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Copper(I) phosphoramidite catalyzed asymmetric conjugate addition of dialkylzinc reagents to α,β-unsaturated nitroacetates; an enantioselective route to β-aryl-nitroalkanes

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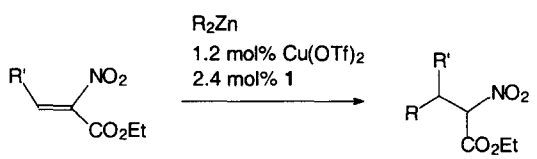
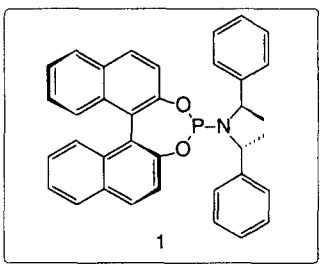
Abstract
The asymmetric copper(I) phosphoramidite catalyzed conjugate addition of dialkylzinc reagents to *E,Z*-mixtures of α,β-unsaturated nitroacetates provided the 1,4-adducts in excellent yields but with low e.e.'s. High enantioselectivities (e.e.'s up to 92%) were obtained with structurally rigid 3-nitrocoumarins, leading to a new route to optically active β-aryl-nitroalkanes.

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.[1] Ligand accelerated catalytic processes, which require only small amounts of precious enantiomerically pure compounds, are particularly attractive for this purpose.[2] A prominent position in this rapidly expanding field of research is occupied by the copper catalyzed 1,4-addition of organozinc reagents.[3,4] 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.[5,6] 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%.[7] In this letter we describe the first results with the $Cu(OTf)_2$/**1** catalyst system in the conjugate addition of dialkylzinc reagents to α,β-unsaturated nitroacetates to give chiral β-substituted nitroacetates (Scheme 1).



Scheme 1



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

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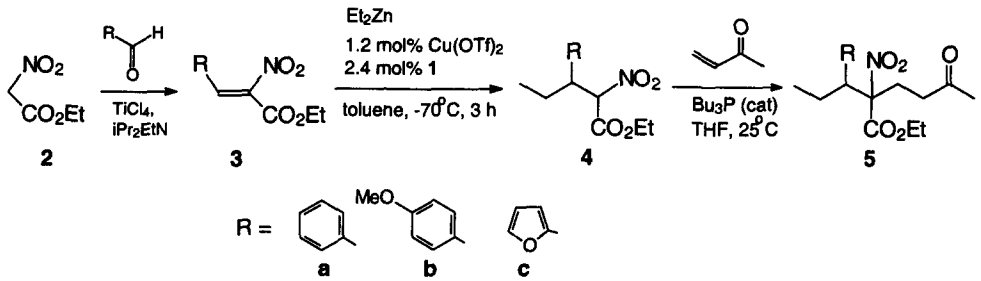
nitroacetates provides an easy access to non-natural α-alkylated α-amino acid derivatives. These compounds have interesting pharmaceutical and biological properties[10] and, therefore, are a challenging synthetic target.[11] Recently, we achieved the synthesis of optically active α-alkylated nitroacetates with e.e.'s up to 80% by a catalytic enantioselective Michael addition of nitroacetates to enones using a chiral AlLiBINOL catalyst.[12] Montgomery *et al.* reported a method for the preparation of structurally diverse α,β-substituted amino acid derivatives for use in combinatorial chemistry, which involves an uncatalyzed conjugate addition of organozinc reagents to α,β-unsaturated nitroacetates as a key step.[13] 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 α,β-unsaturated nitroacetates **3a-c** from benzaldehyde, anisaldehyde, and furfural, respectively, by a mild Knoevenagel condensation with 1 equiv. of ethyl nitroacetate (**2**)[14] in the presence of 1 equiv. of $TiCl_4$ and 4 equiv. of diisopropylethylamine (Scheme 2).[15] 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

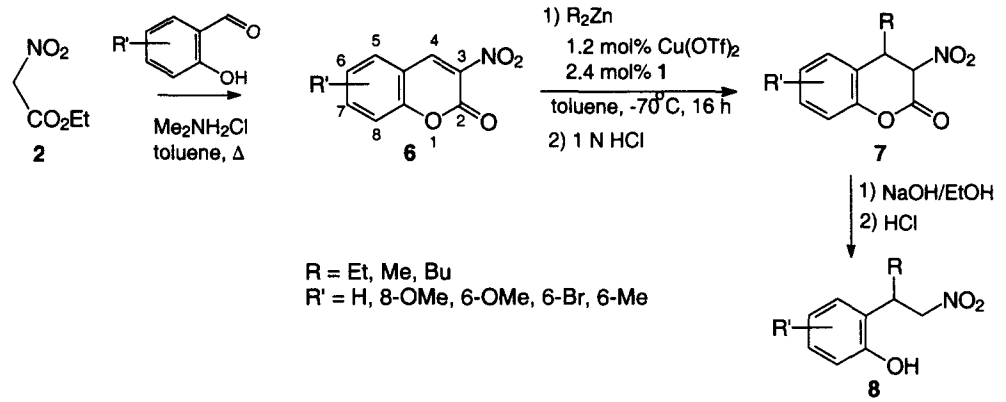
Table 1

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

[a]Isolated yield, [b]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% $Cu(OTf)_2$ and 2.4 mol% chiral phosphoramidite **1** gave β-substituted nitroacetates **4** in excellent yields as diastereomeric mixtures with a diastereomeric ratio (d.r.) near 1:1 (Table 1).[16] 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 Et_2Zn 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 (%)[a]	d.r.[a]	product	yield (%)[b]	e.e. (%)[c]
1	**6a**	H	Et	**7a**	95	10:1	**8a**	79	92 (-)
2	**6a**	H	Me	**7b**	99	10:1	**8b**	89	49 (+)
3	**6a**	H	Bu	**7c**	92	12:1	**8c**	63	88 (-)
4	**6b**	8-OMe	Et	**7d**	99	10:1	**8d**	84	90 (+)
5	**6b**	8-OMe	Me	**7e**	99	10:1	**8e**	57	37 (+)
6	**6c**	6-OMe	Et	**7f**	90	1:1	**8f**	49	16 (+)
7	**6d**	6-Br	Et	**7g**	97	10:1	**8g**	58	30 (+)
8	**6d**	6-Br	Me	**7h**	99	15:1	**8h**	47	40 (-)
9	**6e**	6-Me	Et	**7i**	98	2:1	**8i**	48	30 (+)
10	**6e**	6-Me	Me	**7j**	90	20:1	**8j**	77	36 (-)

[a]Conversion (conv) and diastereomeric ratio (d.r.) were determined by ^{1}H NMR, [b]Isolated yield, [c]Determined by chiral HPLC (Daicel Chiralcel OJ, hexane-iPrOH 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.[17] The conjugate addition of Et_2Zn to **6a** gave, after the usual workup with saturated NH_4Cl, 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).[16,18] 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_2Zn 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_2Cl_2 or THF as solvent decreased the e.e. to 50%.

Variation of both the dialkylzinc reagent (Et_2Zn, Me_2Zn, or Bu_2Zn) 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).[19] Excellent e.e.'s were also obtained in the Bu_2Zn addition to **6a** (88%) and in the Et_2Zn addition to 8-MeO-substituted substrate **6b** (90%). In general, the addition of Me_2Zn 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 $Cu(TfO)_2$/**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

1. 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.
2. Berrisford, D.J.; Bolm, C.; Sharpless, K.B. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1059-1070.
3. 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.
4. For a review of functionalized zinc reagents, see: Knochel, P.; Singer, R.D. *Chem. Rev.* **1993**, *93*, 2117-2188.
5. (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.
6. For a brief review of recent progress, see: Krause, N. *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 283-285.
7. Sewald, N.; Wendisch, V. *Tetrahedron: Asymmetry* **1998**, *9*, 1341-1344.
8. Shipchandler, M.T. *Synthesis* **1979**, 666-686.
9. Seebach, D.; Colvin, E.W.; Lehr, F.; Weller, T. *Chimia* **1979**, *33*, 1-18.
10. (a) Duthaler, R.O. *Tetrahedron* **1994**, *50*, 1539-1650; (b) Williams, R.M. *Synthesis of Optically Active α-Amino Acids*, Pergamon Press, Oxford, **1989**.
11. Wirth, T. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 225-227.
12. Keller, E.; Veldman, N.; Spek, A.L.; Feringa, B.L. *Tetrahedron: Asymmetry* **1997**, *8*, 3403-3413.
13. Fornicola, R.S.; Oblinger, E.; Montgomery, J. *J. Org. Chem.* **1998**, *63*, 3528-3529.
14. Sifniades, S. *J. Org. Chem.* **1975**, *40*, 3562-3566.
15. Lehnert, W. *Tetrahedron* **1972**, *28*, 663-666.
16. Note that the α-position with respect to the ester and nitro groups is prone to epimerization.
17. Dauzonne, D; Royer, R. *Synthesis* **1983**, 836-837.
18. Purification of compounds **7** by chromatography on SiO_2 or Al_2O_3 was hampered by product decomposition. Analytically pure **7a** and **7b** were obtained by crystallization.
19. All new compounds were fully characterized by ^1H and ^{13}C NMR and by HRMS.