Highly Enantioselective Conjugate Addition of Dialkylzinc Reagents to Acyclic Nitroalkenes: A Catalytic Route to β^2-Amino Acids, Aldehydes, and Alcohols

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In recent years, considerable effort has been devoted to catalytic asymmetric conjugate additions of dialkylzinc reagents to nitroalkenes.[1] Significant progress has been made using Cu(I) catalysts with phosphorus-based chiral ligands, cumulating enantioselectivities up to 96% for cyclic nitroalkenes as reported by Hoveyda.[2] Acyclic nitroalkenes, however, constitute a challenging class of substrates, because of the much lower selectivities obtained so far. Furthermore, almost exclusively, Et$_2$Zn as an organometallic reagent has been used.[1] Methodologies that provide high enantioselectivities in this 1,4-addition are highly warranted because the produced nitroalkanes have a wide range of applications.[3] This is due to the versatility of the nitro group, sometimes entitled a "chemical chameleon",[4] that can be transformed into a range of other functional groups including amine, aldehyde, or acid moieties.[5] We envisioned that enantioselective 1,4-addition to acetal substituted nitroalkenes[6] could provide an attractive route to β^2-amino acids and derivatives, which are important building blocks in the synthesis of natural products, β-peptides, and pharmaceuticals (Scheme 1).[7]

We wish to report here that by using phosphoramidite ligand **L1**, developed in our laboratory,[8] for the first time, enantioselectivities up to the 98% level for acyclic nitroalkenes are obtained. Furthermore, the use of acyclic substrates with different alkylzinc reagents provides a catalytic enantioselective route to (functionalized) β^2-amino aldehydes, acids, and alcohols.

Encouraged by the results obtained with our one-pot multisubstrate screening procedure for copper-phosphoramidite catalysts,[1e] various acetal substituted nitropropenes were examined. The synthesis is based on a transacetalization of dimethoxynitropropene (**1a**), prepared via a Henry reaction on multigram scale starting with commercially available dimethoxyacetaldehyde (Scheme 2). Nitroalkenes **1b** and **1c** were obtained in good yield; the (nonoptimized) low yield for **1d** can be explained by the low solubility of the diol under the reaction conditions. In preliminary experiments, we screened four different copper-phosphoramidite catalysts, based on ligands **L1**−**L4**, with respect to their ability to induce enantioselectivity in the 1,4-addition reaction of diethylzinc with nitropropene acetals **1a**−**d** (Table 1).

As can be seen from entries 1−3 in Table 1, bulky chiral substituents at the amine moiety of the ligand are necessary to reach high ee, and comparison of entries 1,4, 5,6, and 7,8 shows that **L1**, with (S)-BINOL as the diol part, gives in all cases better results than bisphenol-based ligand **L4**.[9] It is also found that **L1** is able to generate high ee values (>90%) for nitroalkanes with acetals based on methanol (**2a**) and 2,2-dimethylpropanol (**2c**). The use of acetals based on pinacol (**2b**) and 2,2-diphenylpropanol (**2d**), the latter being very successful in the conjugate addition to cyclopentene-3,5-dione,[10] leads to lower selectivities (<90%). Under optimized reaction conditions, that is, at −55 °C, and slower addition of the dialkylzinc reagent (over 1 min), nitropropene acetals **1a** and **1c**

Scheme 1. Proposed Route to β^2-Amino Acids and Derivatives
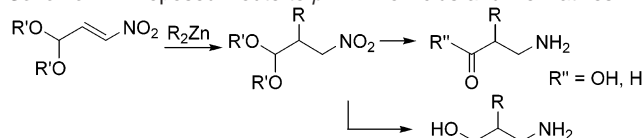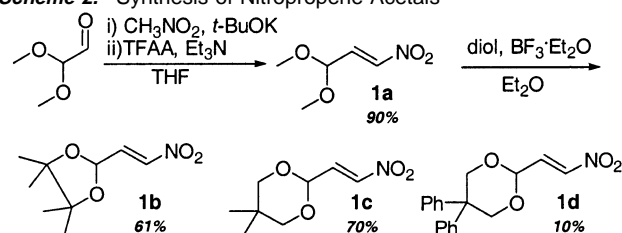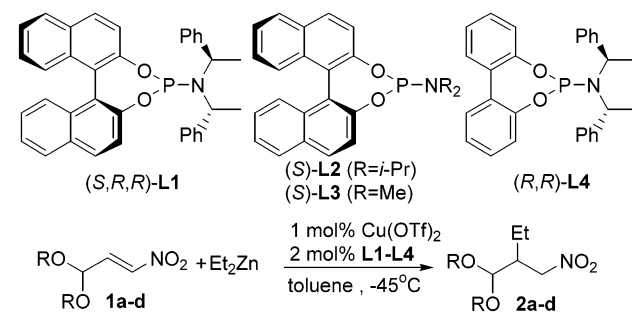

Scheme 2. Synthesis of Nitropropene Acetals

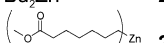**Table 1.** Diethylzinc Additions to Nitropropene Acetals[a]

entry	substrate	ligand	product	yield (%)[b]	ee (%)[d]
1	**1a**	**L1**	**2a**	28[c]	93
2	**1a**	**L2**	**2a**	32[c]	14
3	**1a**	**L3**	**2a**	25[c]	4
4	**1a**	**L4**	**2a**	27[c]	87
5	**1b**	**L1**	**2b**	72	91
6	**1b**	**L4**	**2b**	70	76
7	**1c**	**L1**	**2c**	79	92
8	**1c**	**L4**	**2c**	74	79
9	**1d**	**L1**	**2d**	72	84[e]

[a] Conditions: 1.0 mmol of **1a**−**d**, 1.2 equiv of Et$_2$Zn in 2 mL of toluene; all reactions went to completion in 3 h. [b] Isolated yield. [c] Nonoptimized conditions; see Table 2 for optimized yield. [d] Determined by chiral GC. [e] Determined by chiral HPLC.

were reacted with various alkylzinc reagents using 1 mol % of the copper-phosphoramidite catalyst based on ligand **L1** (Table 2).

Under these optimized conditions, the readily accessible nitropropene acetal **1a** proved to be the most suitable substrate resulting in very high enantioselectivities with simple aliphatic dialkylzinc reagents (entries 1,3,5). A functionalized zinc reagent can also be used, albeit with slightly lower selectivity (entry 6). We were

Table 2. Conjugate Addition of Dialkylzinc Reagents to **1a** and **1c**[a]
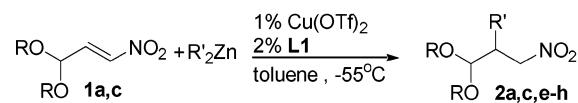
entry	substrate	dialkylzinc	product	yield (%)[b]	e.e. (%)[c]
1	**1a**	Et$_2$Zn	**2a**	78	96
2	**1c**	Et$_2$Zn	**2c**	78	92
3	**1a**	Me$_2$Zn	**2e**	86	98
4	**1c**	Me$_2$Zn	**2f**	58	96
5	**1a**	Bu$_2$Zn	**2g**	75	95
6	**1a**		**2h**	74	88

[a] Conditions: 1.0 mmol of **1a,1c**, 1.2 equiv of R$_2$Zn in 2 mL of toluene; all reactions went to completion (18 h for entries 3,4; 3 h for all others). [b] Isolated yield. [c] Determined by chiral GC.

Scheme 3. Synthesis of β^2-Amino Acid, Aldehyde, and Alcohol[a]
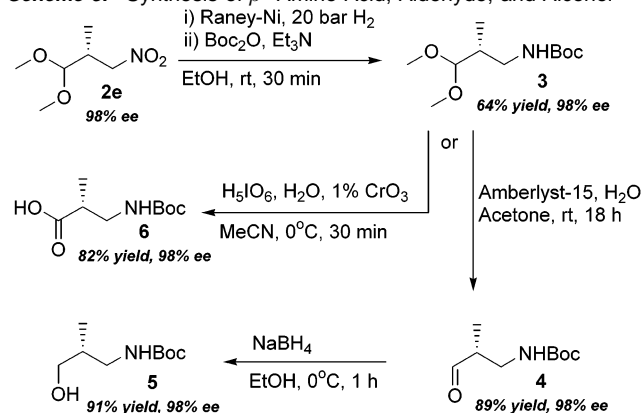
[a] See Supporting Information.

delighted to isolate the Me$_2$Zn 1,4-addition product (*R*)-**2e**[11] with the excellent ee of 98%, as it contains a stereogenic center bearing a methyl substituent, which is a prominent feature in many natural products.[12] A major advantage of this asymmetric synthesis is that the obtained nitroalkanes can be easily converted into (protected) β^2-amino aldehydes, alcohols, and acids (Scheme 3). Raney-nickel-catalyzed reduction of nitroalkane **2e**, followed by Boc-protection, gives amino-acetal **3** which was deprotected to give β^2-amino-aldehyde **4**, a building block used in the total synthesis of cyclamenol A.[13a] Because of the intermediate oxidation state of amino-acetal **3**, oxidation under acidic conditions (H$_5$IO$_6$, 1% CrO$_3$) gives in a single step the corresponding N-Boc-protected β^2-amino acid **6**, used in the total synthesis of cryptophycins.[14]

The corresponding free amino acid has been isolated from human urine and *Iris tingitana*.[15] Furthermore, β-amino-alcohol **5**, a starting material in the synthesis of β-methyl carbapenem antibiotics,[16] was obtained by reduction of aldehyde **4**. Independent ee determinations of **3**−**6** confirmed that no racemization had occurred and all products were isolated with 98% ee.

To the best of our knowledge, this is the first example of a catalytic enantioselective route to these versatile building blocks and an important addition to existing routes, which make use of the chiral pool,[17] (enzymatic) resolution,[18] or chiral auxiliaries.[11]

The practicality of this new catalytic route is demonstrated by (i) the synthesis of **2e** on gram scale by starting with 10 mmol of **1a**, resulting in yields ranging from 86 to 91%,[19] and (ii) the few efficient steps that are needed to obtain the corresponding β^2-amino compounds (Scheme 3), in particular, the aldehydes which are usually obtained via consecutive reduction and oxidation of the acids.[14] Together with the rhodium-catalyzed asymmetric hydrogenation of β-dehydroamino acids using phosphoramidite ligands reported recently by our group,[20] both kinds of β-amino acids (β^2- and β^3-substituted) can be obtained using the same class of monodentate phosphoramidite ligands.

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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JA029817D