

## Copper(I) phosphoramidite catalyzed asymmetric conjugate addition of dialkylzinc reagents to $\alpha,\beta$ -unsaturated nitroacetates; an enantioselective route to $\beta$ -aryl-nitroalkanes

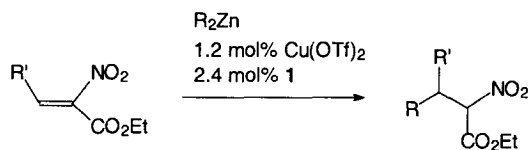
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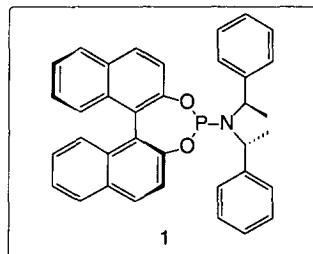
### Abstract

The asymmetric copper(I) phosphoramidite catalyzed conjugate addition of dialkylzinc reagents to *E*,*Z*-mixtures of  $\alpha,\beta$ -unsaturated nitroacetates provided the 1,4-adducts in excellent yields but with low e.e.'s. High enantioselectivities (e.e.'s up to 92%) were obtained with structurally rigid 3-nitrocoumarins, leading to a new route to optically active  $\beta$ -aryl-nitroalkanes. © 1999 Elsevier Science Ltd. All rights reserved.

Enantioselective conjugate addition of an organometallic reagent to a prochiral Michael acceptor is a powerful tool for carbon-carbon bond formation with simultaneous introduction of a new stereogenic center.<sup>1</sup> Ligand accelerated catalytic processes, which require only small amounts of precious enantiomerically pure compounds, are particularly attractive for this purpose.<sup>2</sup> A prominent position in this rapidly expanding field of research is occupied by the copper catalyzed 1,4-addition of organozinc reagents.<sup>3,4</sup> Complete stereocontrol in the catalytic conjugate addition of dialkylzinc reagents to enones was accomplished for the first time in our laboratories using a catalyst comprising copper(II) triflate in combination with a novel phosphoramidite ligand **1**, derived from (*S*)-2,2'-binaphthol and (*R,R*)-bis(1-phenylethyl)amine.<sup>5,6</sup> Recently, Sewald reported the Cu(I) catalyzed 1,4-addition of diethylzinc to nitroolefins in the presence of **1** with an e.e. up to 86%.<sup>7</sup> In this letter we describe the first results with the Cu(OTf)<sub>2</sub>/**1** catalyst system in the conjugate addition of dialkylzinc reagents to  $\alpha,\beta$ -unsaturated nitroacetates to give chiral  $\beta$ -substituted nitroacetates (Scheme 1).



Scheme 1

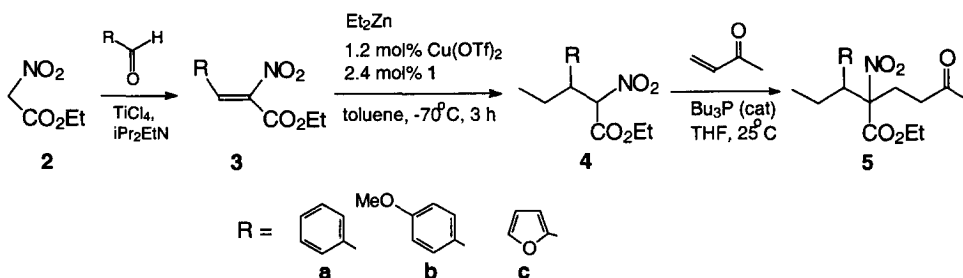


Nitroacetates are versatile building blocks for various organic compounds since the nitro and ester groups can easily be transformed into many other functionalities.<sup>8</sup> Furthermore, the nitroacetate group is a synthetic equivalent of an  $\alpha$ -amino acid.<sup>9</sup> For instance, reduction of the nitro group of  $\alpha$ -alkylated

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nitroacetates provides an easy access to non-natural  $\alpha$ -alkylated  $\alpha$ -amino acid derivatives. These compounds have interesting pharmaceutical and biological properties<sup>10</sup> and, therefore, are a challenging synthetic target.<sup>11</sup> Recently, we achieved the synthesis of optically active  $\alpha$ -alkylated nitroacetates with e.e.'s up to 80% by a catalytic enantioselective Michael addition of nitroacetates to enones using a chiral AILiBINOL catalyst.<sup>12</sup> Montgomery *et al.* reported a method for the preparation of structurally diverse  $\alpha,\beta$ -substituted amino acid derivatives for use in combinatorial chemistry, which involves an uncatalyzed conjugate addition of organozinc reagents to  $\alpha,\beta$ -unsaturated nitroacetates as a key step.<sup>13</sup> Application of Cu(I) phosphoramidite catalysis might provide a convenient enantioselective version of this concise synthesis of highly substituted amino acid derivatives.

We have prepared the highly electrophilic  $\alpha,\beta$ -unsaturated nitroacetates **3a-c** from benzaldehyde, anisaldehyde, and furfural, respectively, by a mild Knoevenagel condensation with 1 equiv. of ethyl nitroacetate (**2**)<sup>14</sup> in the presence of 1 equiv. of  $\text{TiCl}_4$  and 4 equiv. of diisopropylethylamine (Scheme 2).<sup>15</sup> Compounds **3a-c** were obtained as *E/Z*-mixtures in a ratio approximating 1:1. In the case of **3b**, the less polar *Z*-isomer was isolated by column chromatography followed by recrystallization.



**Scheme 2**

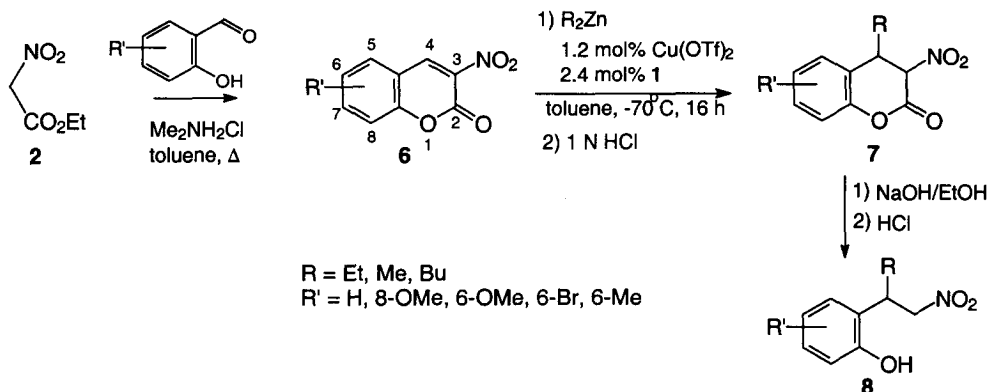
**Table 1**

entry	substrate	R	product	yield (%) <sup>a</sup>	d.r.	product	yield (%) <sup>a</sup>	d.r.	e.e. (%) <sup>b</sup>
1	<b>3a</b>	Ph	<b>4a</b>	64	2:1	-	-	-	26, 25
2	<b>3b</b>	An	<b>4b</b>	90	1:1	<b>5b</b>	91	1:1	23, 10
3	<b>3b(Z)</b>	An	<b>4b</b>	95	1:1	<b>5b</b>	85	1:1	<2, <2
4	<b>3c</b>	Fur	<b>4c</b>	85	2:1	<b>5c</b>	44	3:1	26, 25

<sup>a</sup>Isolated yield, <sup>b</sup>E.e.'s determined for each of the diastereomers by chiral HPLC: **4a**: Daicel Chiralcel OJ, hexane-EtOH 99:1; **5b**, **5c**: Regis Whelk 0.1 (R,R), hexane-EtOH 90:10.

Conjugate addition of diethylzinc to unsaturated nitroacetates **3** in the presence of the in situ prepared catalyst from 1.2 mol%  $\text{Cu}(\text{OTf})_2$  and 2.4 mol% chiral phosphoramidite **1** gave  $\beta$ -substituted nitroacetates **4** in excellent yields as diastereomeric mixtures with a diastereomeric ratio (d.r.) near 1:1 (Table 1).<sup>16</sup> Compounds **4b** and **4c** were subjected to a Michael reaction with methyl vinyl ketone to give the quaternary nitroacetates **5b** and **5c**, respectively. Only moderate e.e.'s were measured for compounds **4a**, **5b**, and **5c**, which is no real surprise realizing that the conjugate addition was performed on a mixture of *E/Z*-isomers. More surprisingly, however, was the almost complete lack of enantioselectivity in the conjugate addition of  $\text{Et}_2\text{Zn}$  to isomerically pure *Z*-**3b** (entry 3). This finding suggests that a *cis*-orientation of the aryl and nitro

groups is unfavorable for the formation of a productive catalyst-substrate complex so that the uncatalyzed reaction can dominate. This observation encouraged us to investigate the conjugate addition of dialkylzinc to 3-nitrocoumarins **6**, with a fixed trans orientation of the aryl and the nitro group (Scheme 3).



**Scheme 3**

**Table 2**

entry	substrate	R'	R	product	conv (%) <sup>a</sup>	d.r. <sup>a</sup>	product	yield (%) <sup>b</sup>	e.e. (%) <sup>c</sup>
1	<b>6a</b>	H	Et	<b>7a</b>	95	10:1	<b>8a</b>	79	92 (-)
2	<b>6a</b>	H	Me	<b>7b</b>	99	10:1	<b>8b</b>	89	49 (+)
3	<b>6a</b>	H	Bu	<b>7c</b>	92	12:1	<b>8c</b>	63	88 (-)
4	<b>6b</b>	8-OMe	Et	<b>7d</b>	99	10:1	<b>8d</b>	84	90 (+)
5	<b>6b</b>	8-OMe	Me	<b>7e</b>	99	10:1	<b>8e</b>	57	37 (+)
6	<b>6c</b>	6-OMe	Et	<b>7f</b>	90	1:1	<b>8f</b>	49	16 (+)
7	<b>6d</b>	6-Br	Et	<b>7g</b>	97	10:1	<b>8g</b>	58	30 (+)
8	<b>6d</b>	6-Br	Me	<b>7h</b>	99	15:1	<b>8h</b>	47	40 (-)
9	<b>6e</b>	6-Me	Et	<b>7i</b>	98	2:1	<b>8i</b>	48	30 (+)
10	<b>6e</b>	6-Me	Me	<b>7j</b>	90	20:1	<b>8j</b>	77	36 (-)

<sup>a</sup>Conversion (conv) and diastereomeric ratio (d.r.) were determined by <sup>1</sup>H NMR, <sup>b</sup>Isolated yield, <sup>c</sup>Determined by chiral HPLC (Daicel Chiralcel OJ, hexane-*i*PrOH 90:10). Sign of optical rotation is given in parentheses, absolute configuration was not determined.

3-Nitrocoumarins **6a-e** were prepared as stable solids from the corresponding salicylaldehydes by a Knoevenagel condensation with ethyl nitroacetate.<sup>17</sup> The conjugate addition of Et<sub>2</sub>Zn to **6a** gave, after the usual workup with saturated NH<sub>4</sub>Cl, a mixture of the expected addition product **7a** (two diastereomers) and a product that was identified by NMR and MS as the ring opened and decarboxylated nitroalkane **8a**. The formation of **8a** could completely be suppressed by quenching the reaction with dilute HCl to give **7a** as the only product with a pH-dependent diastereomeric ratio varying from 1:1 (pH 1) to circa 20:1 (pH 6-7).<sup>16,18</sup> On the other hand, nitroalkane **8a** was isolated as the sole product in high yield after column chromatography

when the reaction mixture was stirred with dilute NaOH for 1 h (pH 8-10) before acidification (pH 4) and extraction. Formation of **8a** was also achieved by stirring a solution of **7a** in NaOH/EtOH at 50 °C for 1 h, although the yield in the latter case was lower, probably due to selfcondensation. Assuming that the conversion of **7a** to **8a** occurs without racemization, the enantioselectivity of the conjugate addition reaction was established by determination of the e.e. of **8a** using chiral HPLC analysis (Table 2, entry 1). Thus, an e.e. of 92% was established for the addition of Et<sub>2</sub>Zn to substrate **6a** in toluene at -70 °C. The e.e. dropped to 83% when the reaction temperature was increased to -15 °C; the use of CH<sub>2</sub>Cl<sub>2</sub> or THF as solvent decreased the e.e. to 50%.

Variation of both the dialkylzinc reagent (Et<sub>2</sub>Zn, Me<sub>2</sub>Zn, or Bu<sub>2</sub>Zn) and the substrate (**6a-e**) yielded the corresponding adducts **7a-j** and, after hydrolysis and decarboxylation, the nitroalkanes **8a-j** in good yields (Table 2).<sup>19</sup> Excellent e.e.'s were also obtained in the Bu<sub>2</sub>Zn addition to **6a** (88%) and in the Et<sub>2</sub>Zn addition to 8-MeO-substituted substrate **6b** (90%). In general, the addition of Me<sub>2</sub>Zn ensued with lower e.e.'s (up to 49%). Furthermore, the presence of a substituent at the 6-position of the 3-nitrocoumarin substrate (**6c-e**) appears to have a negative effect on the enantioselectivity of the conjugate addition, although the origin of the substituent effects remains to be elucidated. In conclusion, we have demonstrated that a highly efficient and enantioselective Cu(TfO)<sub>2</sub>/1 catalyzed conjugate addition of dialkylzinc reagents to α,β-unsaturated nitroacetates is possible when the β-aryl group and the nitro group are fixed in a trans orientation as in 3-nitrocoumarins. Subsequent mild decarboxylation of the addition products affords a new route for the synthesis of optically active β-aryl-nitroalkanes, versatile multifunctional building blocks.

## References and notes

- Reviews: (a) Rossiter, B.E.; Swingle, N.M. *Chem. Rev.* **1992**, *92*, 771-806; (b) Krause, N. *Kontakte (Darmstadt)* **1993**, *1*, 3-13; (c) Krause, N.; Gerold, A. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 186-204; (d) Feringa B.L.; de Vries, A.H.M. in *Advances in Catalytic Processes*, Doyle, M.P., Ed., JAI Press Inc., Greenwich, Connecticut, Vol. 1, **1995**, 151-192.
- Berrisford, D.J.; Bolm, C.; Sharpless, K.B. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1059-1070.
- For recent examples see: (a) Bennett, S.M.W.; Brown, S.M.; Muxworthy, J.P.; Woodward, S. *Tetrahedron Lett.* **1999**, *40*, 1767-1770; (b) Kanai, M.; Nakagawa, Y.; Tomioka, K. *Tetrahedron* **1999**, *55*, 3831-3842; (c) Alexakis, A.; Vastra, J.; Burton, C.; Benhaim, C.; Mangeney, P. *Tetrahedron Lett.* **1998**, *39*, 7869-7872.
- For a review of functionalized zinc reagents, see: Knochel, P.; Singer, R.D. *Chem. Rev.* **1993**, *93*, 2117-2188.
- (a) de Vries, A.H.M.; Meetsma, A.; Feringa, B.L. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2374-2376; (b) Feringa, B.L.; Pineschi, M. Arnold, L.A. Imbos, R.; de Vries, A.H.M. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2620-2623; (c) Naasz, R. Arnold, L.A. Pineschi, M.; Keller, E.; Feringa, B.L. *J. Am. Chem. Soc.* **1999**, *121*, 1104-1105.
- For a brief review of recent progress, see: Krause, N. *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 283-285.
- Sewald, N.; Wendisch, V. *Tetrahedron: Asymmetry* **1998**, *9*, 1341-1344.
- Shipchandler, M.T. *Synthesis* **1979**, 666-686.
- Seebach, D.; Colvin, E.W.; Lehr, F.; Weller, T. *Chimia* **1979**, *33*, 1-18.
- (a) Duthaler, R.O. *Tetrahedron* **1994**, *50*, 1539-1650; (b) Williams, R.M. *Synthesis of Optically Active α-Amino Acids*, Pergamon Press, Oxford, **1989**.
- Wirth, T. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 225-227.
- Keller, E.; Veldman, N.; Spek, A.L.; Feringa, B.L. *Tetrahedron: Asymmetry* **1997**, *8*, 3403-3413.
- Fornicola, R.S.; Oblinger, E.; Montgomery, J. *J. Org. Chem.* **1998**, *63*, 3528-3529.
- Sifniades, S. *J. Org. Chem.* **1975**, *40*, 3562-3566.
- Lehnert, W. *Tetrahedron* **1972**, *28*, 663-666.
- Note that the α-position with respect to the ester and nitro groups is prone to epimerization.
- Dauzonne, D; Royer, R. *Synthesis* **1983**, 836-837.
- Purification of compounds **7** by chromatography on SiO<sub>2</sub> or Al<sub>2</sub>O<sub>3</sub> was hampered by product decomposition. Analytically pure **7a** and **7b** were obtained by crystallization.
- All new compounds were fully characterized by <sup>1</sup>H and <sup>13</sup>C NMR and by HRMS.