Asymmetric Michael addition of a glycine synthon to methyl methacrylate, mediated by disodium TADDOLate

Yuri N. Belokon',*[a] Konstantin A. Kochetkov,[a] Tat'yana D. Churkina,[a] Nikolay S. Ikonnikov,[a] Svetlana A. Orlova,[a] Valeriy V. Smirnov[b] and Alexey A. Chesnokov[b]

[a] *A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, 117813 Moscow, Russian Federation. Fax: +7 095 135 5085*

[b] *Higher Chemical College, Russian Academy of Sciences, 125820 Moscow, Russian Federation*

The disodium salt of (4*R*,5*R*)-(TADDOL), **3**, can be used as a mediator in the asymmetric Michael reaction, *e.g.* 1,4-addition of a glycine synthon **1** to methyl methacrylate **2**, mediated by **3** (10–100 mol%), gives a diastereoisomeric excess of the corresponding product **4** up to 65% and an enantiomeric purity *ca.* 28%; (2*S*,4*R*)-4-methylglutamic acid (ee ≥ 85%), **6**, was obtained starting from (2*S*,4*R*)-**4** (ee 28%) through the recrystallization and decomposition of the latter.

Whereas chiral amides are used extensively, particularly in the enantioselective Michael reaction,[1] there are hardly any applications of chiral alkali metal alkoxides in asymmetric synthesis.[2] These compounds are, however, simple and readily available from the corresponding alcohols, and as such are promising reagents for catalytic asymmetric synthesis, serving as chiral base catalysts. Only recently it was shown for the first time that potassium alkoxides of chiral amino alcohols can be used successfully as catalysts for enantioselective dehydrohalogenation.[3]

We present here preliminary results of our research on the use of a disodium alkoxide of a chiral diol (4*R*,5*R*)-2,2-dimethyl-α,α,α′,α′-tetraphenyl-1,3-dioxolane-4,5-dimethanol (TADDOL)[4] in an asymmetric Michael reaction.

An achiral glycine synthon **1** – a planar nickel(II) Schiff's base complex derived from glycine and *N*-(2-pyridinecarbonyl)-*o*-aminobenzophenone (Scheme 1, A; the two carbon atoms of the glycine moiety are marked as C1 and C2, see the Scheme) was used as a Michael donor. Compound **1** can be easily synthesized in high yield by a two-step procedure from readily available starting materials: α-picolinic acid, *o*-amino-benzophenone, glycine and inorganic nickel(II) salt.[5,6] Compound **1** can be considered as a glycine derivative with both amino and carboxylic groups protected. In addition, the C–H bonds of the glycine moiety in **1** are activated, so that it exhibits rather high CH-acidity (for such complexes pK_a ~ 19, DMSO).[7] Thus, **1** can be readily alkylated and used as a Michael donor at the C2 centre by using bases like MOH and MOAlk (M = Na, K, *etc.*).[5] It is also noteworthy that compound **1** and its derivatives are diamagnetic (which allows us to use NMR spectroscopy) and coloured, which is very convenient for the chromatographic separation and purification of the reaction products.

We have found that sodium alkoxides of simple alcohols which contain only one OH-group (*e.g.* MeOH, Pr^{i}OH, L-menthol), as well as TADDOL monosodium alkoxide, are very poor catalysts in the Michael addition reaction of substrate **1** to methyl methacrylate **2** under standard conditions (CH_2Cl_2, argon atmosphere, room temperature).

At the same time, disodium alkoxide of TADDOL **3**, generated *in situ* by treating TADDOL[†] with 2 equiv. of NaH, was found to be an efficient catalyst for the reaction. In the presence of catalyst **3** (10–100 mol%) the addition of CH-acid **1**[‡] to Michael acceptor **2** (Scheme 1, A) occurs readily, giving at room temperature a pure mono 1,4-addition product which, possessing two asymmetric carbon atoms C2 and C4, exists as two diastereoisomers **4**[§] and **5**,[§] each consisting of a pair of enantiomers. In the Scheme 1 diastereoisomers **4** and **5** are represented as only one enantiomer: (2*S*,4*R*)-**4** and (2*S*,4*S*)-**5**. Both diastereoisomers can be easily separated by preparative TLC (SiO_2 from Merck; $CHCl_3$–EtOAc, 1:1, v/v). The absolute configurations of the nickel(II) complexes **4** (and **5** by default) were established by enantiomeric analysis of the amino acid recovered from the complex **4**.[¶] In the course of the reaction diastereoisomer **4** is formed predominantly, but on increasing the ratio of catalyst **3** from 10 to 100 mol% the diastereoisomeric excess of **4** falls from 65% to 40%. Special experiments with individual scalemic **4** and **5** have proved that the diastereoselectivity of the reaction is reduced by increasing the concentration of the catalyst because of epimerization of the product at the asymmetric centre C2 which slowly takes place upon action of the base **3**. The enantioselectivity of the addition of **1** to **2** was established by comparing the values of the optical rotation of the main diastereoisomer **4** and the calculated value of $[\alpha]_D$ for the enantiomerically pure (2*S*,4*R*)-**4**.[¶] It was found that 1,4-addition of synthon **1** to methyl methacrylate **2**, catalysed by chiral alkoxide **3**, occurs in an enantioselective manner and the enantiomeric excess of (2*S*,4*R*)-**4** (the major diastereoisomer of the addition product) is 20% ee in the presence of 10 mol% of the catalyst and 28% ee in the case of 100 mol% of the catalyst. No attempts were made to optimize the chemical and optical yields by changing the reaction conditions or by using other metals instead of sodium.

The addition product isolated, (2*S*,4*R*)-**4**, with ee 20–28% was then enantiomerically enriched up to ≥ 85% ee by means of a simple recrystallization from MeOH–$CHCl_3$ (Scheme 1, B), adding Et_2O as a precipitating agent. Racemic (±)-**4** crystallized from the solution, so that the mother liquor became enriched

† (4*R*,5*R*)-2,2-Dimethyl-α,α,α′,α′-tetraphenyl-1,3-dioxolane-4,5-dimethanol (TADDOL) was prepared from (2*R*,3*R*)-tartaric acid according to the described procedure:[4] mp 196–198 °C; $[\alpha]_D^{20}$ –61.5° (*c* = 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, δ): 1.05 (s, 6H, CH_3), 4.01 (s, 2H, CH), 7.3–7.5 (m, 20H, ArH). Lit.,[6] mp 193–195 °C; $[\alpha]_D^{RT}$ –66.7° (*c* = 1, $CHCl_3$).

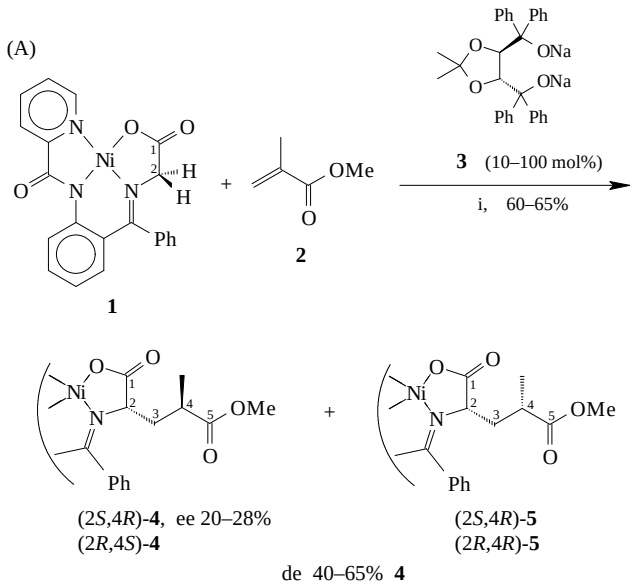
‡ The procedure was elaborated using 0.1–5.0 mmol (0.04–2.08 g) of the CH-acid **1**.

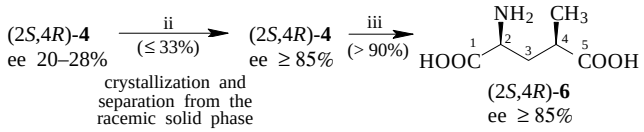
§ Analytical and spectral data for compounds **4** and **5**:

For (±)-**4**: mp ≥ 250 °C (decomp.). ^{1}H NMR ($CDCl_3$, δ): 0.86 (d, 3H, CH_3), 1.56 (m, 1H, CH_2), 2.56 (m, 1H, CH_2), 3.25 (m, 1H, MeCH), 3.50 (s, 3H, OCH_3), 3.99 (m, 1H, CH), 6.76–8.89 (m, 13H, ArH). UV λ_{max}/nm (lg ε) ($CHCl_3$): 306 (3.98); 459 (3.65). Found: C 60.82; H 4.73; N 8.34; Ni 11.14%. Calc. for $C_{26}H_{23}N_3O_5Ni$: C 60.50; H 4.49; N 8.14; Ni 11.37%.

For (±)-**5**: mp ≥ 278 °C (decomp.). ^{1}H NMR ($CDCl_3$, δ): 1.12 (d, 3H, CH_3), 2.04 (m, 1H, CH_2), 2.38 (m, 1H, CH_2), 2.91 (m, 1H, MeCH), 3.33 (s, 3H, OCH_3), 4.00 (m, 1H, CH), 6.70–8.83 (m, 13H, ArH). UV λ_{max}/nm (lg ε) ($CHCl_3$): 305 (3.98); 458 (3.65). Found: C 59.70; H 4.53; N 8.28; Ni 11.99%. Calc. for $C_{26}H_{23}N_3O_5Ni$: C 60.50; H 4.49; N 8.14; Ni 11.37%.

¶ For the enantiomerically pure (2*S*,4*R*)-**4** $[\alpha]_D^{20}$ +3074° (*c* = 0.02, $CHCl_3$) was calculated after the recovery of (2*S*,4*R*)-4-methylglutamic acid **6** from a sample of (2*S*,4*R*)-**4**, with $[\alpha]_D^{20}$ +2628° (*c* = 0.02, $CHCl_3$). The absolute configuration (2*S*,4*R*) of the sample of **6** and its ee (85.5%) were established by enantiomeric GLC (Chirasil-Val type phase, fused silica capillary column 40 m × 0.23 mmID; column temperature 165 °C; carrier gas He: 1.75 bar) by means of a comparison with standard samples of all the stereoisomers of 4-methylglutamic acid (Pr^i ester, *N*-trifluoroacetyl-derivatives), whose absolute configurations were established earlier.[8]





Scheme 1 *Reagents and conditions*: i, combination of **1**:**2** = 1:3, CH_2Cl_2, Ar, room temperature, 15–20 min; ii, MeOH–$CHCl_3$, reflux, then Et_2O to precipitate racemic (±)-**4**, enantiomerically enriched (2*S*,4*R*)-**4** remains in the mother liquor; iii, HCl (aq.), reflux, then NH_3 (aq.).

with the enantiomer (2*S*,4*R*)-**4**. After being separated from the mother liquor (2*S*,4*R*)-**4** (ee ≥ 85%; yield ≤ 33%) was decomposed by refluxing in conc. HCl followed by separation (according to the literature procedure[8]) of *N*-(2-pyridinecarbonyl)-*o*-aminobenzophenone (which can be recycled for the preparation of the initial compound **1**) and (2*S*,4*R*)-4-methylglutamic acid **6** (ee ≥ 85%).

Thus, we have shown that chiral sodium alkoxides can be used as catalysts in the asymmetric Michael reaction. The use of substrate **1** as a protected and activated glycine synthon opens up a new and promising approach to the synthesis of optically active nonproteinogenic α-amino acids (derivatives of glutamic acid and substituted prolines) *via* the catalytic asymmetric Michael addition of **1** to α,β-unsaturated carbonyl compounds or other substrates containing activated C=C bonds.

This work was supported by the INCO-Copernicus program (grant no. JCIS-CT96-0722).

References

1 E. Juaristi, A. K. Beck, J. Hansen, T. Matt, T. Mukhopadhyay, M. Simson and D. Seebach, *Synthesis*, 1993, 1271.
2 (*a*) *Asymmetric Synthesis*, ed. J. D. Morrison, Academic Press, New York, London, Paris, San Diego, San Francisco, Sao Paulo, Sydney, Tokyo, Toronto, 1985, vol. 5; (*b*) J. Vadecard, J. C. Plaquevent, L. Duhamel, P. Duhamel and L. Toupet, *J. Org. Chem.*, 1994, **59**, 2285.
3 M. Amadji, J. Vadecard, J. C. Plaquevent, L. Duhamel and P. Duhamel, *J. Am. Chem. Soc.*, 1996, **118**, 12483.
4 A. K. Beck, B. Bastani, D. A. Plattner, W. Petter, D. Seebach, H. Braunschweiger, P. Gysi and L. L. Vecchia, *Chimia*, 1991, **45**, 238.
5 Yu. N. Belokon', V. I. Maleev, T. F. Savel'eva, N. S. Garbalinskaya, M. B. Saporovskaya, V. I. Bakhmutov and V. M. Belikov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1989, 631 (*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1989, **38**, 557).
6 Yu. N. Belokon', A. G. Bulychev, S. V. Vitt, Yu. T. Struchkov, A. S. Batsanov, T. V. Timofeeva, V. A. Tsyryapkin, M. G. Ryzhov, L. A. Lysova, V. I. Bakhmutov and V. M. Belikov, *J. Am. Chem. Soc.*, 1985, **107**, 4252.
7 M. I. Terekhova, Yu. N. Belokon', V. I. Maleev, N. I. Chernoglazova, K. A. Kochetkov, V. M. Belikov and E. S. Petrov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1986, 905 (*Bull. Acad. Sci. USSR, Div. Chem. Sci.*,1986, **35**, 824).
8 Yu. N. Belokon', A. G. Bulychev, M. G. Ryzhov, S. V. Vitt, A. S. Batsanov, Yu. T. Struchkov, V. I. Bakhmutov and V. M. Belikov, *J. Chem. Soc., Perkin Trans. 1*, 1986, 1865.

Received: Moscow, 5th March 1997
Cambridge, 24th April 1997; Com. 7/01772C