Asymmetric Catalysis

DOI: 10.1002/anie.201406247

Remarkable Enhancement of Enantioselectivity in the Asymmetric Conjugate Addition of Dimethylzinc to (*Z*)-Nitroalkenes with a Catalytic $[(MeCN)_4Cu]PF_6$–Hoveyda Ligand Complex**

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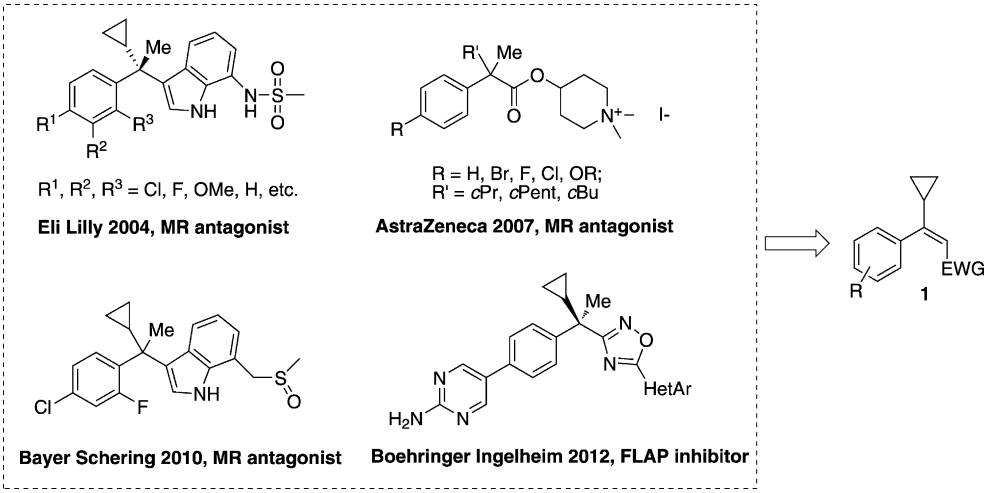
Abstract: *An enantioselective copper-catalyzed asymmetric conjugate addition of Me_2Zn to (Z)-nitroalkenes led to the formation of all-carbon quaternary stereogenic centers with high stereoselectivity. The key features of the new method are the unprecedented use of $[(MeCN)_4Cu]PF_6$ in conjunction with the Hoveyda ligand* ***L1*** *and the use of (Z)-nitroalkene substrates so that undesired nitroalkene isomerization is minimized and enantioselectivity is enhanced dramatically. We also describe a novel, practical, and highly (Z)-selective nitroalkene synthesis.*

All-carbon quaternary stereocenters are increasingly being incorporated into the design and synthesis of novel therapeutic agents. The structures shown in Scheme 1 represent a class of biologically active compounds pursued by several major pharmaceutical companies in the past decade.[1] However, medicinal chemists have met with remarkable challenges during the synthesis of compounds of this type. The preparation of optically pure chiral intermediates has often involved the synthesis of the racemic compounds, followed by tedious, costly, and nonscalable separation by HPLC on a chiral stationary phase,[1a–c,e,f] or the synthesis of diastereomers through the use of a stoichiometric amount of an oxazolidinone-based chiral auxiliary, followed by chromatographic separation of the diastereomers.[1d] Clearly, the development of a more efficient and enantioselective catalytic approach to the synthesis of this family of biologically important compounds is highly desirable. One of our strategies has been to install the all-carbon stereocenter through an asymmetric conjugate addition (ACA) reaction.



Scheme 1. A structural motif of medicinal interest. EWG = electron-withdrawing group.

Over the past two decades, the copper-catalyzed ACA of enones, nitroalkenes, and Meldrum acid derivatives with organozinc, organoaluminum, organomagnesium, or boronic acid reagents has emerged as a powerful approach to access chiral molecules with quaternary stereogenic centers.[2] Whereas there are many documented successes in the ACA of cyclic enones,[3] the use of acyclic substrates has met with formidable challenges.[2g,h,4] Furthermore, although methyl-substituted all-carbon quaternary stereocenters are by far the most commonly occurring all-carbon quaternary stereocenters in natural products, the conjugate addition of Me_2Zn to generate quaternary stereogenic centers is the most challenging transformation and suffers from low reactivity and enantioselectivity.

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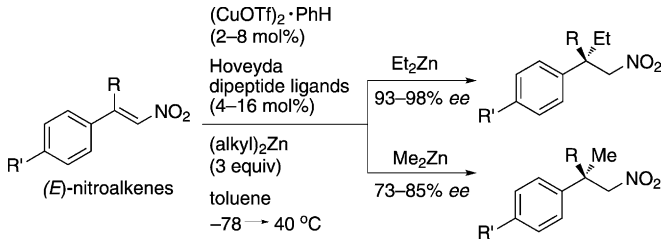
[**] We thank the Boehringer Ingelheim-Pfizer-GlaxoSmithKline-AbbVie Non-Precious Metal Catalysis Consortium for general discussions in this area.

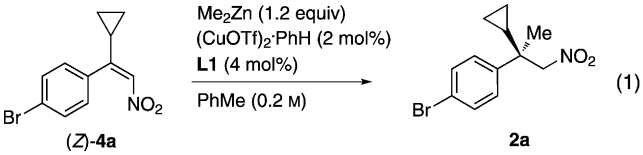
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201406247.

In 2005, Hoveyda and co-workers[4a] reported two interesting examples of the enantioselective ACA of Me_2Zn to *E*-trisubstituted nitroalkenes (R = *n*Pr or *i*Pr; Scheme 2). The products were obtained in 40–85% yield with 73–85% *ee* using complexes of $(CuOTf)_2$·PhH and Hoveyda dipeptide ligands. In sharp contrast, reactions with Et_2Zn and other diorganozinc species gave the corresponding products with up to 98% *ee*. Despite some limited success reported recently in the methylation of acyclic Meldrum acid derivatives[4b] and acyclic enones[4c] with improved enantioselectivity, the ACA of Me_2Zn remains significantly underdeveloped. We now report that with a new Cu^I catalyst, $[(MeCN)_4Cu]PF_6$, the use of which to our knowledge has not previously been reported for this type of transformation, and acyclic (*Z*)-nitroalkenes as substrates, high reactivities and enantioselectivities were observed in the ACA of Me_2Zn to create all-carbon quaternary stereogenic centers.



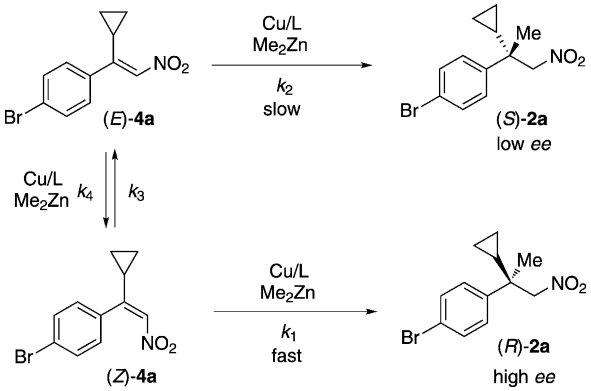
Scheme 2. Pioneering studies by Hoveyda and co-workers on the ACA reaction of (*E*)-nitroalkenes with dialkylzinc reagents. Tf = trifluoromethanesulfonyl.

We first investigated the addition of Me_2Zn to nitroalkenes **4** and **5** under conditions reported by Hoveyda and co-workers (Scheme 3). Preliminary results showed that for the addition of dicyclopropylzinc[5] to (*E*)-**5**, no reaction occurred at −20 °C; after 65 h at 0 °C, only 8% *ee* was observed. On the other hand, the addition of dimethylzinc to (*Z*)-**4** at −30 °C gave product **2** with an encouraging *ee* value of 65% (*S*), with full conversion and 96% yield. The addition to (*E*)-**4** furnished **2** with a slightly higher *ee* value (76% *ee*, *R*), but with poor conversion. Although the reaction with (*E*)-**4** reached full conversion after 72 h at −10 °C, **2** was obtained with only 52% *ee* (*R*). These initial observations led us to decide to focus our research efforts on optimizing the ACA reaction of (*Z*)-**4a** with dimethylzinc [Eq. (1)].

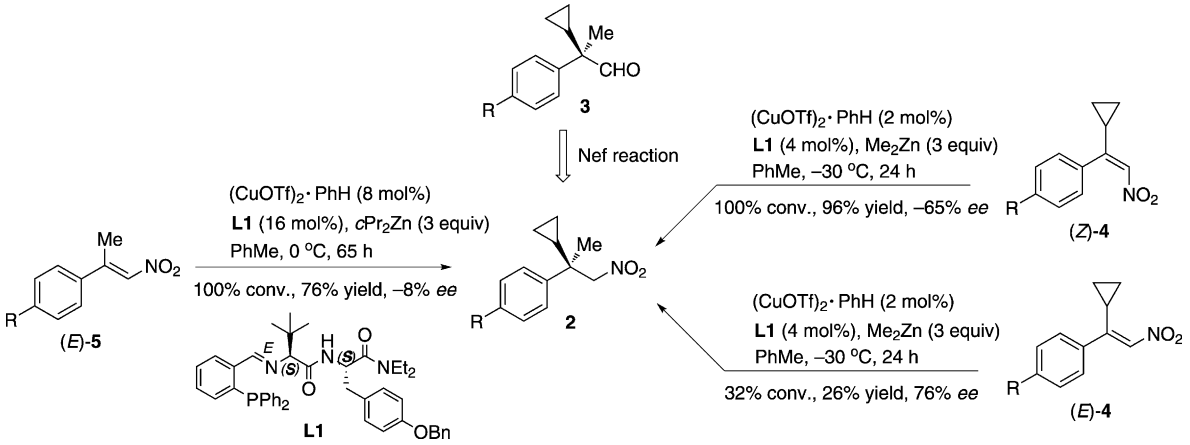


(1)

Further screening confirmed that −30 °C is the optimal temperature for the use of chiral ligand **L1**, under which conditions full conversion and 65% *ee* were observed.[6] Next, we examined a number of chiral ligands and solvents in the hope of improving the enantioselectivity. To our dismay, we did not find a chiral ligand that was better than **L1**. However, during these studies, an interesting observation caught our attention: When non-effective chiral ligands were used, although the desired product of conjugate addition was not observed, we isolated and characterized (*E*)-**4a** (Scheme 4) as the major by-product. The formation of (*E*)-**4a** is strong proof that olefin isomerization of (*Z*)-**4a** took place during the



Scheme 4. *E*/*Z* isomerization of nitroalkenes during asymmetric conjugate addition.



Scheme 3. Comparison of three ACA strategies. R = Br, Bn = benzyl.

Table 1: Investigation of background isomerization with Cu salts during asymmetric conjugate addition to (*Z*)-**4a** or (*E*)-**4a**.

Entry	Reaction mixture[a]	*T* [°C]	(*Z*)-**4a** [%][b]	**2a** [%][b]	(*E*)-**4a** [%][b,c]
1	(*Z*)-**4a** + $(CuOTf)_2$·PhH	25	97	0	3
2	(*Z*)-**4a** + $(CuOTf)_2$·PhH + L1	25	99	0	1
3	(*Z*)-**4a** + $(CuOTf)_2$·PhH + Me_2Zn	−30	43	0	57
4	(*E*)-**4a** + $(CuOTf)_2$·PhH + Me_2Zn	−30	34	0	66
5	(*Z*)-**4a** + $Cu(OCOCF_3)_2$·*x*H_2O + Me_2Zn	−30	47	0	53
6	(*Z*)-**4a** + $(MeCN)_4CuOTf$ + Me_2Zn	−30	70	0	30
7	(*Z*)-**4a** + $(MeCN)_4CuPF_6$ + Me_2Zn	−30	97	0	3
8	(*Z*)-**4a** + $(MeCN)_4CuPF_6$	25	100	0	0
9	(*Z*)-**4a** + $(MeCN)_4CuPF_6$ + L1	25	99	0	1
10	(*E*)-**4a** + $(MeCN)_4CuPF_6$ + Me_2Zn	−30	7	0	93
11	(*Z*)-**4a** + $(MeCN)_4CuBF_4$ + Me_2Zn	−30	98	0	2
12	(*Z*)-**4a** + CuTC + Me_2Zn	−30	95	0	5
13	(*Z*)-**4a** + CuOAc + Me_2Zn	−30	96	0	4

[a] Reaction conditions: 4 mol% Cu, **L1** (4 mol%), Me_2Zn (1.2 equiv), 65 h. [b] The yield is based on the consumption of the substrate and was determined by HPLC analysis. [c] (*E*)-**4a** was isolated and fully characterized (see the Supporting Information for details).

course of the reaction. It has been reported previously[7] that olefin isomerization could be responsible for lower enantioselectivities in conjugate addition reactions owing to the different reactivity and/or selectivity of the (*E*)- and (*Z*)-isomers, as illustrated in Scheme 4. Indeed, in our case, opposite enantioselectivities were observed for the reactions of (*E*)- and (*Z*)-**4a** (Scheme 3).

To fully understand how severe the isomerization was, we investigated the background isomerization with (*Z*)-**4a** and (*E*)-**4a** (Table 1).[6] When (*Z*)-**4a** (1 equiv) and $(CuOTf)_2$·PhH (2 mol%) with or without chiral ligand **L1** (4 mol%) were stirred in toluene in the absence of Me_2Zn, olefin isomerization was minimal, even at room temperature (Table 1, entries 1 and 2). However, in the reaction mixture of pure (*Z*)-**4a** (1 equiv) with $(CuOTf)_2$·PhH (2 mol%) and Me_2Zn (1.2 equiv), isomer (*E*)-**4a** was formed in 57% yield and 43% of (*Z*)-**4a** remained after 65 h at −30°C (Table 1, entry 3). When pure (*E*)-**4a** was used in place of (*Z*)-**4a** in this control experiment, isomer (*Z*)-**4a** was formed in 34% yield (Table 1, entry 4). These observations, coupled with the fact that under the standard reaction conditions with $(CuOTf)_2$·PhH, **2a** was formed with a moderate *ee* value of 65%, suggested that nitroolefin isomerization during the course of ACA is probably the cause of the poor enantioselectivity. Accordingly, if we could suppress the undesired nitroolefin isomerization during the ACA reaction, we might be able to improve the enantioselectivity significantly. We suspected that the nature of the Cu salt could play a critical role in the observed olefin isomerization and examined the effect of a variety of Cu salts on olefin isomerization. As with $(CuOTf)_2$·PhH, the use of $Cu(OCOCF_3)_2$·*x*H_2O or $[(MeCN)_4Cu]OTf$ resulted in significant olefin isomerization (Table 1, entries 5 and 6). In contrast, the use of a catalytic amount of $[(MeCN)_4Cu]PF_6$ and Me_2Zn (1.2 equiv) induced only 3% olefin isomerization (Table 1, entry 7). Under the same conditions with (*E*)-**4a** as the starting material, 7% olefin isomerization was observed (Table 1, entry 10). Similarly, $[(MeCN)_4Cu]BF_4$, CuTC, and CuOAc also induced low levels of isomerization (Table 1, entries 11–13).

These four Cu salts were then further evaluated in the actual ACA reactions (Table 2). The ACA reaction was very sluggish with $Cu(OCOCF_3)_2$·*x*H_2O (Table 2, entry 3), CuTC (entry 5), or CuOAc (entry 7). Reactions with $[(MeCN)_4Cu]BF_4$ (Table 2, entry 4) or $[(MeCN)_4Cu]OTf$ (entry 6) were not satisfactory in terms of their enantioselectivity and/or reactivity. To our delight, the use of $[(MeCN)_4Cu]PF_6$ led to superior enantioselectivity as compared to the reaction with $(CuOTf)_2$·PhH. This observation is consistent with the background-isomerization results in Table 1, thus suggesting that $[(MeCN)_4Cu]PF_6$ indeed significantly suppressed the undesired olefin isomerization and that (*Z*)-**4a** was more advantageous as a substrate than isomer (*E*)-**4a** with regard to both reactivity and enantioselectivity (Table 2, entries 8 and 9). Thus, through the use of $[(MeCN)_4Cu]PF_6$ as the catalyst and the (*Z*)-nitroalkene **4a** as the substrate, dramatically improved enantioselectivity was observed in the ACA reaction with Me_2Zn. Interestingly, when $(CuOTf)_2$·PhH was used as the catalyst, the ACA of (*Z*)-**4a** gave the *S* enantiomer of **2a** as the major product, whereas the ACA of (*E*)-**4a** gave the *R* enantiomer as the major product. However, when $[(MeCN)_4Cu]PF_6$ was used as the catalyst, ACA of either (*Z*)-**4a** or (*E*)-**4a** gave (*R*)-**2a** as the major product, thus suggesting that nucleophilic attack by Me_2Zn from the *Re* face was favored, irrespective of the nitroolefin geometry.

Table 2: Screening of Cu salts in the ACA of (*Z*)-**4a** or (*E*)-**4a**.[a]

Entry	Substrate	Cu^I (mol%)	**L1** [mol%]	*t* [h]	Conv. [%][b]	*ee* [%][c]
1	(*Z*)-**4a**	$(CuOTf)_2$·PhH (2)	4	24	100 (96)	65 (*S*)
2	(*E*)-**4a**	$(CuOTf)_2$·PhH (2)	4	24	32 (26)	76 (*R*)
3	(*Z*)-**4a**	$Cu(OCOCF_3)_2$·*x*H_2O (4)	4	65	5 (3)	–
4	(*Z*)-**4a**	$[(MeCN)_4Cu]BF_4$ (4)	4	65	42 (42)	50 (*S*)
5	(*Z*)-**4a**	CuTC (4)	4	65	5 (1)	–
6	(*Z*)-**4a**	$[(MeCN)_4Cu]OTf$ (4)	4	24	10 (98)	63 (*S*)
7	(*Z*)-**4a**	CuOAc (4)	4	65	8 (5)	–
8	(*Z*)-**4a**	$[(MeCN)_4Cu]PF_6$ (4)	4	65	98 (95)	95 (*R*)
9	(*E*)-**4a**	$[(MeCN)_4Cu]PF_6$ (4)	4	96	16 (15)	85 (*R*)

[a] Reactions were carried out in toluene at −30°C. [b] The reported conversion is based on the consumption of the substrate and was determined by HPLC analysis. The number in parenthesis indicates the HPLC assay yield. [c] The *ee* value was determined by HPLC on a chiral stationary phase. The absolute configuration was determined by our internal program and by analogy.

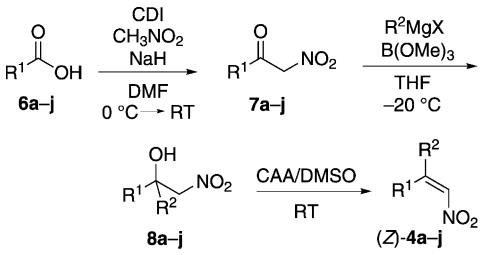
To explore the scope of the $[(MeCN)_4Cu]PF_6$–**L1**-catalyzed ACA reaction of (*Z*)-nitroalkenes with Me_2Zn, we first needed an efficient and stereoselective method for the synthesis of *Z* nitroalkenes. These compounds have been synthesized previously by the β-elimination of mesylates,[8a] by the oxidative elimination of β-phenylselenides[8b] or β-

sulfides,[8c] by the photoisomerization of *E* nitroalkenes,[8d] and by dehydration of the corresponding tertiary alcohols,[8e] but the reported methods suffer from long reaction times, low yields, poor functional-group compatibility, and low *Z*/*E* selectivity, which often requires chromatographic separation of the two isomers. After intensive investigations, we discovered a new method for the efficient and highly *Z*-selective synthesis of nitroalkenes [Eq. (2) and Table 3].

Table 3: Synthesis of nitroalkenes (*Z*)-**4a–j**.

Entry	R^1; $R^{2[a]}$	Yield of **7** [%][b]	Yield of **8** [%][b]	Yield of (*Z*)-**4** [%][b]	*Z*/*E* ratio of **4**[c]
1	4-BrC_6H_4; *c*Pr	96	88	85 (**4a**)	≥99:1
2	4-ClC_6H_4; *c*Pr	93	84	82 (**4b**)	≥99:1
3	6-Cl-3-Py; *c*Pr	72	91	76 (**4c**)	≥99:1
4	4-BrC_6H_4; Et	96	83	82 (**4d**)	≥99:1
5	4-BrC_6H_4; *n*Pr	96	85	88 (**4e**)	≥99:1
6	4-BrC_6H_4; *i*Pr	96	90	87 (**4f**)	≥99:1
7	4-ClC_6H_4; *n*Bu	93	81	86 (**4g**)	≥99:1
8	6-Cl-3-Py; *n*Bu	72	87	73 (**4h**)	≥99:1
9	4-BrC_6H_4; *c*Hex	96	79	92 (**4i**)	≥99:1
10	4-BrC_6H_4; *c*Pent	96	78	98 (**4j**)	≥99:1

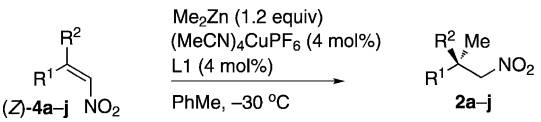
[a] *c*Pr = cyclopropyl, *c*Hex = cyclohexyl, *c*Pent = cyclopentyl, 6-Cl-3-Py = 6-chloro-3-pyridyl. [b] Yield of the isolated product. [c] The *Z*/*E* ratio was determined by ^{1}H NMR spectroscopy of the crude product.



(2)

The commercially available carboxylic acids **6** were activated by CDI in DMF to form a reactive *N*-acyl imidazole species, which reacted with the carbanion generated from nitromethane and NaH to give nitroketones **7**.[9] Nitroketones **7** are crystalline solids and were conveniently precipitated from the reaction mixtures upon the addition of aqueous HCl. They were converted into nitroalcohols **8** by the $B(OMe)_3$-mediated addition of a Grignard reagent.[10] The use of $B(OMe)_3$ is critical for this transformation to avoid the otherwise serious retro-Henry reaction. Nitroalcohols **8** underwent facile dehydration in a chloroacetic anhydride (CAA)–DMSO system to afford (*Z*)-nitroalkenes **4** in high yield with high diastereoselectivity. The use of CAA is critical for the desired reaction rate and high *Z*/*E* selectivity. Most (*Z*)-nitroalkenes **4** are crystalline solids that can be crystallized out during workup, thus eliminating the need for chromatographic separation and making practical scaleup possible.

These (*Z*)-nitroalkenes **4** were then subjected to our newly established ACA conditions to give nitroalkanes **2** [Eq. (3) and Table 4]. High yields and high enantioselectivities were observed for all substrates for the formation of the all-carbon quaternary stereogenic center. Pyridine derivatives



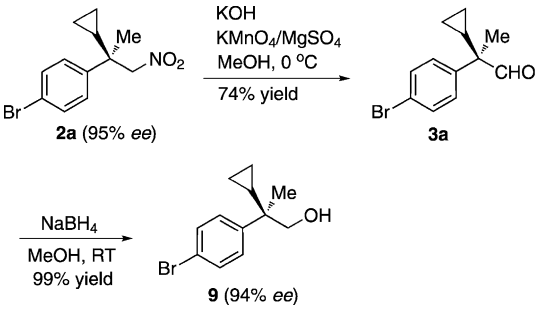
(3)

Table 4: ACA of nitroalkenes (*Z*)-**4a–j**.

Entry	(*Z*)-**4a–j** (R^1; R^2)	Yield [%][a]	*ee* [%][b]
1	(*Z*)-**4a** (4-BrC_6H_4; *c*Pr)	91 (**2a**)	95
2	(*Z*)-**4b** (4-ClC_6H_4; *c*Pr)	92 (**2b**)	91
3	(*Z*)-**4c** (6-Cl-3-Py; *c*Pr)	91 (**2c**)	93
4	(*Z*)-**4d** (4-BrC_6H_4; Et)	88 (**2d**)	93
5	(*Z*)-**4e** (4-BrC_6H_4; *n*Pr)	94 (**2e**)	95
6	(*Z*)-**4f** (4-BrC_6H_4; *i*Pr)	92 (**2f**)	98
7	(*Z*)-**4g** (4-ClC_6H_4; *n*Bu)	91 (**2g**)	89
8	(*Z*)-**4h** (6-Cl-3-Py; *n*Bu)	92 (**2h**)	93
9	(*Z*)-**4i** (4-BrC_6H_4; *c*Hex)	96 (**2i**)	94
10	(*Z*)-**4j** (4-BrC_6H_4; *c*Pent)	91 (**2j**)	94

[a] Yield of the isolated product. [b] The *ee* value of the product was determined by HPLC on a chiral stationary phase.

were also found to be suitable substrates (Table 4, entries 3 and 8). It is well-established that nitroalkanes can be readily converted into a range of functionalities, such as aldehydes,[11] carboxylic acids,[12] amines,[13] oximes,[14] and nitriles.[14b,15] Thus, the current methodology could be used to access a library of biologically important compounds with all-carbon stereogenic centers in an efficient and practical way. As an example, nitroalkane **2a** was converted in a Nef reaction into aldehyde **3a**, which was then reduced to the chiral alcohol **9** [Eq. (4)].



(4)

In conclusion, we have described a highly enantioselective copper-catalyzed asymmetric conjugate addition with Me_2Zn for the formation of all-carbon quaternary stereogenic centers. The key features of the new methodology are the unprecedented use of $[(MeCN)_4Cu]PF_6$ as the catalyst and the employment of (*Z*)-nitroalkene substrates. We also developed a novel and practical synthesis of (*Z*)-nitroalkenes. Considering the low cost of the sustainable Cu catalyst and the ready availability of the Hoveyda dipeptide ligand **L1**, the present discovery provides a practical synthetic route to biologically active and synthetically useful molecules with a methyl-substituted all-carbon quaternary chiral center. Extensions of this methodology to other diorganozinc

reagents and other heterocyclic compounds are being pursued in our laboratories.

Received: June 15, 2014
Revised: August 11, 2014
Published online: September 15, 2014

Keywords: asymmetric conjugate addition · copper · nitroalkenes · quaternary stereocenters · zinc

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