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Cu−Catalyzed Enantioselective Conjugate Addition of Alkylzincs to Cyclic Nitroalkenes: Catalytic Asymmetric Synthesis of Cyclic α-Substituted Ketones

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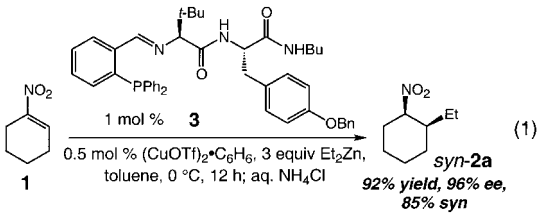
We have reported that amino acid-based chiral ligands, in the presence of Cu(I) salts and alkylzinc reagents, promote efficient and highly enantioselective conjugate additions[1] and allylic substitutions.[2] The conjugate addition protocols are of particular note because of their effectiveness with cyclopentenyl and aliphatic acyclic substrates, systems that had previously proved problematic.[3] A related class of transformations, for which an effective method has not been reported, is the catalytic enantioselective additions of alkylmetals to nitroolefins. Such catalytic processes are valuable, since (depending on the workup conditions) nitronates may be converted to synthetically versatile compounds (e.g., nonracemic α-substituted ketones). Others have examined catalytic asymmetric conjugate additions involving nitroalkenes. One reported variant is the catalytic process of Hayashi,[4] where arylboronic acids are used with high reactivity and selectivity; the related *alkyl* addition products, however, cannot be obtained by the Rh-catalyzed procedure. Various other disclosures involve catalytic additions of alkylzincs to α,*β*-unsaturated nitroalkenes;[5] these reactions mostly involve acyclic substrates, are largely limited to additions of Et_2Zn, and afford products in low selectivities. Herein, we report an efficient method for catalytic asymmetric addition of alkylzincs to small-, medium-, and large-ring nitroolefins, promoted by readily available amino acid-based chiral phosphines.[6] Selectivities are typically >90% ee, and the derived ketones can be readily obtained.

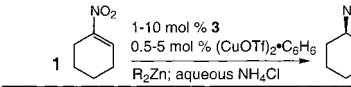
With commercially available Et_2Zn and **1**, screening studies indicated that reactions with phosphine **3** and $(CuOTf)_2{\cdot}C_6H_6$ in toluene at 0 °C are optimal. We established that, as depicted in eq 1, treatment of **1** with Et_2Zn, 1 mol % **3** and 0.5 mol % $(CuOTf)_2{\cdot}C_6H_6$ delivers **2a** in 96% ee and 92% yield (>98% conv, 12 h, 0 °C; 85% syn).[7]

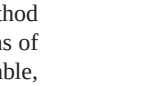


(1)

Additional results are summarized in Table 1. As these data indicate, the Cu-catalyzed processes are not limited to reactions with Et_2Zn: **2b**−**d** are synthesized efficiently and with high enantioselectivity (>98% conv, ≥93% ee). Several points regarding catalytic asymmetric reactions of **1** are noteworthy: (1) Catalytic reactions proceed to >98% conv but are less selective in alternative solvents (e.g., CH_2Cl_2, THF, Et_2O). (2) Enantioselectivities remain unchanged or decrease when the reaction temperature is below 0 °C.

Table 1. Asymmetric Conjugate Addition of Alkylzincs to **1**[a]



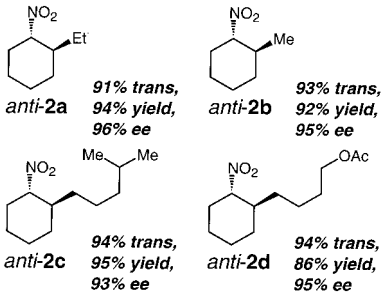
entry	alkylzinc reagent		3, Cu salt (mol %)	conv (%);[b] yield (%)[c]	syn:anti[d]	ee (%)[e]
1	Me_2Zn	**b**	10, 5	>98; 72	83:17	95
2		**c**	1, 0.5	>98; 89	83:17	93
3		**d**	10, 5	>98; 76	81:19	95

[a] Conditions: toluene, 0 °C, 12 h, N_2 atm (24 h for entry 3). [b] Determined by analysis of the 400 MHz ^{1}H NMR spectrum of unpurified reaction mixtures. [c] Isolated yields after chromatography. [d] Determined by GLC and analysis of 400 MHz ^{1}H NMR spectra. [e] Determined by chiral GLC analysis (Chiraldex GTA column).

(3) Use of excess chiral ligand (vs Cu(I) salt) does not lead to enhancement in rate or ee. (4) The less reactive Me_2Zn (entry 1) and carbonyl-containing alkylzinc **5** (entry 3) require higher catalyst loadings and longer reaction times than the more reactive (4-methylpentyl)$_2$Zn **4** in entry 2 (10 mol % vs 1 mol % **3** for >98% conv in 12 h).

In all the reactions involving **1**, the syn product is formed as the major diastereomer (eq 1 and Table 1).[8] However, as the data depicted in Scheme 1 illustrate, treatment of syn chiral nitroalkanes **2a**−**d** with 1 equiv of DBU (22 °C, 12 h) leads to the efficient formation of the corresponding trans isomers without a lowering of enantiomeric excess. The present protocol thus allows access to both *syn*- and *anti*-nitrocyclohexane diastereomers in high yield and enantiopurity.

Scheme 1. Synthesis of Anti Products upon Treatment with DBU[a]



[a] Conditions: 1 equiv DBU, Et_2O, 22 °C, 12 h; yields are of isolated materials after chromatography.

The Cu-catalyzed asymmetric conjugate addition can be performed with the smaller five-membered ring nitroalkenes with high enantioselectivity. As the example in eq 2 illustrates, addition to **6** proceeds to afford **7** in 93% ee and 61% yield (>98% conv). In

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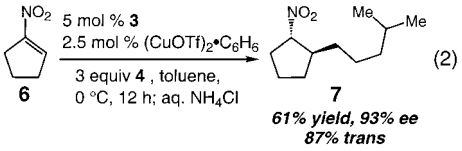
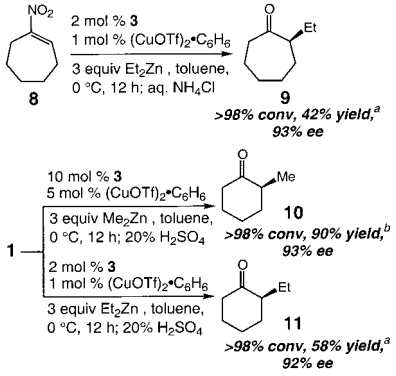
contrast to reactions of **1**, however, anti-**7** is formed as the predominant isomer.[9]



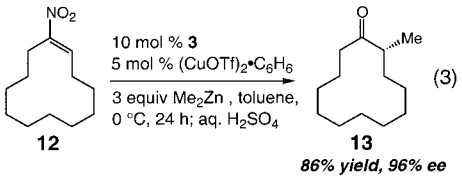
The catalytic asymmetric process can be effected on medium-ring electrophiles. A representative example, involving the seven-membered nitroalkene **8**, is depicted in Scheme 2. The reaction proceeds as smoothly as the cases involving substrates **1** and **6**. However, unlike the smaller-ring systems, the same workup procedure (aqueous NH_4Cl) leads to the exclusive formation of the *ketone* product in 93% ee and 42% isolated yield (>98% conv; low yield partly due to volatility). As the reactions in Scheme 2 further illustrate (**1**→**10** and **11**), a similar Nef reaction can be carried out in situ with six-membered ring conjugate addition products, without significant loss of optical purity, but only when workup is changed to the addition of a 20% aqueous solution of H_2SO_4.[10]

Scheme 2. Catalytic Enantioselective Synthesis of Cyclic Ketones

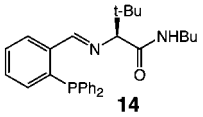


[a] Isolated yield (volatile product). [b] GLC yield (volatile products; decane used as standard).

Macrocyclic nitroalkenes readily undergo Cu-catalyzed asymmetric conjugate addition in the presence of phosphine **3**. As shown in eq 3, treatment of 12-membered ring **12** (>20:1 *E*:*Z*) with 10 mol % of the chiral Cu complex and 3 equiv of Me_2Zn, followed by treatment with 10% H_2SO_4 for 1 h leads to the formation of ketone **13** in 96% ee and 86% yield.



A final note regarding the identity of the chiral ligand should be mentioned. Although our studies clearly indicate that bis(amino acid) ligand **3** is the optimal choice for all the above substrates, in certain—but not all—cases the more easily accessible ligand **14** can be sufficient. As an example, addition of Me_2Zn to **1** is promoted by **14** (identical conditions to those in Table 1) to afford **2b** in 96% ee and 75% isolated yield (82% syn). However, in contrast to ligand **3**, the corresponding addition to **12** proceeds only to ≤25% conversion when **14** is employed (after 24 h; 82% ee). Studies aimed at delineation of factors that determine the identity of the optimal catalysts in this class of asymmetric transformations are in progress.



Development of additional catalytic asymmetric C−C bond forming reactions promoted by amino acid-based ligands and their application to enantioselective synthesis is also underway.

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

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(7) Absolute stereochemistry of products is based on optical rotations obtained from ketones **9**, **10**, **11**, and **13** in comparison with the reported values (see the Supporting Information for details).

(8) The corresponding anti isomers are obtained with similar levels of enantioselectivity. For a plausible rationale for the predominant formation of the syn isomer, see ref 4 and references therein.

(9) A similar trend was observed in the study by Hayashi and co-workers (see ref 4).

(10) Control experiments indicate that the reduction in product enantiopurity is due to adventitious isomerization upon in situ Nef reaction.

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