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Enantioselective Synthesis of Nitroalkanes Bearing All-Carbon Quaternary Stereogenic Centers through Cu-Catalyzed Asymmetric Conjugate Additions

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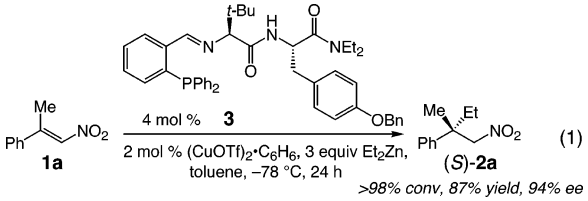
Discovery of methods for catalytic asymmetric conjugate additions (ACA) involving carbon nucleophiles is an important objective in chemical synthesis.[1] Nitroalkenes represent a notable class of substrates for catalytic ACA, since the resulting nitroalkanes can be converted to synthetically useful N- and O-containing optically enriched organic molecules.[2] We have reported a method for Cu-catalyzed ACA of dialkylzinc reagents to cyclic nitroalkenes, through which, after appropriate acidic workup (in situ Nef), the corresponding small, medium, and macrocyclic ketones that contain an α-stereogenic center can be synthesized efficiently and in >92% ee.[3] Feringa and co-workers later disclosed a protocol for Cu-catalyzed ACA of dialkylzincs reagents to acyclic nitroalkenes that bear a γ-acetal; optically enriched products were transformed to α-alkyl-β-amino acids.[4]

Despite the above advances, as well as noteworthy observations reported by other laboratories,[5] there has been no report of an efficient catalytic[6] ACA of an alkylmetal to a nitroalkene that leads to the formation of an all-carbon quaternary stereogenic center.[7] Optically enriched organic molecules that contain a quaternary carbon are important due to their relevance to the synthesis of biologically active compounds.[6] Moreover, in contrast to the aforementioned methods that deliver a tertiary carbon stereogenic site, protocols that lead to quaternary carbon stereogenic centers cannot be substituted by alternative strategies involving enantioselective hydrogenations or conjugate hydride additions.[8] The absence of such protocols is likely because efficient addition of carbon nucleophiles to a highly substituted olefin requires an especially effective catalyst.

Herein, we disclose the first catalytic method for ACA of alkylmetals to nitroalkenes that leads to the formation of nitroalkanes containing an all-carbon quaternary carbon stereogenic center. Cu-catalyzed reactions proceed efficiently, in up to 98% ee, and can be carried out with a variety of dialkylzinc reagents and nitroolefins. The synthetic utility of the method is highlighted by efficient conversion of representative optically enriched nitroalkanes to the corresponding carboxylic acids.

We began our studies by examining the ability of chiral peptide-based ligand **3**, previously established[9] to be effective in Cu-catalyzed ACA of dialkylzinc reagents to acyclic disubstituted nitroalkenes, to promote additions to the derived trisubstituted nitroolefins. Nitroolefin **1a** (>98% *E*) was employed as the test substrate. As illustrated in eq 1, we established that in the presence of 4 mol % **3**, 2 mol % $(CuOTf)_2 \cdot C_6H_6$, and 3 equiv of Et_2Zn, the catalytic ACA proceeds at −78 °C to >98% conv in 24 h to afford (*S*)-**2a** in 94% ee and 87% yield after silica gel chromatography. When the catalytic ACA is performed at −30 °C, **2a** is obtained in 92% ee and 89% isolated yield (>98% conv, 24 h). In the absence of **3**, there is only ∼20% conversion to **2a** (under conditions otherwise identical to eq 1).



With the aforementioned promising observation in hand, we set out to establish the scope of the Cu-catalyzed protocol. The results of these studies are summarized in Table 1. As illustrated in entries 1, 3−4, and 6 of Table 1, catalytic additions of dialkylzinc reagents with longer chains or a heteroatom functionality proceed to afford the desired chiral nitroalkanes in good isolated yield[10] and with excellent enantioselectivity (85−96% ee). Nonetheless, longer reaction times (entries 3 and 4) and/or higher catalyst loading (entry 3) may be required for complete conversion at the optimal temperature (see below). The catalytic asymmetric procedure is effective with electron deficient substrate **1b** (entries 2−4) and naphthyl-substituted **1c** (entries 5 and 6).[11]

As the findings in entries 7−9 of Table 1 indicate, under the conditions used effectively for catalytic ACA of **1a**−**1c**, with nitroalkenes **1d** and **1e** (R = *n*-Pr and *i*-Pr) as substrates, reaction efficiency and enantioselectivity suffer noticeably. Although >98% conv is observed with Et_2Zn, in the case of the less reactive Me_2Zn,[12] higher temperatures are required to ensure reasonably high conversion that can lead to lower ee. For example, when the reaction in entry 8 is performed at −15 °C, **2i** is obtained in 85% ee but with ∼20% conv after 72 h (16 mol % **3**).

To address the above shortcomings, we examined the ability of a small selection of chiral phosphines to promote Cu-catalyzed ACA in entries 7−9 of Table 1. These ligands were selected on the basis of the hypothesis that with nitroalkenes bearing olefin substituents larger than Me, reduced steric hindrance at the chiral binding pocket may lead to more facile ACA. A faster reaction could then be performed at lower temperatures, giving rise to improved product optical purity. The effects of alteration of peptide structure (diastereomeric **4**), removal of one amino acid side chain (**5** and **6**) or the AA2 moiety (**7**), were examined (e.g., AA2 in **5** is Gly). As the data in Table 2 indicate, chiral phosphines **4** and **5** readily (>98% conv at 0 °C) deliver nitroalkane **2j** in 93% and 90% ee with 84% and 48% isolated yield, respectively (versus 79% ee and 53% isolated yield with **3**).

As illustrated in eq 2, similar studies indicated that chiral phosphine **5** gives rise to the formation of **2h** in 85% ee and 64% isolated yield (versus 75% ee and 40% yield with **3**). When this Cu-catalyzed transformation is performed at lower temperature, reaction efficiency suffers (57% conv, 86% ee after 72 h at 22 °C); when peptide **4** is used, less improvement in asymmetric induction is observed (80% ee). In contrast to transformations shown in entries 7 and 9 of Table 1, none of the ligands shown in Table 2 give rise to higher enantioselectivity for the reaction in entry 8 (**1e** → **2i**).[13]

With the availability of a catalytic method for enantioselective synthesis of nitroalkanes bearing quaternary carbon stereogenic centers, a range of other optically enriched molecules become accessible. Reduction to the derived amines through Pd-catalyzed

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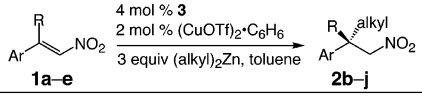
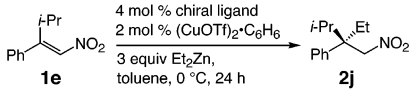
Table 1. Cu-Catalyzed ACA of Dialkylzinc Reagents Promoted by **3**[a]

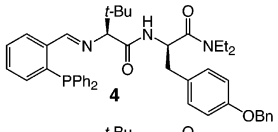
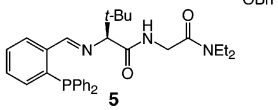
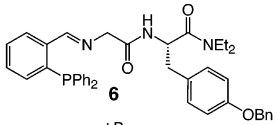
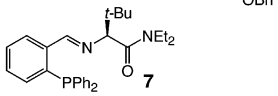


entry	Ar	R		(alkyl)$_2$Zn	product	T (°C); time (h)	conv (%);[b] yield (%)[c]	ee (%)[d]
1	Ph	Me	**1a**	Bu_2Zn	**2b**	–30; 24	95; 55	93
2	*p*-ClC$_6$H$_4$	Me	**1b**	Et_2Zn	**2c**	–78; 24	>98; 76	98
3[e]	*p*-ClC$_6$H$_4$	Me	**1b**	Bu_2Zn	**2d**	–78; 72	93; 71	96
4	*p*-ClC$_6$H$_4$	Me	**1b**	$[(CH_2)_4OAc]_2Zn$	**2e**	–30; 72	>98; 83	85
5	2-naphthyl	Me	**1c**	Et_2Zn	**2f**	–78; 24	>98; 79	95
6	2-naphthyl	Me	**1c**	Bu_2Zn	**2g**	–30; 72	>98; 81	85
7	Ph	*n*-Pr	**1d**	Me_2Zn	**2h**	22; 48	61; 40	75
8[e]	Ph	*i*-Pr	**1e**	Me_2Zn	**2i**	0; 72	95; 85	73
9	Ph	*i*-Pr	**1e**	Et_2Zn	**2j**	0; 24	>98; 53	79

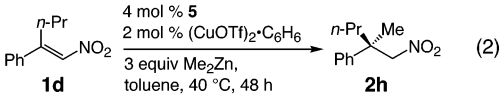
[a] Reactions carried out under N_2 atm. [b] Based on consumption of substrate; determined by ^{1}H NMR analysis. [c] Isolated yields. [d] Determined by chiral GLC and HPLC; see the Supporting Information. Absolute stereochemistry is by inference (determined for **2a**; see the SI). [e] 16 mol % **3** and 8 mol % $(CuOTf)_2{\cdot}C_6H_6$ used.

Table 2[a]



entry	chiral ligand	conv (%);[b] yield (%)[c]	ee (%)[d]
1	 **4**	***>98; 84***	***93***
2	 **5**	>98; 48	90
3	 **6**	>98; 50	<2
4	 **7**	>98; 52	–14

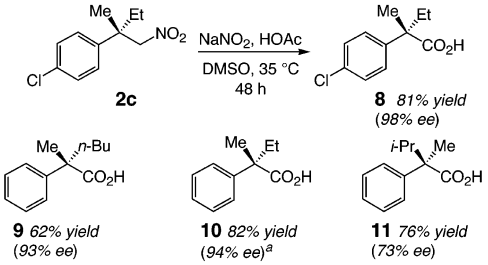
[a–d] See footnotes for Table 1.



>98% conv, 64% yield, 85% ee

hydrogenation is one well-established possibility.[14] Another convenient protocol, outlined most recently, allows for facile conversion of nitroalkanes to the corresponding nitriles and aldoximes, which can undergo efficient and stereoselective [3 + 2] cycloadditions.[15] Another synthetically useful functionalization involves oxidation of the nitromethylene group to the corresponding carboxylic acid (**8**−**11**, Scheme 1).[16] These transformations proceed under mild conditions to afford the desired carboxylic acids bearing an adjacent quaternary carbon stereogenic center. Optically enriched carboxylic acids, represented in Scheme 1, are not easily accessible by catalytic asymmetric or diastereoselective alkylations of enolates that bear a chiral auxiliary.

Scheme 1. Functionization of Optically Enriched ACA Products



[a] Reaction performed at 50 °C.

In brief, we report the first examples of catalytic ACA of alkylmetals to acyclic nitroalkenes, leading to the formation of all-carbon quaternary carbon stereogenic centers. The optically enriched nitroalkanes may be transformed efficiently to synthetically versatile optically enriched molecules, such as the derived amines, nitriles, aldoximes, and carboxylic acids. Development of efficient methods for synthesis and identification of optimal catalyst(s) for ACA of trisubstituted nitroalkenes bearing a nonaryl substituent (e.g., alkyl) is 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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(13) Reactions of substrates **1a**−**c** are less efficient and less selective with phosphines **4**−**7**. As an example, in the presence of **4** and **5**, **2c** is formed in 89% (>98% conv) and 66% ee (13% conv) (vs 98% conv and 98% ee with **3**).

(14) For example, reduction of **2c** (600 psi H_2, 10% Pd(C), MeOH, 40 h) affords the optically enriched primary amine in 63% isolated yield; see SI for details.

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