Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 46 (2005) 1529–1532
Tetrahedron Letters

Cu-catalysed asymmetric 1,4-addition of Me_3Al to nitroalkenes. Synthesis of (+)-ibuprofen

Damien Polet and Alexandre Alexakis*

Department of Organic Chemistry, University of Geneva, 30 Quai Ernest Ansermet, CH-1211 Geneva, Switzerland

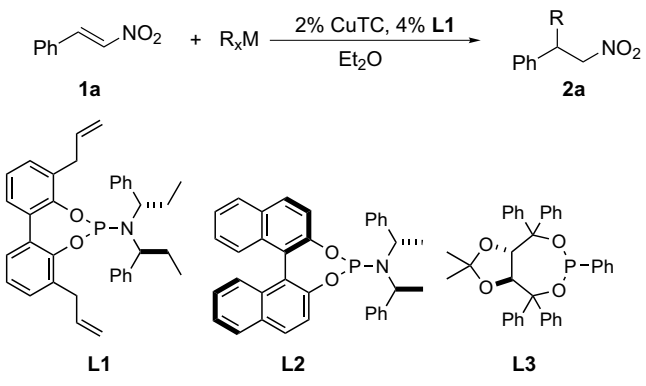
Received 9 December 2004; revised 22 December 2004; accepted 5 January 2005
Available online 20 January 2005

Abstract—Trimethylaluminium undergoes enantioselective (ee up to 93%) copper-catalysed Michael addition to various nitroalkenes. Copper thiophenecarboxylate (CuTC) (2 mol %) and 4 mol % of a chiral phosphoramidite ligand are sufficient for a complete and clean reaction. The synthesis of (+)-ibuprofen is described with 82% ee.

The nitro group is of remarkable synthetic importance, as it can be readily available and the synthetic intermediates containing it can be transformed to a wide variety of valuable organic compounds such as aldehydes, amines, carboxylic acids, nitriles and nitrile oxides.[1] Therefore, it is of great interest to be able to get access to optically enriched molecules containing this moiety. The asymmetric conjugate addition reaction[2] is one of the widely used method for this purpose as it allows the enantioselective creation of carbon–carbon bonds from nitroalkenes.[3] Both rhodium[3a,b] and copper[3c–o] have been found to efficiently catalyse this reaction, the first one with aryl boronates, the latter with dialkylzinc reagents. In the copper-catalysed version, several dialkylzinc reagents have been added to a variety of nitroalkenes, bearing aryl or alkyl substituents, functionalized or not. The only difficult group to introduce is the methyl group, though it is the most valuable from a synthetic point of view. Although excellent results have been obtained by Hoveyda and Feringa,[4] the poor reactivity of dimethylzinc generally results either in lower enantioselectivity or lower yields.

We have recently disclosed new phosphoramidite ligands, which afforded the highest reported enantioselectivities (up to 96%) in the copper-catalysed conjugate addition of diethylzinc to nitrostyrene derivatives.[5] Particularly, ligand **L1** (Table 1) was found to be the best ligand for substrates such as nitroalkenes under our classical conditions, in Et_2O with 2% copper thiophenecarboxylate (CuTC) and 4% chiral ligand (Table 1, entry 1). In comparison, ligands **L2**[3d] (entry 2) and **L3**[3f] (entry 4) gave moderate to good ee's. However, using **L1**, the less reactive dimethyl zinc did not allow us to get good enantioselectivities (entries 4 and 5), even at −15 °C (entry 6).

Recently, triorganoaluminium reagents have been shown to be good candidates for the asymmetric copper-catalysed conjugate addition, in place of dialkylzincs.[6] The increased Lewis acidity of Al versus Zn allows the reaction to occur on more demanding systems. There is also one example of the use of trimethylaluminium copper-catalysed 1,4-addition to β-nitroacrylates, which constitute a particular class of nitroolefins.[7]



Keywords: Copper; Aluminium; Nitro; Conjugate addition; Asymmetry; Ibuprofen.
* Corresponding author. Tel.: +41 22 379 65 22; fax: +41 22 379 32 15; e-mail: alexandre.alexakis@chiorg.unige.ch

0040-4039/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2005.01.007

Table 1. Addition of different organometallic species to nitrostyrene

Entry	R_xM	Ligand	Condition[a]	Temp. (°C)	Yield (%)[b]	ee%[c]
1[d]	Et_2Zn	**L1**	A	−30	(>99)	95(*S*)
2[e]	Et_2Zn	**L2**	A[f]	−78	(90)	48(*S*)
3[g]	Et_2Zn	**L3**	A[f]	−30	100	81(*S*)
4	Me_2Zn	**L1**	A	−30	(0)	Nd
5	Me_2Zn	**L1**	A	0	(63)	42(*S*)
6	Me_2Zn[h]	**L1**	A	−15	(71)	59(*S*)
7	Me_3Al	**L1**	B	−30	61	78(*S*)

[a] Method A: CuTC (0.008 mmol) and ligand (0.016 mmol) were dissolved in diethylether (2 mL) and stirred at room temperature for 0.3 h. The mixture was then cooled to the indicated temperature and dialkylzinc (0.49 mmol, 2 M in hexane) was added dropwise before nitrostyrene (0.4 mmol, in solution in 0.5 mL toluene). The reaction mixture was stirred for 16 h. Method B: CuTC (0.008 mmol) and ligand (0.016 mmol) were dissolved in diethylether (2 mL) and stirred at room temperature for 0.3 h prior to nitrostyrene addition (0.4 mmol, in solution in 0.5 mL toluene). The mixture was then cooled to the indicated temperature and Me_3Al (1 mmol, 2 M in toluene) was added dropwise within 1 min. The reaction mixture was stirred for 16 h at the indicated temperature.
[b] Isolated yields. In parentheses, conversion measured by GC.
[c] Measured by chiral GC or SFC. In parentheses, absolute configuration.
[d] Taken from Ref. 5a.
[e] Taken from Ref. 3d.
[f] In toluene with $Cu(OTf)_2$ as copper salt.
[g] Taken from Ref. 3f.
[h] 10 equiv of dimethylzinc.

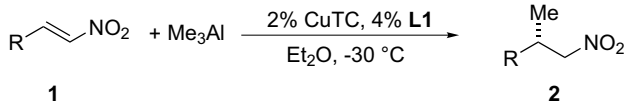
In order to explore more thoroughly the behaviour of triorganoaluminium species, we wondered if trimethylaluminium could afford good enantioselectivities on simple unactivated nitroalkenes. By using 2.5 equiv of trimethylaluminium at −30 °C and slightly changing the experimental conditions, we were able to introduce the methyl group in good yield (61%) and good enantioselectivity (78%, Table 1, entry 7).

Following this successful attempt, we screened several other nitroalkenes as well. The results are shown in Table 2. The electron-donating properties of the substituent on the phenyl moiety gave proportional improvement in terms of enantioselectivity: the *para*-methyl improved to 86% and the *para*-methoxy to 93% ! (entries 2 and 3). A contrario, an electron-withdrawing substituent such as *para*-chloro was deleterious in terms of ee (entry 4). Heteroaryl (thienyl and furyl) substrates could also give good ee's (entries 5 and 6). In addition to aryl substituted substrates, an alkyl substituted one was tested (cyclohexyl, entry 7) and the corresponding 1,4-adduct was obtained with an ee of 78%, identical to nitrostyrene. The acetal substituent also gave an improved ee (88%, entry 8) compared to the nitrostyrene, confirming that an electron-rich group should be attached to the nitroolefin.

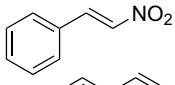
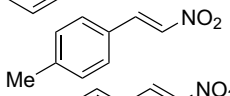
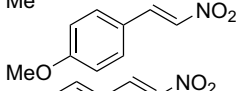
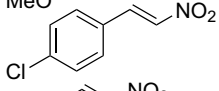
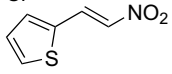
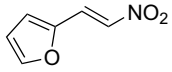
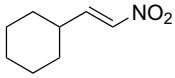
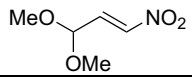
The nitro group could be transformed into many other functionalities. The reduction to the amino group has been described on substrates **2**, with Raney nickel.[8] As another example of the numerous transformations described in the literature to convert the nitro group,[1a] the oxidation of the primary nitroalkanes to the corresponding carboxylic acids was envisaged (Scheme 1).

Using the Mioskowski's variant of Kornblum's transformation,[9] we were able to do this oxidation without racemization, affording **3** in nearly quantitative yield and with complete conservation of the enantiomeric excess. With this transformation in hands, we thought that the whole sequence could be profitable to the synthesis of the molecules belonging to the profen family.

Table 2. Addition of trimethylaluminium onto various nitroalkenes[a]

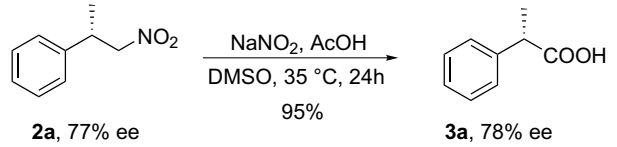


1 **2**

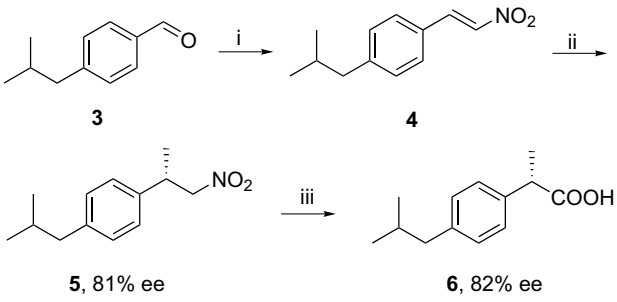
Entry	Substrate	Yield (%)[b]	ee (%)[c]
1		61	78 (*S*)
2		66	86 (−)
3		60	93 (−)
4		73	56 (−)
5		73	91 (−)
6		50	84 (−)
7		77	78 (+)
8		64	88 (−)

[a] Cond. CuTC (0.008 mmol) and ligand (0.016 mmol) were dissolved in diethylether (2 mL) and stirred at room temperature for 0.3 h prior to nitroalkene addition (0.4 mmol, in solution in 0.5 mL toluene). The mixture was then cooled to −30 °C and Me_3Al (1 mmol, 2 M in toluene) was added dropwise within 1 min. The reaction mixture was stirred for 16 h at −30 °C.
[b] Isolated yields after silicagel chromatography.
[c] Measured by chiral SFC or chiral GC.

This sequence was applied to the synthesis of (+)-ibuprofen, a well-known nonsteroidal anti-inflammatory



Scheme 1. Oxidation of nitroalkane **2a** into carboxylic acid according to Ref. 9b.



Scheme 2. Reagents and conditions: (i) $MeNO_2$, $AcONH_4$, AcOH, 55%; (ii) 2.5 equiv Me_3Al, 2 mol % CuTC, 4 mol % **L1**, Et_2O, −30 °C, 81%; (iii) $NaNO_2$, AcOH, DMSO, 35 °C, 80%.

drug (NSAID) (Scheme 2).[10] We had first to synthesize the corresponding nitroolefin from the commercially available 4-isobutylbenzaldehyde **3**.[11] The one-pot Henry condensation followed by dehydration afforded **4** in 55% yield after distillation. We then proceeded to the copper-catalysed 1,4-addition of trimethylaluminium onto **4** affording **5** in good yield (81%) as well as with acceptable enantioselectivity (ee 82%). The transformation of the primary nitroalkane **5** to (+)-ibuprofen **6** (80%, ee 82%) was then achieved following the elegant literature procedure.[9b]

In summary, we have shown that trimethylaluminium could advantageously replace dimethylzinc in the copper-catalysed conjugate addition to a wide variety of nitroalkenes. Yields and enantioselectivities are generally good to excellent (up to 93%). Coupled with the oxidative transformation of the nitro group, the sequence could provide with an excellent entry to the family of aryl propionic acid derivatives.

Acknowledgements

The authors thank the BASF company for the generous gift of chiral amines, the Swiss National Research Foundation No. 20-068095.02 and COST action D24/0003/01 (OFES contract No. C02.0027) for financial support.

References and notes

1. (a) Ono, N. *The Nitro Group in Organic Synthesis*; Wiley-VCH: New York, 2001; (b) Berner, O. M.; Tedeschi, L.; Enders, D. *Eur. J. Org. Chem.* **2002**, 1877–1894.
2. Key reviews on 1,4-addition: (a) Rossiter, B. E.; Swingle, N. M. *Chem. Rev.* **1992**, *92*, 771–806; (b) Feringa, B. L. *Acc. Chem. Res.* **2000**, *33*, 346–353; (c) Tomioka, K.; Nagaoka, Y. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 2000; p 1105; (d) Sibi, M. P.; Manyem, S. *Tetrahedron* **2000**, *56*, 8033–8061; (e) Krause, N.; Hoffmann-Röder, A. *Synthesis* **2001**, 171–196; (f) Alexakis, A.; Benhaim, C. *Eur. J. Org. Chem.* **2002**, 3221–3236; (g) Alexakis, A. In *Methodologies in Asymmetric Catalysis*, Malhotra, S. V., Ed. ACS Symposium Series 880; Washington, 2004; Chapter 4, pp 43–59.
3. For Rh-catalysed 1,4-addition of aryl boronates onto nitroalkenes, see: (a) Hayashi, T. *Synlett* **2001**, 879–887; (b) Hayashi, T.; Senda, T.; Ogasawara, M. *J. Am. Chem. Soc.* **2000**, *122*, 10716–10717; For Cu-catalysed 1,4-addition of alkylzinc reagents onto nitroalkenes, see: (c) Alexakis, A.; Vastra, J.; Mangeney, P. *Tetrahedron Lett.* **1997**, *38*, 7745–7748; (d) Sewald, N.; Wendisch, V. *Tetrahedron: Asymmetry* **1998**, *9*, 1341–1344; (e) Versleijen, J. P. G.; Van Leusen, A. M.; Feringa, B. L. *Tetrahedron Lett.* **1999**, *40*, 5803–5806; (f) Alexakis, A.; Benhaim, C. *Org. Lett.* **2000**, *2*, 2579–2581; (g) Ongeri, S.; Piarulli, U.; Jackson, R. F. W.; Gennari, C. *Eur. J. Org. Chem.* **2001**, 803–807; (h) Alexakis, A.; Rosset, S.; Allamand, J.; March, S.; Guillen, F.; Benhaim, C. *Synlett* **2001**, 1375–1378; (i) Alexakis, A.; Benhaim, C.; Rosset, S.; Humam, M. *J. Am. Chem. Soc.* **2002**, *124*, 5262–5263; (j) Duursma, A.; Minnaard, A. J.; Feringa, B. L. *Tetrahedron* **2002**, *58*, 5773–5778; (k) Kang, J.; Lee, J. H.; Lim, D. S. *Tetrahedron: Asymmetry* **2003**, *14*, 305–315; (l) Alexakis, A.; Winn, C. L.; Guillen, F.; Pytkowicz, J.; Roland, S.; Mangeney, P. *Adv. Synth. Catal.* **2003**, *345*, 345–348; (m) Rimkus, A.; Sewald, N. *Synthesis* **2004**, 135–146; (n) Arink, A. M.; Braam, T. W.; Keeris, R.; Jastrzebski, J. T. B. H.; Benhaim, C.; Rosset, S.; Alexakis, A.; Van Koten, G. *Org. Lett.* **2004**, *6*, 1959–1962; (o) Choi, H.; Hua, Z.; Ojima, I. *Org. Lett.* **2004**, *6*, 2689–2691.
4. For successful attempts, see: (a) Luchaco-Cullis, C. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 8192–8193; (b) Duursma, A.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2003**, *125*, 3700–3701; (c) Mampreian, D. M.; Hoveyda, A. H. *Org. Lett.* **2004**, *6*, 2829–2832.
5. (a) Alexakis, A.; Polet, D.; Rosset, S.; March, S. *J. Org. Chem.* **2004**, *69*, 5660–5667; (b) Alexakis, A.; Polet, D.; Benhaim, C.; Rosset, S. *Tetrahedron: Asymmetry* **2004**, *15*, 2199–2203.
6. (a) Woodward, S.; Fraser, P. K. *Chem. Eur. J.* **2003**, *9*, 776–783; (b) Liang, L.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2002**, *13*, 1393–1396; (c) Alexakis, A.; D'Augustin, M.; Palais, L. *Angew. Chem., Int. Ed.* **2005**, *44*, in press.
7. Recently, Wendisch reported the use of trimethylaluminium in the copper-catalysed 1,4-addition to nitro acrylates: Eilitz, U.; Lessmann, F.; Seidelmann, O.; Wendisch, V. *Tetrahedron: Asymmetry* **2003**, *14*, 3095–3097.
8. Schafer, H.; Seebach, D. *Tetrahedron* **1995**, *51*, 2305–2324.
9. (a) Kornblum, N.; Blackwood, R. K.; Mooberry, D. D. *J. Am. Chem. Soc.* **1956**, *78*, 1501–1504; (b) Matt, C.; Wagner, A.; Mioskowski, C. *J. Org. Chem.* **1997**, *62*, 234–235.
10. For a review on ibuprofen and congeners syntheses see: Rieu, J.-P.; Boucherle, A.; Cousse, H.; Mouzin, G. *Tetrahedron* **1986**, *42*, 40954131.
11. Typical procedure: CuTC (0.021 g, 0.110 mmol) and **L1** (0.121 g, 0.221 mmol) were dissolved in diethylether (28 mL) at room temperature. The mixture was stirred for 0.3 h and charged with nitroalkene **4** (1.132 g, 5.515 mmol) before being cooled down to −35 °C (cryostat). Due to the scale of the reaction, trimethylaluminium (13.8 mmol, 2 M solution in toluene) was added dropwise over 4 h via a syringe pump. The reaction mixture was

stirred for an additional 12 h at −35 °C. The flask was removed from the cooling bath, and 5 mL of an aq satd solution of NH_4Cl were added dropwise, followed by 10 mL of a 10% aq solution of HCl. After the solution reached room temperature, the latter was extracted with diethylether. The organic phase was dried over magnesium sulfate, concentrated and the crude product was purified by chromatography (pentane/diethylether 7:3) to afford 0.993 g (81%) of **5** as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.14 (d of AB sys, 2H, J = 8.6 Hz), 7.11 (d of AB sys, 2H, J = 8.6 Hz), 4.54 (dd, 1H, J = 11.9, 7.1 Hz), 4.46 (dd, 1H, J = 11.8, 8.3 Hz), 3.61 (m, 1H), 2.45 (d, 2H, J = 7.1 Hz), 1.85 (sept, 1H, J = 6.8 Hz), 1.37 (d, 3H, J = 6.8 Hz), 0.90 (d, 6H, J = 6.6 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 141.1, 138.1, 129.7, 126.6, 82.1, 45.0, 38.3, 30.2, 22.4, 18.8. MS (EI) 221 ($M^{+\cdot}$, 8), 174 (81), 147 (13), 131 (100), 117 (58), 105 (19), 91 (45). HRMS (HR) calcd for $[C_{13}H_{19}NO_2Na]^+$ 244.13135, found 244.13067. $[\alpha]_D^{20}$ −40.8 (c = 1.165, $CHCl_3$) for 81% ee. Ee was measured by chiral SFC (Chiralcel OD-H column, 1% MeOH 2 mL/min): *S*-(−) enantiomer: 3.42′; *R*-(+) enantiomer: 3.66′.

(+)-Ibuprofen (**6**). Compound **5** (0.993 g, 4.487 mmol), sodium nitrite (0.93 g, 13.5 mmol) and acetic acid (2.6 mL, 44.9 mmol) were dissolved in 10 mL of freshly distilled dimethylsulfoxide. The resulting mixture was stirred at 35 °C for 24 h, before being acidified with a 10% aqueous solution of HCl. The product was then extracted with diethylether and the combined extracts dried over sodium sulfate and concentrated in vacuo. Purification by distillation under reduced pressure (Kugelrohr 0.2 mmHg, 140 °C) afforded 0.742 g (80 %) of (+)-ibuprofen **6** as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 10.0–8.0 (br s, 1H), 7.22 (d, 2H, J = 8.1 Hz), 7.10 (d, 2H, J = 8.1 Hz), 3.71 (q, 1H, J = 7.1 Hz), 2.45 (d, 2H, J = 7.0 Hz), 1.83 (sept., 1H, J = 6.8 Hz), 1.50 (d, 3H, J = 7.3 Hz), 0.89 (d, 6H, J = 6.8 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 180.8, 140.9, 137.0, 129.4, 127.3, 45.1, 45.0, 30.2, 22.4, 18.1. MS (EI) 207 (8), 206 ($M^{+\cdot}$, 46), 163 (100), 161 (95), 119 (65), 115 (16), 107 (43), 91 (68), 77 (14). MS (HR) calcd for $[C_{13}H_{18}O_2Na]^+$ 229.1204, found 229.1199. $[\alpha]_D^{20}$ +38.5 (c = 1.075, $CHCl_3$) for 82% ee, lit. $[\alpha]_D^{20}$ +54.5 (c = 1.1, $CHCl_3$) for 97.2% ee (Harrington-Frost, N.; Leuser, H.; Calaza, M. I.; Kneisel, F. F.; Knochel, P. *Org. Lett.* **2003**, *5*, 2111–2114). Ee was measured by chiral SFC (Chiralcel OJ column, 5% MeOH during 2 min, then 1%/min 2 mL/min): *R*-(−) enantiomer: 3.31′. *S*-(+) enantiomer: 3.60′.