58 (m, 1H), 1.56−1.50 (m, 1H), 1.40−1.33 (m, 1H), 1.24 (s, 3H), 1.21 (d, J = 6.5 Hz, 1H), 1.48 (s, 3H), 1.04−0.94 (m, 2H), 0.86−0.78 (m, 1H), 0.79 (d, J = 6.6 Hz, 3H). ^{13}C NMR (101 MHz, D_2O) δ 172.0, 71.91, 62.1, 47.1, 43.6, 42.7, 33.5, 30.6, 24.9, 22.2, 21.0, 18.4. HRMS calcd for $C_{12}H_{24}NO_3$ $(M + H)^+$ 230.1753, found 230.1751. $[\alpha]^{22}_D$ −21.9 [*c* 1.75, H_2O].

(6a*S*,9*R*,10a*R*,11a*S*)-1-Hydroxy-6,6,9-trimethyloctahydro-6*H*-[1,4]oxazino[3,4-*b*][1,3]benzoxazin-3(4*H*)-one (3): To the amino-acid auxiliary **2** (900 mg, 3.92 mmol) in 1,4-dioxane (40 mL) was added an aqueous solution of glyoxal (40% w/w, 2.25 mL, 19.6 mmol) and the reaction was heated at 70 °C for 1 h. The solvent was removed in vacuo and the crude product was directly purified by flash chromatography over SiO_2 (EtOAc/Hex 75:25 + 0.1% AcOH) to afford the desired product **3** (869 mg, 82% yield) as a white solid (exists as an inconsequential 5:1 mixture of epimers at the carboxy-lactol position). The compound should be stored in the freezer and utilized within 24 h as it slowly reverts back to the starting material. ^{1}H NMR (major epimer, 400 MHz, d_6-DMSO) δ 7.75 (d, J = 6.4 Hz, 1H, exchangeable proton), 5.25 (d, J = 5.4 Hz, 1H), 4.51 (s, 1H), 3.63 (d, J = 17.8 Hz, 1H), 3.33 (d, J = 17.8 Hz, 1H), 3.61−3.45 (m, 1H, embedded in the DMSO signal), 1.83−1.77 (m, 1H), 1.72−1.63 (m, 1H), 1.59−1.45 (m, 3H), 1.28−0.81 (m, 3H), 1.08 (s, 3H), 1.06 (s, 3H), 0.88 (d, J = 6.4 Hz, 3H). ^{13}C NMR (101 MHz, d_6-DMSO) δ 168.8, 96.3, 82.2, 75.6, 55.7, 44.3, 44.1, 41.1, 34.8, 31.2, 25.4, 24.8, 22.6, 19.0. HRMS calcd for $C_{14}H_{24}NO_4$ $(M + H)^+$ 270.1715, found 270.1670. $[\alpha]^{22}_D$ −39.0 [*c* 0.55, EtOH].

General Procedure for the Addition−Lactonization Reaction. A solution of the organo-cerium reagent was prepared by adding the corresponding Grignard reagent (2 equiv) to dry $CeCl_3$ (2.1 equiv) in dry THF (0.2 M) at −40 °C, and the reaction was stirred for 30 min. To lactol **3** in dry THF (0.2 M) at 0 °C was added 60% NaH (1 equiv) and the reaction was stirred for 15 min and then cooled to −78 °C. The organo-cerium reagent was then transferred via syringe to the deprotonated lactol **3** and, after 30 min, the reaction was raised to −40 °C and stirred for an additional 30 min. The reaction was quenched by the addition of saturated NH_4Cl and diluted with EtOAc and brine, then the crude product was extracted with EtOAc (3×) and dried over Na_2SO_4. The reaction afforded only partial lactonization and was completed by addition of toluene along with acetic acid (a few hundred microliters) and concentrating it in vacuo on a rotavap with the bath adjusted at 70 °C. This process was repeated several times until all of the intermediate was completely lactonized as judged by TLC and LCMS.

(1*S*,6a*S*,9*R*,10a*R*,11a*S*)-6,6,9-Trimethyl-1-(phenylethynyl)octahydro-6*H*-[1,4]oxazino[3,4-*b*][1,3]benzoxazin-3(4*H*)-one (4a): The crude ^{1}H NMR showed a ratio of 4:1 for the two diastereoisomers. The crude product was then purified by flash chromatography over SiO_2 (EtOAc/Hex, 2:8) to afford the major nonpolar product **4a** (275 mg, 40% yield) and the minor product (70 mg, 10% yield). ^{1}H NMR (400 MHz, d_4-MeOH) δ 7.47−7.45 (m, 2H), 7.39−7.33 (m, 3H), 5.41 (d, J = 2.2 Hz, 1H), 4.98 (d, J = 2.2 Hz, 1H), 3.82 (d, J = 18.2 Hz, 1H), 3.63 (d, J = 18.2 Hz, 1H), 3.69−3.66 (m, 1H), 1.97−1.94 (m, 1H), 1.75−1.72 (m, 1H), 1.66−1.61 (m, 2H), 1.54−1.45 (m, 1H), 1.26 (s, 3H), 1.15 (s, 3H), 1.12−0.93 (m, 3H), 0.95 (d, J = 6.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.5, 131.5, 128.8, 128.2, 121.8, 87.3, 81.9, 79.8, 77.1, 71.8, 56.3, 43.2, 42.4, 40.5, 34.6, 31.3, 24.5, 24.3, 21.2, 20.0. Minor (more polar) isomer: ^{1}H NMR (400 MHz, d_4-MeOH) δ 7.50 (d, J = 1.4 Hz, 2H), 7.49−7.36 (m, 3H), 5.45 (d, J = 2.3 Hz, 1H), 5.02 (d, J = 2.4 Hz, 1H), 3.76 (dd, J = 18.2, 92.9 Hz, 2H), 3.74−3.69 (m, 1H), 2.00−1.97 (m, 1H), 1.78−1.75 (m, 1H), 1.70−1.64 (m, 2H), 1.58−1.52 (m, 1H), 1.29 (s, 3H), 1.18 (s, 3H), 1.20−0.97 (m, 3H), 0.98 (d, J = 6.6 Hz, 3H).

(1*S*,6a*S*,9*R*,10a*R*,11a*S*)-6,6,9-trimethyl-1-(oct-1-yn-1-yl)octahydro-6*H*-[1,4]oxazino[3,4-*b*][1,3]benzoxazin-3(4*H*)-one (4b): The crude ^{1}H NMR showed a ratio of 5:1 for the two diastereoisomers. The crude product was purified by flash chromatography over SiO_2 (EtOAc/Hex, 2:8) to afford the major nonpolar product **4b** (400 mg, 45% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.82 (s, 1H), 4.55 (s, 1H), 3.58−3.25 (m, 3H), 2.06 (t, J = 7.0 Hz, 2H), 1.79−1.68 (m, 1H), 1.60−1.51 (m, 1H), 1.48−1.39 (m, 1H), 1.38−1.30 (m, 4H), 1.25−1.18 (m, 2H), 1.27−0.99 (m, 4H), 1.02 (s, 3H), 0.97 (s, 3H), 0.93−0.67 (m, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.0, 89.1, 82.1, 76.4, 74.8, 71.8, 56.0, 43.9, 43.8, 40.9, 34.8, 31.3, 31.3, 28.4, 28.2, 25.3, 24.8, 22.6, 22.1, 19.4, 18.7, 14.1. Minor (more polar) isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.09 (s, 1H), 4.74 (s, 1H), 3.83−3.49 (m, 3H), 2.40−2.15 (m, 2H), 2.06−1.95 (m, 1H), 1.81−1.65 (m, 2H), 1.68−1.44 (m, 4H), 1.52−1.31 (m, 2H), 1.46−1.18 (m, 4H), 1.23 (s, 3H), 1.13 (s, 3H), 1.09−0.85 (m, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.7, 89.6, 79.9, 77.2, 73.2, 71.6, 56.4, 43.9, 42.5, 40.8, 34.9, 31.5, 31.4, 28.5, 28.2, 25.4, 24.9, 22.6, 22.1, 21.1, 18.9, 14.1.

(1*S*,6a*S*,9*R*,10a*R*,11a*S*)-6,6,9-trimethyl-1-(3-phenylprop-1-yn-1-yl)octahydro-6*H*-[1,4]oxazino[3,4-*b*][1,3]benzoxazin-3(4*H*)-one (4c): The crude ^{1}H NMR showed a ratio of 5:1 for the two

diastereoisomers. The crude product was purified by flash chromatography over SiO_2 (EtOAc/Hex, 2:8) to afford the major nonpolar product **4c** (262 mg, 46% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25−7.14 (m, 4H), 7.14−7.07 (m, 1H), 4.94 (d, J = 2.7 Hz, 1H), 4.66 (d, J = 2.7 Hz, 1H), 3.65−3.30 (m, 5H), 1.82−1.73 (m, 1H), 1.64−1.55 (m, 1H), 1.53−1.44 (m, 1H), 1.42−1.32 (m, 2H), 1.07 (s, 3H), 1.03 (s, 3H), 1.05−0.80 (m, 3H), 0.81 (d, J = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.8, 135.7, 128.4, 127.8, 126.7, 86.3, 81.8, 76.7, 76.5, 71.6, 56.0, 43.9, 43.6, 40.8, 34.7, 31.3, 25.3, 25.0, 24.7, 22.1, 19.5. HRMS calcd for $C_{23}H_{30}NO_3$ $(M + H)^+$ 368.2220, found 368.2234. Minor (more polar) isomer (21 mg, 4% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, J = 7.5 Hz, 2H), 7.35 (t, J = 7.5 Hz, 2H), 7.32−7.24 (m, 1H), 5.16 (s, 1H), 4.80 (d, J = 2.4 Hz, 1H), 3.83−3.52 (m, 5H), 2.10−2.00 (m, 1H), 1.81−1.72 (m, 1H), 1.69−1.48 (m, 3H), 1.24 (s, 3H), 1.23−0.99 (m, 3H), 1.15 (s, 3H), 0.99 (d, J = 6.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.4, 135.8, 128.4, 127.8, 126.6, 86.6, 79.8, 77.0, 75.6, 71.4, 56.3, 43.7, 42.5, 40.7, 34.7, 31.4, 25.3, 25.1, 24.7, 22.1, 20.7.

(1*S*,6a*S*,9*R*,10a*R*,11a*S*)-6,6,9-trimethyl-1-(4-phenylbut-1-yn-1-yl)octahydro-6*H*-[1,4]oxazino[3,4-*b*][1,3]benzoxazin-3(4*H*)-one (4d): The crude ^{1}H NMR showed a ratio of 5:1 for the two diastereoisomers. The crude product was then purified by flash chromatography over SiO_2 (EtOAc/Hex, 2:8) to afford the major nonpolar product **4d** (333 mg, 43% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27−7.19 (m, 2H), 7.19−7.13 (m, 3H), 4.91 (s, 1H), 4.61 (s, 1H), 3.66−3.32 (m, 3H), 2.77 (t, J = 7.4 Hz, 2H), 2.47 (t, J = 7.5 Hz, 2H), 1.88−1.78 (m, 1H), 1.71−1.61 (m, 1H), 1.62−1.49 (m, 1H), 1.45−1.35 (m, 2H), 1.09 (s, 3H), 1.07 (s, 3H), 1.04−0.87 (m, 3H), 0.87 (d, J = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.8, 140.3, 128.4, 128.3, 126.3, 88.1, 81.9, 76.4, 75.6, 71.7, 55.9, 43.8, 43.8, 40.8, 34.7, 34.5, 31.3, 25.3, 24.7, 22.1, 20.9, 19.3. HRMS calcd for $C_{24}H_{32}NO_3$ $(M + Li)^+$ 388.2478, found 388.2478. $[\alpha]^{22}_D$ −42.8 [c 0.96, EtOH]. Minor (more polar) isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.23 (m, 5H), 5.08 (s, 1H), 4.72 (s, 1H), 3.79−3.47 (m, 3H), 2.89 (t, J = 7.5 Hz, 2H), 2.59 (t, J = 7.6 Hz, 2H), 2.06−1.95 (m, 1H), 1.82−1.72 (m, 1H), 1.66−1.52 (m, 3H), 1.39−0.96 (m, 3H), 1.23 (s, 3H), 1.13 (s, 3H), 0.98 (d, J = 6.3 Hz, 3H).

General Procedure for the P-2 Ni Semihydrogenation Reaction. To $Ni(OAc)_2(H_2O)_4$ (0.35 equiv) in EtOH (0.1 M) under N_2 was added a solution of $NaBH_4$ in EtOH (1.0 M, 0.35 equiv) and a fine black precipitate was formed. A hydrogen balloon was then added and the reaction was stirred for 30 min at RT. TMEDA (1.4 equiv) was then added and the reaction mixture was cooled to 0 °C. The alkyne **4** in EtOH (0.1 M) was added via syringe and the reaction was stirred for 15 min. The reaction was warmed to rt and stirred another 45 min. The reaction vessel was purged with dry nitrogen and diluted with DCM. Water was added and the crude product was extracted with DCM (2×), then the combined organic fractions were dried over Na_2SO_4, filtered, and concentrated in vacuo.

(1*S*,6a*S*,9*R*,10a*R*,11a*S*)-6,6,9-trimethyl-1-(2-phenylethenyl) octahydro-6*H*-[1,4]oxazino[3,4-*b*][1,3]benzoxazin-3(4*H*)-one (5a): The crude product was purified by flash chromatography over SiO_2 (EtOAc/Hex, 2:8) to afford the desired alkene **5a** (96 mg, 96% yield) as a yellow oil. ^{1}H NMR (400 MHz, d_4-MeOH) δ 7.44−7.32 (m, 5H), 6.87 (d, J = 11.6 Hz, 1H), 5.85 (dd, J = 11.5, 9.9 Hz, 1H), 5.12 (dd, J = 9.5, 2.0 Hz, 1H), 4.76 (d, J = 2.4 Hz, 1H), 3.80 (d, J = 18.3 Hz, 1H), 3.60 (d, J = 18.3 Hz, 1H), 3.63−3.57 (m, 1H), 1.92−1.88 (m, 1H), 1.77−1.74 (m, 1H), 1.69−1.51 (m, 3H), 1.23 (s, 3H), 1.20 (s, 3H), 1.17−0.98 (m, 3H), 0.96 (s, J = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, d_4-MeOH) δ 170.7, 136.8, 136.4, 129.7, 129.5, 128.9, 127.0, 82.8, 78.5, 77.7, 57.1, 44.9, 44.6, 41.9, 36.0, 32.5, 25.7, 25.6, 22.6, 20.1.

(1*S*,6a*S*,9*R*,10a*R*,11a*S*)-6,6,9-trimethyl-1-[(1*Z*)-oct-1-en-1-yl] octahydro-6*H*-[1,4]oxazino[3,4-*b*][1,3]benzoxazin-3(4*H*)-one (5b): The crude product was purified by flash chromatography over SiO_2 (EtOAc/Hex, 15:85) to afford the desired product **5b** (310 mg, 77% yield) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.70 (dt, J = 10.9, 7.6 Hz, 1H), 5.48 (t, J = 10.0 Hz, 1H), 5.06 (dd, J = 9.2, 2.5 Hz, 1H), 4.50 (d, J = 2.6 Hz, 1H), 3.77−3.40 (m, 3H), 2.21−2.02 (m, 2H), 1.95−1.87 (m, 1H), 1.75−1.68 (m, 1H), 1.63−1.56 (m, 1H), 1.54−1.43 (m, 2H), 1.43−1.34 (m, 2H), 1.34−1.25 (m, 6H), 1.14 (s, 3H), 1.12 (s, 3H), 1.12−0.94 (m, 3H), 0.94 (d, J = 6.5 Hz, 3H), 0.89 (t, J = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.6, 136.7, 124.9, 81.9, 76.9, 76.4, 55.8, 43.9, 43.8, 40.9, 34.8, 31.7, 31.4, 29.3, 28.9, 27.9, 25.4, 24.8, 22.6, 22.2, 19.6, 14.1.

(1*S*,6a*S*,9*R*,10a*R*,11a*S*)-6,6,9-trimethyl-1-[(1*Z*)-3-phenylprop-1-en-1-yl]octahydro-6*H*-[1,4]oxazino[3,4-*b*][1,3]benzoxazin-3 (4*H*)-one (5c): The crude product was purified by flash chromatography over SiO_2 (EtOAc/Hex, 2:8) to afford the desired product **5c** (92 mg, 70% yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22−7.14 (m, 2H), 7.10 (d, J = 7.6 Hz, 3H), 5.82−5.71 (m, 1H), 5.52 (t, J = 10.0 Hz, 1H), 5.11−5.05 (m, 1H), 4.41 (m, 1H), 3.70−3.22 (m, 5H), 1.85−1.75 (m, 1H), 1.66−1.57 (m, 1H), 1.53−1.46 (m, 1H), 1.45−1.35 (m, 2H), 1.02 (s, 6H), 1.33−0.85 (m, 3H), 0.84 (d, J = 6.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.3, 139.3, 134.6, 128.5, 128.4, 126.2, 125.8, 81.7, 76.7, 76.2, 55.7, 43.9, 43.9, 40.8, 34.7, 34.0, 31.2, 25.3, 24.7, 22.1, 19.2.

(1*S*,6a*S*,9*R*,10a*R*,11a*S*)-6,6,9-Trimethyl-1-[(1*Z*)-4-phenylbut-1-en-1-yl]octahydro-6*H*-[1,4]oxazino[3,4-*b*][1,3]benzoxazin-3(4*H*)-one (5d): The crude product was purified by flash chromatography over SiO_2 (EtOAc/Hex, 2:8) to afford the desired product **5d** (268 mg, 83% yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (t, J = 7.4 Hz, 2H), 7.22 (t, J = 8.5 Hz, 3H), 5.74 (q, J = 8.9 Hz, 1H), 5.53 (1 H, t, J = 10.1 Hz), 4.96 (1 H, d, J = 9.4 Hz), 4.21 (s, 1H), 3.74 (d, J = 17.7 Hz, 1H), 3.51 (d, J = 17.7 Hz, 1H), 3.46−3.37 (m, 1H), 2.87−2.76 (m, 1H), 2.76−2.62 (m, 1H), 2.56−2.46 (m, 2H), 1.96−1.86 (m, 1H), 1.75 (s, 1H), 1.65−1.54 (m, 1H), 1.55−1.42 (m, 3H), 1.12 (s, 3H), 1.11 (s, 4H), 1.04 (d, J = 28.2 Hz, 1H), 0.97 (d, J = 6.5 Hz, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.3, 141.1, 134.9, 128.5, 128.2, 125.9, 125.7, 81.4, 76.5, 76.2, 55.6, 43.7, 43.4, 40.7, 35.3, 34.7, 31.3, 29.6, 25.3, 24.7, 22.1, 19.7. HRMS m/e calcd $(M + H^+)$ 384.2533, found 384.2543. HRMS calcd for $C_{24}H_{34}NO_3$ $(M + H)^+$ 384.2533, found 384.25426. $[\alpha]^{22}_D$ −80.7 [c 1.14, $CHCl_3$].

General Procedure for the Cu-Promoted S_N2' Reaction of Alkyl Nucleophiles. To CuBr·Me_2S (2.5 equiv) under an inert atmosphere of dry nitrogen was added dry THF and Me_2S (7:3, 0.1 M). The suspension was cooled to −40 °C and the corresponding Grignard reagent (2.5 equiv) was added dropwise. After being stirred for 15 min, the solution was cooled to −78 °C and **5** in a minimal amount of THF was added dropwise. The mixture was warmed to −20 °C and stirred for another 30 min. The reaction was quenched with H_2O (a few milliliters), warmed to rt, a large excess of formic acid was added (5−10 mL), and the reaction mixture was stirred overnight at 50 °C. Brine was then added and the crude product was extracted with Et_2O (3×). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated in vacuo.

(2*E*,4*R*)-4-Phenylhex-2-enal (6a): The crude product was purified by flash chromatography on SiO_2 (Et_2O/Hex, 2:8) to yield the desired γ-substituted aldehyde **6a** (45 mg, 55% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.55 (d, J = 7.8 Hz, 1H), 7.39−7.35 (m, 2H), 7.33−7.27 (m, 1H), 7.22−7.20 (m, 2H), 6.96 (dd, J = 7.5, 15.6 Hz, 1H), 6.13 (dd, J = 7.9, 15.7 Hz, 1H), 3.46 (dd, J = 7.5, 14.9 Hz, 1H), 1.95−1.82 (m, 2H), 0.94 (t, J = 7.4 Hz, 3H). HRMS calcd for $C_{12}H_{14}O$ $(M + H)^+$ 175.1117, found 175.1116. $[\alpha]^{22}_D$ −11.5 [c 1.00, H_2O]. Chiral HPLC resolution conditions of the saturated alcohol (prepared by reducing the aldehyde with $NaBH_4$ in MeOH, and hydrogenating the alkene with Pd/C in EtOAc): column purchased from Regis Technology Inc., (*R*,*R*) Whelk-O1 (4.6 × 250 mm), 2% IPA/98% hexanes, 1.0 mL/min, 220 nM, ee = 98%.

(2*E*,4*S*)-4-Ethyldec-2-enal (6b): The crude product was purified by flash chromatography on SiO_2 (Et_2O/Hex, 2:8) to yield the desired γ-substituted aldehyde **6b** (22 mg, 67% yield). ^{1}H NMR (400 MHz,

$CDCl_3$) δ 9.54 (d, J = 7.9 Hz, 1H), 6.65 (dd, J = 15.6, 9.0 Hz, 1H), 6.11 (dd, J = 15.6, 7.9 Hz, 1H), 2.41−2.07 (m, 1H), 1.61−1.49 (m, 2H), 1.48−1.35 (m, 2H), 1.51−1.05 (m, 8H), 0.98−0.82 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.2, 163.3, 132.9, 44.8, 34.0, 31.7, 29.3, 27.2, 27.1, 22.6, 14.1, 11.6. $[\alpha]^{22}_D$ +1.1 [c 0.71, $CHCl_3$]. Chiral HPLC resolution conditions of the Mosher ester of the corresponding allylic alcohol (prepared by reducing the aldehyde using $NaBH_4$ in MeOH): Chiralcel OJ (4.6 × 250 mm), 2% EtOH/98% hexanes, 1.0 mL/min, 220 nM, Rt = 4.7 and 6.8 min, ee = 92%.

(2*E*,4*S*)-4-Benzylhex-2-enal (6c): The crude product was purified by flash chromatography on SiO_2 (EtOAc/Hex, 2:8) to afford the desired γ-substituted aldehyde **6c** (33 mg, 72% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.40 (d, J = 7.9 Hz, 1H), 7.24−7.16 (m, 2H), 7.15−7.08 (m, 1H), 7.08−7.02 (m, 2H), 6.58 (dd, J = 15.7, 8.6 Hz, 1H), 5.93 (dd, J = 15.7, 7.8 Hz, 1H), 2.81−2.69 (m, 1H), 2.67−2.56 (m, 1H), 2.54−2.42 (m, 1H), 1.64−1.47 (m, 1H), 1.44−1.29 (m, 1H), 0.84 (t, J = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.1, 160.8, 138.3, 132.3, 128.2, 127.6, 125.5, 45.4, 39.6, 25.6, 10.8. HRMS calcd for $C_{13}H_{17}O$ $(M + H)^+$ 189.1266, found 189.1266. $[\alpha]^{22}_D$ +42.1 [c 1.1, $CHCl_3$]. Chiral HPLC resolution conditions: Chiralcel OJ (4.6 × 250 mm), 5% EtOH/95% hexanes + 0.25% Et_3N, 1.0 mL/min, 220 nM, Rt = 6.4 and 10.0 min, ee = 85%.

(2*E*,4*S*)-4-Ethyl-6-phenylhex-2-enal (6d): The crude product was purified by flash chromatography on SiO_2 (Et_2O/Hex, 2:8) to yield the desired γ-substituted aldehyde **6d** (42 mg, 72% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.57 (d, J = 7.9 Hz, 1H), 7.32 (t, J = 7.5 Hz, 2H), 7.27−7.16 (m, 3H), 6.69 (dd, J = 15.7, 9.0 Hz, 1H), 6.16 (dd, J = 15.7, 7.9 Hz, 1H), 2.73−2.53 (m, 2H), 2.37−2.25 (m, 1H), 1.95−1.83 (m, 1H), 1.81−1.67 (m, 1H), 1.69−1.57 (m, 1H), 1.55−1.40 (m, 1H), 0.92 (t, J = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.1, 162.5, 141.7, 133.4, 128.5, 128.4, 126.0, 44.2, 35.6, 33.5, 27.2, 11.5. HRMS calcd for $C_{14}H_{19}O$ $(M + H)^+$ 203.1430, found 203.1429. $[\alpha]^{22}_D$ +12.8 [c 0.293, $CHCl_3$]. Chiral HPLC resolution conditions: Chiralpak AD (4.6 × 250 mm), 10% MeOH/10% IPA/80% hexanes, 1.0 mL/min, 220 nM, Rt = 6.7 and 7.2 min, ee = 98%.

(2*E*,4*R*)-4-Cyclohexyl-6-phenylhex-2-enal (6e): The crude product was purified by flash chromatography on SiO_2 (Et_2O/Hex, 2:8) to yield the desired γ-substituted aldehyde **6e** (11 mg, 52% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.57 (d, J = 7.9 Hz, 1H), 7.35−7.27 (m, 2H), 7.26−7.14 (m, 3H), 6.74 (dd, J = 15.6, 9.7 Hz, 1H), 6.13 (dd, J = 15.6, 7.9 Hz, 1H), 2.69−2.59 (m, 1H), 2.55−2.45 (m, 1H), 2.25−2.19 (m, 1H), 2.00−1.91 (m, 1H), 1.81−1.63 (m, 6H), 1.35−0.85 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.9, 161.6, 141.8, 134.2, 128.5, 128.4, 126.0, 48.6, 41.8, 33.8, 33.0, 31.0, 29.9, 26.5. $[\alpha]^{22}_D$ +3.3 [c 0.92, $CHCl_3$]. Chiral HPLC resolution conditions: Chiralcel OJ (4.6 × 250 mm), 2% IPA, 2% EtOH, 96% hexanes + 0.25% Et_3N, 1.0 mL/min, 220 nM, Rt = 6.3 and 8.0 min, ee = 96%.

(2*E*,4*S*)-5,5-Dimethyl-4-(2-phenylethyl)hex-2-enal (6f): The crude product was purified by flash chromatography on SiO_2 (Et_2O/Hex, 2:8) to afford the desired γ-substituted aldehyde **6f** (48 mg, 68% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.61 (d, J = 7.9 Hz, 1H), 7.36−7.28 (m, 2H), 7.27−7.15 (m, 3H), 6.76 (dd, J = 15.6, 10.3 Hz, 1H), 6.16 (dd, J = 15.5, 7.9 Hz, 1H), 2.70−2.60 (m, 1H), 2.47−2.35 (m, 1H), 2.11−1.96 (m, 2H), 1.71−1.56 (m, 1H), 0.94 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.8, 160.6, 141.7, 135.0, 128.5, 128.4, 126.0, 53.6, 34.4, 33.5, 30.5, 27.7. HRMS calcd for $C_{16}H_{23}O$ $(M + H)^+$ 231.1743, found 231.1752. $[\alpha]^{22}_D$ −7.3 [c 2.13, $CHCl_3$]. Chiral HPLC resolution conditions: Chiralcel OJ (4.6 × 250 mm), 2% IPA/98% hexanes, 1.0 mL/min, 220 nM, Rt = 9.4 and 10.7 min, ee = 94%.

General Procedure for the Cu-Promoted S_N2' Reaction of Aryl and Vinyl Nucleophiles. To CuI (2 equiv) under an inert atmosphere of dry nitrogen was added dry THF (0.1 M). The suspension was cooled to −40 °C and the corresponding Grignard reagent (4 equiv) was added dropwise at −40 °C. After being stirred for 15 min, the solution was cooled to −78 °C and a solution of $BF_3 \cdot OEt_2$ (1.0 M in THF, 0.5 equiv) was added dropwise. After 5 min of stirring, allylic compound **5** (in a minimal amount of THF) was added dropwise and the reaction mixture was stirred for another 30 min. The reaction was quenched with H_2O (a few milliliters), warmed to rt, a large excess of formic acid was added (5−10 mL), and the reaction mixture was stirred overnight at 50 °C. Brine was then added and the crude product was extracted with Et_2O (3×). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated in vacuo.

(2*E*,4*S*)-4,6-Diphenylhex-2-enal (6g): The crude product was purified by flash chromatography on SiO_2 (Et_2O/Hex, 2:8) to yield the desired γ-substituted aldehyde **6g** (12 mg, 56% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.56 (d, J = 7.9 Hz, 1H), 7.44−7.37 (m, 2H), 7.36−7.29 (m, 3H), 7.27−7.21 (m, 3H), 7.20−7.14 (m, 2H), 6.97 (dd, J = 15.7, 7.4 Hz, 1H), 6.14 (dd, J = 15.7, 7.8 Hz, 1H), 3.63−3.54 (m, 1H), 2.63 (t, J = 7.8 Hz, 2H), 2.22 (q, J = 7.7 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.9, 160.7, 141.2, 141.1, 132.0, 129.0, 128.5, 128.4, 127.9, 127.3, 126.2, 48.1, 36.1, 33.4. HRMS calcd for $C_{18}H_{19}O$ $(M + H)^+$ 251.1430, found 251.1410. $[\alpha]^{22}_D$ +8.3 [c 0.90, $CHCl_3$]. Chiral HPLC resolution conditions: Chiralcel OJ (4.6 × 250 mm), 20% IPA/20% EtOH/60% hexanes, 1.0 mL/min, 220 nM, Rt = 6.4 and 8.3 min, ee = 98%.

(2*E*,4*S*)-4-(4-Methoxyphenyl)-6-phenylhex-2-enal (6h): The crude product was purified by flash chromatography on SiO_2 (Et_2O/Hex, 2:8) to afford the desired γ-substituted aldehyde **6h** (21 mg, 51% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.55 (d, J = 7.81 Hz, 1H), 7.36−7.28 (m, 3H), 7.23 (t, J = 7.3 Hz, 1H), 7.20−7.12 (m, 3H), 6.98−6.89 (m, 3H), 6.11 (dd, J = 15.6, 7.8 Hz, 1H), 3.85 (s, 3H), 3.54 (q, J = 7.4 Hz, 1H), 2.69−2.55 (m, 2H), 2.24−2.10 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.0, 161.1, 158.8, 141.3, 132.9, 131.7, 128.9, 128.5, 128.4, 126.1, 114.4, 55.3, 47.3, 36.1, 33.4. HRMS calcd for $C_{19}H_{21}O_2$ $(M + H)^+$ 281.1536, found 281.1531. $[\alpha]^{22}_D$ +5.7 [c 0.70, $CHCl_3$]. Chiral HPLC resolution conditions: Chiralcel OJ (4.6 × 250 mm), 20% IPA/20% EtOH/60% hexanes, 1.0 mL/min, 220 nM, Rt = 11.2 and 16.2 min, ee = 96%.

(2*E*,4*S*)-4-(4-Fluorophenyl)-6-phenylhex-2-enal (6i): The crude product was purified by flash chromatography on SiO_2 (Et_2O/Hex, 2:8) to yield the desired γ-substituted aldehyde **6i** (29 mg, 75% yield). ^{1}H NMR (400 HMz, $CDCl_3$) δ 9.61 (d, J = 7.8 Hz, 1H), 7.41−7.09 (m, 9H), 6.98 (dd, J = 15.9, 7.1 Hz, 1H), 6.15 (dd, J = 15.6, 7.8 Hz, 1H), 3.63 (q, J = 8.0 Hz, 1H), 2.69−2.63 (m, 2H), 2.30−2.17 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.8, 141.0, 132.0, 129.4, 129.3, 128.6, 128.4, 126.2, 116.2, 116.0, 115.8, 47.3, 36.1, 33.3. $[\alpha]^{22}_D$ 3.93 [c 0.535, $CHCl_3$]. Chiral HPLC resolution conditions: Chiralcel OJ (4.6 × 250 mm), 25% EtOH/75% hexanes, 1.0 mL/min, 220 nM, Rt = 11.3 and 16.0 min, ee = 92%.

(2*E*,4*R*,5*E*)-4-(2-Phenylethyl)hepta-2,5-dienal (6j): The crude product was purified by flash chromatography on SiO_2 (Et_2O/Hex, 2:8) to afford the desired γ-substituted aldehyde **6j** (7 mg, 43% yield). ^{1}HNMR (400 MHz, $CDCl_3$) δ 9.54 (d, J = 7.83 Hz, 1H), 7.37−7.26 (m, 2H), 7.27−7.17 (m, 3H), 6.75 (dd, J = 15.6, 7.0 Hz, 1H), 6.13 (dd, J = 15.6, 7.8 Hz, 1 H), 5.76−5.67 (m, 1 H), 5.35−5.26 (m, 1H), 3.41−3.32 (m, 1H), 2.80−2.56 (m, 2H), 1.98−1.73 (m, 2H), 1.63 (d, J = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.1, 160.2, 141.4, 131.6, 129.8, 128.5, 128.4, 127.2, 39.9, 36.0, 33.2, 29.7. $[\alpha]^{22}_D$ −31.4 [c 0.35, $CHCl_3$]. Chiral HPLC resolution conditions: Chiralcel OD (4.6 × 250 mm), 5% IPA/95% hexanes, 1.0 mL/min, 220 nM, Rt = 10.5 and 13.5 min, ee = 95%.

■ ASSOCIATED CONTENT

Supporting Information. Copies of ^{1}H and ^{13}C NMR spectra for all new compounds, all NMR data for the structural assignment of compound **5a**, and all chiral HPLC

chromatograms for compounds **6a**−**j**. This material is available free of charge via the Internet at http://pubs.acs.org.

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