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COMMUNICATIONS

Published on Web 01/12/2002

# Cu-Catalyzed Asymmetric Conjugate Additions of Alkylzinc Reagents to Acyclic Aliphatic Enones

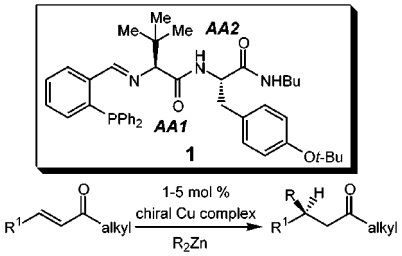
Hirotake Mizutani, Sylvia J. Degrado, and Amir H. Hoveyda*

*Department of Chemistry, Merkert Chemistry Center, Boston College, Chestnut Hill, Massachusetts 02467*

Received October 3, 2001

We recently reported Cu-catalyzed asymmetric conjugate additions of alkylzincs to cyclic enones, where peptidic phosphines serve as chiral ligands to deliver the desired products in high yields and enantioselectivities.[1] A noteworthy aspect of the latter study is that it offers a solution to the problem of asymmetric conjugate additions to unfunctionalized cyclopentenones (up to >98% ee),[2] a class of substrates that typically undergoes reactions with lower efficiency and asymmetric induction than their larger ring analogues.[3] Despite significant progress made in the area of Cu-catalyzed conjugate additions to cyclic enones, extension of such protocols to include highly enantioselective reactions of *aliphatic acyclic* enones has proved to be far from routine.[4−6] Promising data have been reported in certain cases; however, $Et_2Zn$ is nearly always the alkylating agent probed, the majority of studies has involved aromatic enones, and selectivities are rarely >90% ee when aliphatic substrates are used.[4g,k] Herein we report the results of our investigations regarding the development of highly efficient and enantioselective catalytic conjugate additions of acyclic aliphatic $\alpha,\beta$-unsaturated ketones. These processes are readily extended to a variety of alkylzinc reagents and are promoted by Cu complexes of chiral dipeptide phosphine **1** (Scheme 1).

***Scheme 1***




Brief preliminary catalyst screening, involving methyl ketone **2** and $Et_2Zn$ (entry 1, Table 1), indicated that phosphine **1** consistently provides high reactivity and enantioselectivity. Thus, as shown in entry 1 of Table 1, treatment of unsaturated methyl ketone **2** with 1 mol % $(CuOTf)_2 \cdot C_6H_6$, 2.4 mol % **1**, and 3 equiv of $Et_2Zn$ at −20 °C (toluene, 3 h) leads to formation of chiral ketone **3**[7] in 93% ee and 90% yield after silica gel chromatography.[8] As the data in entries 2−4 of Table 1 illustrate, altering the electronic character of the $\beta$-aryl substituent does not affect reaction efficiency or asymmetric induction; ketones **5**, **7**, and **9** are isolated in >70% yields and in 94%, 92%, and 90% ee, respectively. Catalytic asymmetric conjugate addition to the fully aliphatic enone **10** (entry 5) affords **11** in 95% ee and 85% yield within 1 h at 22 °C.[7] High enantioselectivity is observed in the formation of **13** (entry 6), despite the small $\beta$-Me substituent in **12**. The reaction of the sterically hindered *i*-Pr ketone **14** (entry 7) occurs smoothly within an hour at 22 °C, yielding **15** in 90% ee (75% yield). When the derived *t*-Bu ketone **16** is employed (entry 8), the rate of reaction suffers significantly (69% conversion after 36 h), and **17** is obtained with diminished enantiopurity (58% ee).[9] The process depicted in entry 9 of Table 1 illustrates that efficient and highly enantioselective catalytic additions can be carried out in the presence of a bulky substituent at the $\beta$ carbon of the enone. The functional group tolerance of the catalytic method is illustrated in the reaction of acylated enone **20**, yielding chiral **21** in 88% yield and 89% ee (entry 10).

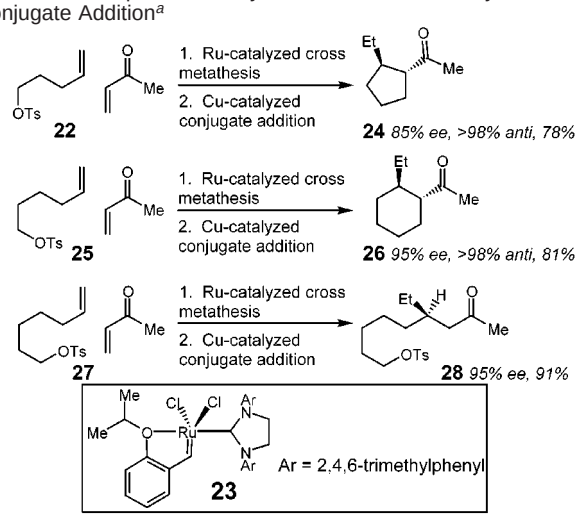
Many of the requisite substrates can be readily accessed through Ru-catalyzed olefin cross metathesis, and the purported Zn-enolate intermediate can be employed for additional functionalization. As illustrated in Scheme 2, reaction of tosylate **22** with methylvinyl ketone ($CH_2Cl_2$, 22 °C) in the presence of 2.5 mol % recyclable Ru catalyst **23**[10] affords the corresponding unsaturated tosyl-enone (>96% trans) which is then treated with 5 mol % **1** and 1 mol % $(CuOTf)_2 \cdot C_6H_6$ to give cyclopentyl ketone **24** in 85% ee, >98% diastereoselectivity, and 78% overall isolated yield (1 h, 22 °C).[11]

***Table 1.*** Cu-Catalyzed Enantioselective Conjugate Addition of $Et_2Zn$ to Aliphatic Acyclic Enones[a]

| entry | substrate | product | time (h); temp (°C) | yield (%)[b] | ee (%);[c] config[d] |
|---|---|---|---|---|---|
| 1 | R = Ph **2** | **3** | 3; –20 | 90 | 93; *S* (+) |
| 2 | R = *p*-OMePh **4** | **5** | 3; –20 | 93 | 94; (+) |
| 3 | R = *p*-$NO_2$Ph **6** | **7** | 3; –20 | 72 | 92; (+) |
| 4 | R = *p*-$CF_3$Ph **8** | **9** | 3; –20 | 87 | 90; (+) |
| 5 | *n*-pent, Me **10** | *n*-pent, Et, H **11** | 1; +22 | 85 | 95; *R* (+) |
| 6 | Me, *n*-hex **12** | Me, Et, H, *n*-hex **13** | 1; +22 | 87 | 90; (+) |
| 7 | *n*-pent, *i*-Pr **14** | *n*-pent, Et, H, *i*-Pr **15** | 1; +22 | 75 | 90; (+) |
| 8 | *n*-pent, *t*-Bu **16** | *n*-pent, Et, H, *t*-Bu **17** | 24; +22 | 42 | 58; (+) |
| 9 | *i*-Pr, Me **18** | *i*-Pr, Et, H, Me **19** | 1; +22 | 69 | 91; (+) |
| 10 | OAc, Me **20** | OAc, Et, H, Me **21** | 1; +22 | 88 | 89; (+) |

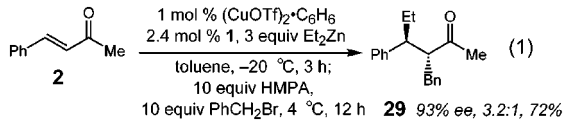
[a] Conditions: 1 mol % $(CuOTf)_2 \cdot C_6H_6$, 2.4 mol % **1**, 3 equiv of $Et_2Zn$, toluene; 5 mol % **1** for entries 6 and 10. [b] Isolated yields after chromatography; all conversion >98% except for entry 8 (GLC). [c] Selectivities determined by chiral GLC ($\gamma$-DEX entry 1; CDGTA entries 3−6, 9; $\beta$-DEX entries 7−8, 10) or HPLC (chiralcel OJ, entry 2). [d] Sign of optical rotation.

***Scheme 2.*** Sequential Catalytic Cross Metathesis/Asymmetric Conjugate Addition[a]

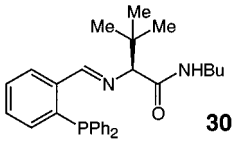



[a] Conditions: (1) 2.5 mol % **23**, $CH_2Cl_2$; (2) 5 mol % **1**, 1 mol % $(CuOTf)_2 \cdot C_6H_6$, 3 equiv of $Et_2Zn$, toluene, 22 °C, 1 h; >98% conversion; isolated overall yields; ee's by chiral GLC or HPLC (Supporting Information).

A similar protocol leads to the formation of cyclohexyl ketone **26** (95% ee, >98% anti, 81% yield). Repeated attempts to prepare the corresponding seven-membered ring product from reaction of tosylate **27** resulted in the formation of conjugate addition product **28** in 95% ee and 91% overall yield after chromatography. As the example in eq 1 demonstrates, (**2** → **29**), enolate alkylation may be effected intermolecularly as well.[12]

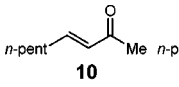
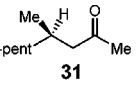
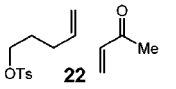
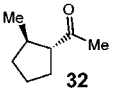
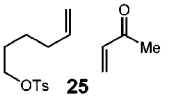
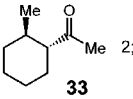
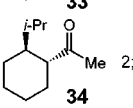



Several points regarding the data in Table 1 and Scheme 2 are noteworthy: (1) The identity of the peptide moiety of the chiral ligand is critical to enantioselectivity. For example, when the chiral ligand related to **1**, but with AA1 = L-Val and AA2 = L-Phe, is used in catalytic alkylations of **2** and **20** (entries 1 and 10, Table 1), ketones **3** and **21** are obtained in 89% ee and 5% ee (70% and 88% yields, respectively). (2) The AA2 moiety must be present to ensure high asymmetric induction. Catalytic addition of $Et_2Zn$ to **10** in the presence of 2.4 mol % **30** proceeds to completion within




1 h, but affords **11** in only 59% ee (vs 95% ee with **1**). (3) In most reactions examined, optimal selectivities are conveniently attained at ambient temperature.[13] Only reactions in entries 1−4 of Table 1 proceed with lower levels of enantioselectivity at 22 °C (e.g., **3** is obtained in 78% ee) and produce notable amounts of unidentified byproducts. (4) A comparison of the levels of enantioselectivity in reactions of enones **20** (entry 10, Table 1) and those described in Scheme 2 suggests the presence of Lewis basic functionalities within a certain distance of the reactive enone group can lead to lowering of asymmetric induction. It is plausible that, as suggested by extensive mechanistic data related to other processes promoted by this class of chiral ligands, the peptidic Schiff base−metal complex

***Table 2.*** Cu-Catalyzed Enantioselective Conjugate Addition of Various Alkylzinc Reagents to Aliphatic Acyclic Enones[a]

| entry | substrate | product | time (h); temp (°C) | conv (%); yield (%)[b] | ee (%);[c] config[d] |
|---|---|---|---|---|---|
| 1 |  10 |  31 | 2; +22 | 90; 71 | 94; *R* (+)[e] |
| 2 |  22 |  32 | 2; 0 then 12; +22 | >98; 67 | 80; (–)[f] |
| 3 |  25 |  33 | 2; +22 then 12; +50 | >98; 75 | 95; (–)[f] |
| 4 | |  34 | 2; +22 then 12; +50 | >98; 82 | 74; (–)[f] |

[a] Conditions: see Scheme 2. [b] Isolated yields after chromatography; all conversion >98% (by GLC and TLC). [c] Enantioselectivities determined by chiral GLC ($\gamma$-DEX for entry 1, CDGTA for entries 2−4). [d] Sign of optical rotation. [e] See Supporting Information for proof of absolute stereochemistry. [f] >98% trans diastereoselectivity (by GLC).

serves as a bifunctional catalyst.[14] It may be suggested that the resident acetate or sulfonate sites can disrupt the delivery of the alkylmetal by the peptide moiety of the chiral ligand; the importance of the AA2 unit to enantioselectivity is consistent with this proposal. Detailed studies to clarify these and other issues are in progress.

The Cu-catalyzed alkylations presented here are not limited to additions of $Et_2Zn$; representative data are shown in Table 2. The relatively less reactive $Me_2Zn$ and $(i\text{-Pr})_2Zn$ can be employed in these asymmetric conjugate additions efficiently and with appreciable asymmetric induction. As illustrated in entries 3 and 4 (Table 2), in situ intramolecular alkylations deliver optically enriched functionalized carbocycles (>98% trans diastereoselectivity). Similar to transformations with $Et_2Zn$, reactions of $Me_2Zn$ typically provide higher levels of enantioselectivity than the sterically bulky $(i\text{-Pr})_2Zn$.

To the best of our knowledge, this study outlines the most general, efficient, and enantioselective catalytic protocol for effecting catalytic asymmetric conjugate additions of alkylmetals to acyclic aliphatic enones. The ease of preparation of the chiral catalysts and substrates, the functional group compatibility of the requisite alkylmetals, the possibility of using alkylzincs other than $Et_2Zn$, together with the efficiency and high levels of asymmetric induction, should render the present approach of notable utility in asymmetric organic synthesis. Design and development of additional catalytic asymmetric conjugate additions promoted by various peptide-based ligands are in progress and will be reported shortly.[15]

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

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(7) For proof of the identity of major product enantiomer, see the Supporting Information.

(8) The order of addition can be critical to obtaining optimal levels of enantioselectivity (treatment of a solution of Cu salt and ligand with dialkylzinc before addition of substrate leads to slightly higher yields and enantioselectivities).

(9) When the peptidic Schiff base corresponding to **1** but with L-Val and L-Phe as AA1 and AA2 is used (2 mol % Cu salt and 4.8 mol % ligand), **17** is obtained in 70% ee and 42% isolated yield.

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(12) In the absence of HMPA, the yield of alkylation products is <20%.

(13) With the majority of reactions studied (other than entries 1−4, Table 1), higher enantioselectivities and yields are obtained at 22 °C (vs 0 or 40 °C). For example, in reaction of **12** with $Et_2Zn$, 82% ee and 81% yield are observed at 0 °C and 85% ee and 65% yield at +40 °C (see entry 6, Table 1 for comparison).

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(15) This research was supported by grants from the NIH (GM-47480 and GM-57212).

JA0122849