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# Enantioselective Synthesis of α-Alkyl-β,γ-unsaturated Esters through Efficient Cu-Catalyzed Allylic Alkylations

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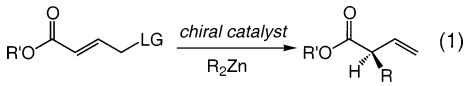
Catalytic methods for enantioselective synthesis of α-alkyl carbonyls, where C−C bond formation proceeds by alkylation of the derived enolate, have been the subject of several recent disclosures.[1] An alternative strategy would involve allylic alkylation of an α,β-unsaturated carbonyl that bears a leaving group at its γ site with a nucleophile (eq 1).[2] A catalytic enantioselective allylic substitution[3] may therefore be effected to access synthetically versatile α-alkyl-β,γ-unsaturated carbonyls in the optically enriched form.



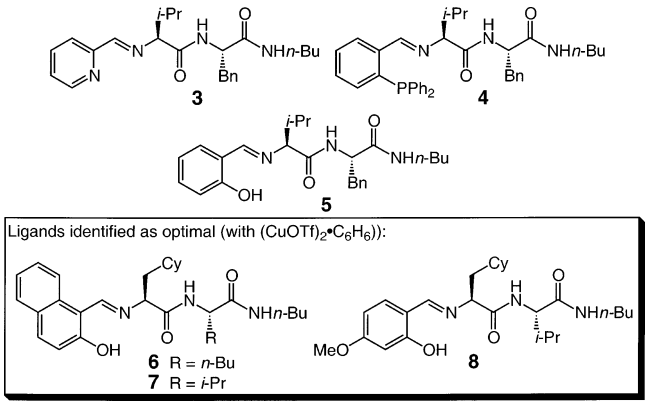
(1)

Herein we report an efficient Cu-catalyzed enantioselective method for allylic alkylations of unsaturated esters bearing a primary γ-phosphate with alkylzincs. Reactions deliver products in 87−97% ee and are effected by a peptidic Schiff base that can be recovered and reused. The utility of the method is illustrated in a total synthesis of topoisomerse II inhibitor (*R*)-elenic acid.[4]

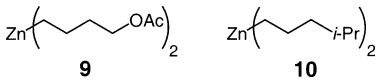
Catalytic additions of $Et_2Zn$ to **1a** (Table 1) were chosen as the representative reaction for our screening studies.[5] Selection of a phosphate was based on past findings regarding allylic substitutions involving such electrophiles with alkylzincs.[3b] We initially focused on reactions promoted by different Cu salts with phosphine and pyridyl ligands represented by **3** and **4** (Chart 1), because such systems have proven optimal in other Cu-catalyzed processes.[2d,3b,6] These investigations indicated that with CuCN and **3** or **4** (10 mol %, THF, −30 °C), (*S*)-**2a** is formed with >98% regioselectivity in ∼25% ee; enantioselectivity slightly improved to ∼35% ee with $(CuOTf)_2{\cdot}C_6H_6$ and **4**, but the regioselectivity was lower (4:1; >98% conv in all cases). Whereas solvent screening led to little improvement in alkylations with CuCN, in toluene the $(CuOTf)_2{\cdot}C_6H_6$/**4** combination delivered (*S*)-**2a** in 90% ee but without regioselectivity. To identify more desirable conditions, the activities of various other Schiff base ligands (such as **5**) and their derived amines and amides were also screened (∼20 ligands examined). These studies indicated that (*R*)-**2a** is formed in 68% ee and 5:1 regioselection with 10 mol % **5** and 5 mol % $(CuOTf)_2{\cdot}C_6H_6$ (toluene, −30 °C). We then determined that in THF the desired regioisomer is generated with >20:1 selectivity. Subsequent screening (∼100 ligands) indicated that Schiff bases **6**−**8** provide the highest efficiency, regio-, and enantioselectivity. As shown in entry 1 of Table 1, reaction of **1a** with $Et_2Zn$ is promoted by **6** to proceed in 95% ee, 17:1 regioselectivity, and in 93% yield.

As illustrated in Table 1, various alkylzincs react with unsaturated esters to afford the desired products with high enantioselectivity.[7] The following points merit mention: (1) Lower catalyst loadings (1 mol %) deliver similarly high levels of selectivity (entries 4 and 8). (2) Although results with ligands **7** and **8** are shown in entries 4 and 5, selectivities observed with **6** are not substantially lower (within 5% ee). (3) Chiral ligands are recyclable; for example, **6**

***Chart 1***

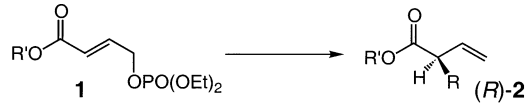



was isolated in >98% yield after the reaction in entry 7 and reused to deliver equally high reactivity and selectivity. (4) Whereas reactions with **1e** uniformly afford a single regioisomer, with smaller carboxylic esters, selectivity suffers when sterically demanding alkylzincs **9** and **10** are employed. (5) Commercially available




$(CuOTf)_2{\cdot}PhMe$ (Aldrich) can be used; as an example, (*R*)-**2f** is formed with the same regioselectivity but in 84% ee and 70% yield (under otherwise identical conditions as in Table 1).[8]

***Table 1.*** Enantioselective Cu-Catalyzed Allylic Substitutions[a]



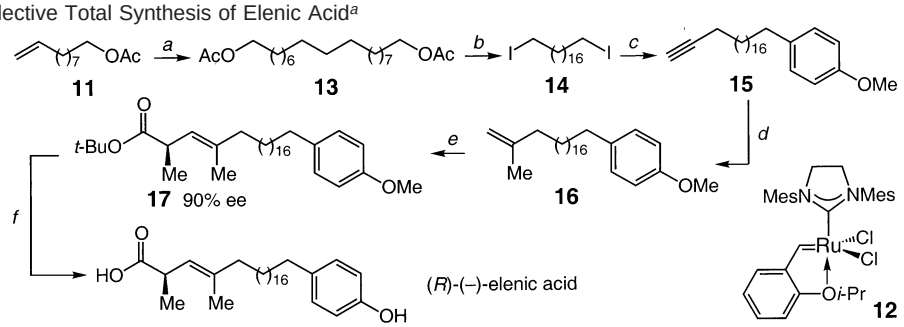

| entry | R′ | | alkylzinc | ligand (mol %) | product | yield[b] (%) | $S_N2':S_N2$[c] | ee[d] (%) |
|---|---|---|---|---|---|---|---|---|
| 1 | Me | **1a** | $Et_2Zn$ | **6**, 10 | **2a** | 93 | 17:1 | 95 |
| 2 | Me | **1a** | **9** | **6**, 10 | **2b** | 72 | 8:1 | 92 |
| 3 | Me | **1a** | **10** | **6**, 10 | **2c** | 64 | 7:1 | 87 |
| 4 | *n*-Bu | **1b** | $Et_2Zn$ | **7**, 1 | **2d** | 83 | 20:1 | 94 |
| 5 | allyl | **1c** | $Et_2Zn$ | **8**, 10 | **2e** | 47 | 13:1 | 93 |
| 6 | allyl | **1c** | **9** | **6**, 10 | **2f** | 86 | 8:1 | 94 |
| 7 | *i*-Pr | **1d** | $Et_2Zn$ | **6**, 10 | **2g** | 79 | 17:1 | 94 |
| 8 | *i*-Pr | **1d** | $Et_2Zn$ | **6**, 1 | **2g** | 72 | >20:1 | 97 |
| 9 | *t*-Bu | **1e** | $Me_2Zn$[e] | **6**, 10 | **2h** | 80 | >20:1 | 90 |
| 10 | *t*-Bu | **1e** | $Et_2Zn$ | **6**, 10 | **2i** | 68 | >20:1 | 97 |
| 11 | *t*-Bu | **1e** | **9** | **6**, 10 | **2j** | 85 | >20:1 | 95 |
| 12 | *t*-Bu | **1e** | **10** | **6**, 10 | **2k** | 75 | >20:1 | 90 |

[a] Conditions: $(CuOTf)_2{\cdot}C_6H_6$ equivalent to one-half the indicated ligand amount, 3 equiv of alkylzinc, THF, −50 °C (entries 3, 9, and 12 were carried out at −30 °C), 12 h, $N_2$ atm. [b] Isolated yields. [c] Determined by GLC (entries 1, 4−5, 7−8) or 400 MHz $^1H$ NMR. [d] Determined by GLC (CDGTA column for entry 1, β-DEX column for others); except for entries 1 and 9, analyses were performed on derived alcohols. [e] Six equivalents of $Me_2Zn$ was used with a reaction time of 48 h.



10.1021/ja0300618 CCC: $25.00 

***Scheme 1.*** Enantioselective Total Synthesis of Elenic Acid[a]




[a] (a) 5 mol % **12**, $Cl(CH_2)_2Cl$, 2 h, then $H_2$ (200 psi); 92%. (b) (1) $K_2CO_3$, MeOH, $CH_2Cl_2$; 80%. (2) $I_2$, $PPh_3$, imid., $Et_2O$, MeCN; 98%. (c) (1) *p*-$OMeC_6H_4MgBr$, 10 mol % CuI, THF, 4 °C; 49%. (2) LiCCH·EDA, DMSO, THF; 79%. (d) $Cp_2ZrCl_2$, $Me_3Al$, $CH_2Cl_2$, 66%. (e) 1 equiv of **2h** (90% ee), 2 equiv of **16**, 35 mol % **12**, THF, 40 °C, 24 h, 3:1 *E*:*Z*; 40%. (f) $BBr_3$, $CH_2Cl_2$, −78 to 22 °C; 85%.

The Cu-catalyzed asymmetric alkylation has been used in a convergent total synthesis of (*R*)-(−)-elenic acid (Scheme 1). One-pot catalytic homodimerization/hydrogenation[9] of **11** with 5 mol % **12** (Aldrich)[10] delivers **13** in 92% yield. Conversion to diiodide **14** and subsequent alkylations afford alkyne **15**, which is converted to **16** by Zr-mediated alkylalumination.[11] Cross-metathesis between **16** and optically enriched **2h**, obtained from enantioselective alkylation of **1e** with $Me_2Zn$ (entry 9, Table 1), proceeds in the presence of 35 mol % **12** to afford **17** in 40% yield (80% based on recovered **16**) and 3−4:1 *E*:*Z* selectivity.[12] Model studies involving cross-metathesis of **2h** and 2-methyl-1-hexene indicate that <5% erosion of enantiopurity occurs when **12** is used; reactions with Grubbs' catalyst[13] under identical conditions lead to 10% diminution in ee. Treatment of **17** with $BBr_3$ delivers (*R*)-elenic acid.[14]

Studies toward the development of other catalytic asymmetric allylic alkylations are in progress.

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**Supporting Information Available:** Experimental procedures and spectral and analytical data for reaction products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) Isolated yields are at times moderate due to product volatility.

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