Pergamon

Tetrahedron: *Asymmetry* 10 (1999) 1723–1728

TETRAHEDRON: *ASYMMETRY*

# Enantiomerically enriched (*R*)- and (*S*)-α-methylphenylalanine via asymmetric PTC *C*-alkylation catalysed by NOBIN

Yuri N. Belokon',[a,*] Konstantin A. Kochetkov,[a] Tatiana D. Churkina,[a] Nikolai S. Ikonnikov,[a] Stepan Vyskocil[b,*] and Henri B. Kagan[c,*]

[a]*A.N. Nesmeyanov Institute of Organo-Element Compounds, Russian Academy of Sciences, 117813, Moscow, Vavilov 28, Russia*

[b]*Charles University, Faculty of Science, Department of Organic Chemistry, 12840, Prague 2, Hlavova 2030, Czech Republic*

[c]*Université de Paris Sud. 91405, Orsay Cedex, Institut de Chimie Moléculaire d'Orsay, Laboratoire de Synthèse Asymétrique, Associated to CNRS, Paris, France*

Received 24 March 1999; accepted 12 May 1999

**Abstract**

Enantiopure 2-hydroxy-2′-amino-1,1′-binaphthyl (NOBIN) is shown to catalyse *C*-alkylation of aldimine Schiff's bases of alanine ester under phase-transfer catalysis conditions (solid NaOH or NaH, toluene, ambient temperature, 10% NOBIN). Using (*R*)-NOBIN, the final (*S*)-α-methylphenylalanine was obtained in up to 68% ee.

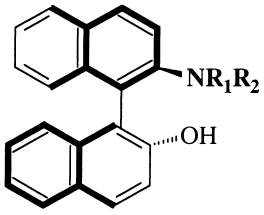

## 1. Introduction

Ion-pair-mediated reactions under phase-transfer conditions (phase-transfer catalysis, PTC) have been increasingly useful in organic synthesis since their introduction.[1] Until recently, there have been no successful applications of PTC conversions to catalytic asymmetric synthesis, except for a few cases involving the use of cinchona alkaloid-derived quaternary ammonium salts.[2] A significant improvement (ee higher than 90%) of the asymmetric alkylation of a glycine Schiff's base under PTC conditions using *N*-(9-anthracenylmethyl)-modified cinchonidinium salt as a catalyst and CsOH as a base has been reported by two independent groups.[3,4] Recently, O'Donnell introduced neutral, non-ionic phosphazene bases.[5] However, all the chiral catalysts of the quaternary ammonium-type are efficient only at low temperatures.[2–5] Thus, the search for novel, active and stable chiral phase-transfer catalysts continues.

Recently, we have found that a mixture of NaH and (4*R*,5*R*)-2,2-dimethyl-α,α,α′,α′-tetraphenyl-1,3-dioxolane-4,5-dimethanol (TADDOL), a chiral, hydrophobic, chelating diol, served as a chiral base

* Corresponding authors. E-mail: yubel@ineos.ac.ru

0957-4166/99/$ - see front matter 
*PII:* S0957-4166(99)00185-8



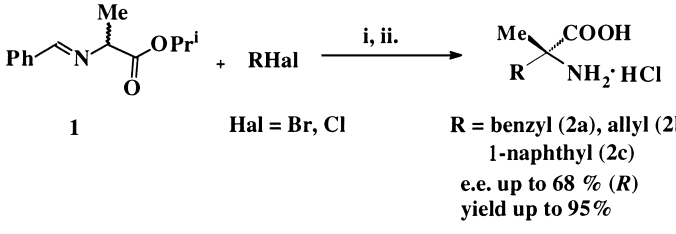

(*R*)- or (*S*)-**3**, $R_1 = R_2 = H$ (NOBIN)
(*S*)-**4**, $R_1 = H$, $R_2 = Me$
(*S*)-**5**, $R_1 = R_2 = Me$
(*R*)-**6**, $R_1 = H$, $R_2 = Pr^i$
(*R*)-**7**, $R_1 = H$, $R_2 = C_6H_{11}$
(*R*)-**8**, $R_1 = H$, $R_2 = Ad$
(*S*)-**9**, $R_1 = H$, $R_2 = Ph$
(*R*)-**10**, $R_1 = H$, $R_2 = (CH_2)_2OH$

Figure 1.

to induce asymmetry in Michael addition reaction of an achiral glycine derivative, resulting in the enantiomerically enriched (28% ee) γ-substituted glutamic acid.[6] Furthermore, we have shown that TADDOL can function as a chiral phase-transfer catalyst in the enantioselective alkylation. Thus, reaction of Schiff's bases **1**, derived from alanine esters and benzaldehyde, with active alkyl halides at ambient temperatures gave (after hydrolysis) α-methyl-α-amino acids **2** in good chemical yields and with ee reaching 93%.[7] TADDOL functioned in the reaction as a chelating agent for the alkali ions and thus made the ion-pair (formed by the corresponding carbanion and alkali ions) soluble in organic solvents. This modification combined the synthetic simplicity of the PTC-approach[2] with the rigidity of the mutual orientations of the chiral ligand and the substrate in the transition state of the reaction, similar to the case of transition metal complex catalysis.[8] We reasoned that another important class of organic chelating agents, for example 2,2′-disubstituted-1,1′-binaphthyls, might function in the same way, activating the ion-pair by the complexation of an alkali ion. To this end, we set out to use BINOL and NOBIN **3** and its derivatives **4**–**10**.[9] Herein, we report on the application of these ligands in a catalytic asymmetric synthesis of α-methyl substituted α-amino acids, that represent an important class of nonproteinogenic amino acids.[2b,10]

## 2. Results and discussion

The alkylation of the Schiff's base **1**, formed from benzaldehyde and racemic alanine isopropyl ester, served as a model reaction. The alkylations of the substrate with active alkyl bromides were conducted in toluene (rigorously dried before use) at ambient temperature (20°C) using NaH or solid NaOH (ground under argon) as bases. BINOL and NOBIN or NOBIN derivatives **4**–**10** (Fig. 1) were used as chiral promoters of the reaction. After 12 h the reaction was quenched with HCl (aq.) and the liberated amino ester was hydrolysed (see Scheme 1). The ee of the resulting amino acids **2** was established by chiral GLC.




Scheme 1. (i) NOBIN (0.1–1.0 equiv.), NaOH (4 equiv.) or NaH (2 equiv.), toluene, Ar, 20°C, 4 h; (ii) 6 N HCl (aq.): (1) 20°C, 15 min, extraction of NOBIN; (2) reflux

While BINOL proved to be inefficient as both the catalyst and asymmetry-inducing agent, compounds **3**–**10** proved to be more successful. The results are shown in Table 1.

Table 1
The asymmetric alkylation of alanine ester **1** mediated by aminonaphthols **3–10** [a]

| Run | catalyst **3-10** | $R_1(R_2)$ in **3-10** | base | catalyst (equiv) | yield .% [b] | e.e. of **2** (conf.) [c] |
|---|---|---|---|---|---|---|
| 1 | (*S*)-**3** | H(H) | NaH | 0.1 | 60 | 68 (*R*)[d] |
| 2 | (*S*)-**3** | H(H) | NaOH | 0.1 | >90 | 62(*R*) |
| 3 | (*S*)-**3** | H(H) | NaOH | 1.0 | 90 | 48(*R*) |
| 4 | (*R*)-**3** | H(H) | NaOH | 0.1 | >90 | 60(*S*) |
| 5[e] | (*S*)-**3** | H(H) | NaOH | 0.1 | >90 | 67(*R*) |
| 6[f] | (*S*)-**3** | H(H) | NaOH | 0.1 | 60 | 18(*R*) |
| 7[g] | (*S*)-**3** | H(H) | NaOH | 0.1 | 50 | 10(*R*) |
| 8 | (*S*)-**3** | H(H) | KOH | 0.1 | >90 | 43(*R*) |
| 9[h] | (*S*)-**3** | H(H) | NaOH | 0.1 | >90 | 46(*R*) |
| 10 | (*S*)-**4** | H(Me) | NaOH | 0.1 | >90 | 31(*R*) |
| 11 | (*S*)-**5** | Me(Me) | NaOH | 1.0 | 90 | 15(*R*) |
| 12 | (*R*)-**6** | H($Pr^i$) | NaOH | 0.1 | >90 | 8(*S*) |
| 13 | (*R*)-**7** | H(c-$C_6H_{11}$) | NaOH | 0.1 | >90 | 11(*S*) |
| 14 | (*R*)-**8** | H(2-Ad) | NaOH | 0.1 | >90 | 10(*S*) |
| 15 | (*S*)-**9** | H(Ph) | NaOH | 0.1 | >90 | 3(*R*) |
| 16 | (*R*)-**10** | H[$(CH_2)_2OH$] | NaOH | 0.1 | >90 | 17(*S*) |

[a] Concentration of the substrate was 0.4 M; the reactions were conducted at 20 °C over 12 h in toluene with the molar ratio of alanine derivatives **1**: BnBr : **3-10** : NaOH (NaH) = 1.0 : 1.2 : 0.1–1.0 : 4.0 (2.0); racemic **1** was used for the reactions. [b] Determined by $^1$H NMR, using leucine as an internal standard. [c] See experimental section for details of chiral GLC analysis of crude products. [d] After crystallization **2a** was obtained in 40% yield with >99% e.e. [e] Using allylbromide as an alkylating agent. [f] Using 1-chloromethylnaphthalene as an alkylating agent. [g] The reaction was conducted at 65 °C. [h] CuBr (1 mmol) was added to the reaction mixture.

As can be seen from the data, enantiopure NOBIN was efficient as an asymmetric promoter of the alkylation reactions (ee in the range of 48–68%) with both types of bases and active alkylating agents (see Table 1, runs 1–5). (*S*)-NOBIN furnished (*R*)-α-methylphenylalanine (α-MePhe) **2a**, (*R*)-α-allylalanine **2b** and (*R*)-α-(1-naphthylmethyl)alanine **2c** (runs 1–3, 5–7) whereas (*R*)-NOBIN gave (*S*)-**2a** (run 4).

The reaction occurs readily and does not give any side products under the standard conditions. The chemical yields were very high; toluene was found to be the best solvent for the reaction to proceed with good yield and ee. In hexane, the reaction was very slow and both ee of the product and its chemical yield were below several percents. The ee of the product depended strongly on the structure of the catalyst. The unsubstituted NOBIN gave **2a** with up to 68% ee (run 2). The enantiomeric purity of **2a** could then be increased substantially by crystallisation, as demonstrated previously.[7,11] The asymmetric allylation of the substrate with allyl bromide mediated by (*S*)-**3** under the standard PTC-conditions gave (*R*)-**2b** in good chemical yield and 67% ee (run 5), whereas reaction with 1-(chloromethyl)naphthalene gave (*R*)-**2c**

with 18% ee (run 6). The increase of the reaction temperature to 65°C resulted in the decrease of ee of the product (*R*)-**2a** (run 7).

The choice of the cation of the base employed also proved to be of importance. Thus, for example, LiOH was completely inactive, while with KOH the ee of the final (*R*)-**2a** dropped to 43% (run 8). Addition of 1 mmol of CuBr (run 9) to the reaction mixture also led to a decrease in ee of the product, while the addition of $MgSO_4$ had no effect.

The introduction of sterically demanding alkyl groups at the nitrogen of NOBIN brought a decrease in the ee of the final product **2a**. Thus, when (*S*)-**4**, the *N*-methyl derivative of NOBIN, was used (*R*)-**2a** was obtained with 31% ee (run 10). With the *N*,*N*-dimethyl derivative (*S*)-**5**, the product (*R*)-**2a** obtained was of 15% ee (run 11). *N*-Isopropyl (*R*)-**6**, *N*-cyclohexyl (*R*)-**7**, *N*-(2-adamantyl) (*R*)-**8** and *N*-phenyl (*S*)-**9** derivatives gave (*R*)- or (*S*)-**2a** in even lower enantioselectivities (runs 12–15). Catalyst (*R*)-**10** with an additional hydroxyethyl group gave (*S*)-**2a** of 17% ee (run 16). Thus, the introduction of substituents at the N-atom of NOBIN (**4**–**10**) invariably decreased the ee of the reaction (Table 1, runs 10–16). In all cases, catalysts **3**–**10** could be easily recovered from the reaction media and repeatedly used.

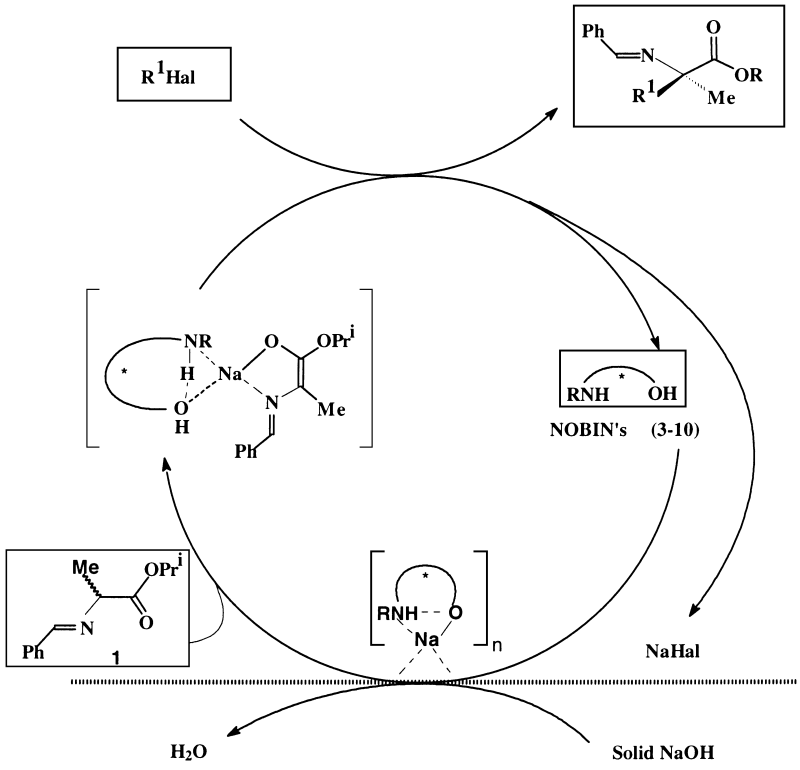
We believe that under the experimental conditions NOBIN functioned as a chiral base, ionising the substrate. The $pK_a$ of **1**, determined in DMSO, is in the range of 17–20,[12] whereas that of NOBIN is most likely about 18 (the measured $pK_a$ value of phenol in DMSO is 18,[13] whereas the value for aniline is 30[14]). Hence, NOBIN is likely to be first ionised at its OH-group in an aprotic solvent in order to function as a base. On the other hand, the rigid structure of NOBIN could provide the necessary features to make it a hydrophobic complexing agent for cations. The transition state of the alkylation should involve both NOBIN derivatives **3**–**10** and the alkali metal ion as revealed by the comparison of the solid NaOH and KOH (runs 2 and 8). Finally, an intermolecular hydrogen bond between the ionised substrate and NOBIN may stabilise the complex of the enolate ion pair with NOBIN. In fact, the structure of the complex would be the same, regardless of whether the sodium salt of NOBIN served initially as a hydrophobic base or the neutral NOBIN functioned as a chelating agent in the same manner as disclosed for another chiral catalyst of Li-enolate alkylations.[15] In our case, the unreactive aggregates of the sodium enolates generated from **1**[16] may be activated for the *C*-alkylation by the complexation with NOBIN (Scheme 2).

Apparently, the good performance of the substrate **1** stems from the ability of the carbanion to chelate the sodium ion in the mixed chiral complex with NOBIN (see Scheme 2). The latter effect provides a rigid structure where the *Si*-face of the carbanion is effectively shielded from the electrophilic attack. However, the mixed complex of the catalyst and the substrate or its enolate might have a much more complicated structure.

In summary, our results offer a useful addition to the development of a new generation of efficient chiral catalysts for asymmetric *C*-alkylation of C–H-acids, under PTC conditions. The conditions for the alkylation were not optimised and higher ee of the alkylation could be expected when lower temperatures, improved catalysts, etc. are employed. Our results compare favourably with other methods of asymmetric PTC alkylations, employing chiral derivatives of alkaloids,[2–5] in terms of the catalysts' stability and recovery and the ambient temperature of the reaction. Thus, a host of new asymmetric alkylations of various C–H-acids can be envisaged, using our approach, with chelates tailored for each particular application.

## 3. Experimental

Synthesis of **1** was performed as described earlier.[7] For preparation of aminonaphthols **3**–**9** see the literature.[9] Compound **10** was prepared by reaction of **3** with ethylene oxide.[17] Toluene was distilled




Scheme 2. Possible mechanism of NOBIN's mediated asymmetric PTC-alkylation of **1**

from sodium prior to use. All the synthesised compounds had the appropriate physical and chemical data. GLC enantiomeric analyses of (a) α-methylphenylalanine **2a**, (b) α-allylalanine **2b**, and (c) α-(1-naphthylmethyl)alanine **2c** were performed on a Chirasil-L-Val type phase, by using their *N*-trifluoroacetyl *n*-propyl esters. Fused silica capillary column 40 m×0.23 mm ID. Film 0.12 μm. Col. temp.: (a) 125°C, (b) 75°C, (c) 160°C. Carrier gas He: 1.80 bar.

The alkylation of the substrate **1** was carried out as follows: a 25 mL flask containing a stirring bar was flame dried in vacuo and filled with Ar. (*S*)-NOBIN **3** (0.0285 g, 0.1 mmol) and NaOH (0.16 g, 4 mmol, ground under Ar before use) (or NaH, oil covered) was added and mixed during 30 min. Then, a solution of the Schiff's base **1** (0.22 g, 1 mmol, distilled in vacuo under Ar) in dry toluene (2 mL) and benzyl bromide (0.14 mL, 1.2 mmol) were added to the flask. The mixture was stirred at room temperature (20°C) for 12 h and then aq. HCl (6 N, 6 mL) was added. The stirring was continued for an additional 15 min at the ambient temperature. The aqueous layer was separated, the toluene layer was washed with 6 N HCl and the aqueous layers were combined. The aqueous solution was refluxed for 1 h and (*R*)-**2a** was purified by the ion-exchange technique (DOWEX-50, $H^+$ form). The yield was determined using $^1H$ NMR analysis of the reaction mixture with (*S*)-leucine as an internal standard, and the ee was determined by chiral GLC. The crude amino acid thus produced could be recrystallised from a $Pr^iOH$–$H_2O$ mixture to give the enantiomerically pure **2a**: $[\alpha]_D^{25}$ +17.8 (*c* 0.2, $H_2O$), ee >99% by GLC; (the data for the sample of (*S*)-**2a** obtained by an earlier developed method:[11] $[\alpha]_D^{25}$ −17.8 (*c* 0.2, $H_2O$)). α-Allylalanine **2b** and α-(1-naphthylmethyl)alanine **2c** also were checked with samples of the amino acids.[7] Pure NOBIN could be recovered from the toluene layer after its evaporation in vacuo, followed by crystallisation from toluene.

## Acknowledgements

The work was supported by the EU through INCO-Copernicus grant IC15-CT96-0722, the Russian Fund for Fundamental Sciences (Grant No. 99-03-32970), the Grant Agency of the Czech Republic (Grant No. 203/98/1185), and the Grant Agency of Charles University (Grant No. 18/98).

## References

1. Makosza, M. *Pure Appl. Chem*. **1975**, *43*, 439–462.
2. (a) Dolling, U.; Hughes, D.; Bhattacharya, A.; Ryan, K.; Karady, S.; Weinstock, L.; Grabowski, E. In *Phase Transfer Catalysis, New Chemistry, Catalysts, and Applications (ACS Symposium Series: 326)*; Starks, M., Ed.; Am. Chem. Soc.: Washington, DC, 1987, vol. 326, pp. 67–73; O'Donnell, M. J.; Bennett, W.; Wu, S. *J. Am. Chem. Soc*. **1989**, *111*, 2353–2355; (b) O'Donnell, M. J.; Wu, S. *Tetrahedron: Asymmetry* **1992**, *3*, 591–594; O'Donnell, M. J.; Wu, S.; Huffman, J. C. *Tetrahedron.* **1994**, *50*, 4507–4518; Arai, S.; Shioiri, T. *Tetrahedron Lett*. **1998**, *39*, 2145–2148; Arai, S.; Ishida, T.; Shioiri, T. *Tetrahedron Lett*. **1998**, *39*, 8299–8302.
3. Corey, E.; Xu, F.; Noe, M. *J. Am. Chem. Soc*. **1997**, *119*, 12414–12415; Corey, E.; Noe, M.; Xu, F. *Tetrahedron Lett*. **1998**, *39*, 5347–5350; Corey, E.; Bo, Y.; Busch-Petersen, J. *J. Am. Chem. Soc*. **1998**, *120*, 13000–13001.
4. Lygo, B.; Crosby, J.; Lowdon, T. R.; Wainwright, P. G. *Tetrahedron Lett*. **1997**, *38*, 2343–2346; Lygo, B.; Wainwright, P. G. *Tetrahedron Lett*. **1997**, *38*, 8595–8598; Lygo, B.; Wainwright, P. G. *Tetrahedron Lett*. **1998**, *39*, 1599–1602.
5. O'Donnell, M. J.; Delgano, F.; Hostettler, C.; Schwesinger, R. *Tetrahedron Lett.* **1998**, *39*, 8775–8778.
6. Belokon, Yu. N.; Kochetkov, K. A.; Churkina, T. D.; Ikonnikov, N. S.; Orlova, S. A.; Smirnov, V. V.; Chesnokov, A. A. *Mendeleev Commun*. **1997**, 137–138; Belokon, Yu. N.; Kochetkov, K. A.; Churkina, T. D.; Ikonnikov, N. S.; Orlova, S. A.; Smirnov, V. V.; Chesnokov, A. A. *Izv. Ross. Akad. Nauk, Ser. Khim*. **1998**, *47*, 76–83 (*Bull. Rus. Acad. Sci., Div. Chem. Sci*. **1998**, *47*, 74–81).
7. Belokon, Yu. N.; Kochetkov, K. A.; Churkina, T. D.; Ikonnikov, N. S.; Chesnokov, A. A.; Larionov, O. A.; Parmar, V. S.; Kumar, R.; Kagan, H. B. *Tetrahedron: Asymmetry* **1998**, *9*, 851–857; Belokon, Yu. N.; Kochetkov, K. A.; Churkina, T. D.; Ikonnikov, N. S.; Chesnokov, A. A.; Larionov, O. A.; Kagan, H. B. *Izv. Ross. Akad. Nauk, Ser. Khim*. **1999**, *48*, 926–932 (*Bull. Rus. Acad. Sci., Div. Chem. Sci*. **1999**, *48*, 917–923).
8. Trost, B. M. *Angew. Chem., Int. Ed. Engl*. **1995**, *34*, 258–281; Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; John Wiley: New York, 1993.
9. Smrcina, M.; Polakova, J.; Vyskocil, S.; Kocovsky, P. *J. Org. Chem*. **1993**, *58*, 4534–4538; Smrcina, M.; Vyskocil, S.; Maca, B.; Polasek, M.; Claxton, T. A.; Abbott, A. P.; Kocovsky, P. *J. Org. Chem*. **1994**, *59*, 2156–2163; Smrcina, M.; Vyskocil, S.; Polivkova, J.; Polakova, J.; Kocovsky, P. *Collect. Czech. Chem. Commun.* **1996**, *61*, 1520–1524; Smrcina, M.; Vyskocil, S.; Polivkova, J.; Polakova, J.; Sejbal, J.; Hanus, V.; Polasek, M.; Verrier, H.; Kocovsky, P. *Tetrahedron: Asymmetry* **1997**, *8*, 537–546; Vyskocil, S.; Jaracz, S.; Smrcina, M.; Sticha, M.; Hanus, V.; Polasek, M.; Kocovsky, P. *J. Org. Chem.* **1998**, *63*, 7727–7737.
10. Wirth, T. *Angew. Chem., Int. Ed. Engl*. **1997**, *36*, 225–227; Chinchilla, R.; Falvello, L.; Galindo, N.; Najera, C. *Angew. Chem., Int. Ed. Engl*. **1997**, *36*, 995–997; Cativiela, C.; Diaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **1998**, *9*, 3517–3599; Alonso, F.; Davies, S. G.; Elend, A. S.; Haggitt, J. L. *J. Chem. Soc., Perkin Trans. 1* **1998**, 257–264.
11. Belokon, Yu. N.; Bakhmutov, V. I.; Chernoglazova, N. I.; Kochetkov, K. A.; Vitt, S. V.; Garbalinskaya, N. S.; Belikov, V. M. *J. Chem. Soc., Perkin Trans. 1* **1988**, 305–312.
12. O'Donnell, M. J.; Bennett, W.; Bruder, W.; Jacobsen, W.; Knuth, K.; LeClef, B.; Polt, R.; Bordwell, F.; Mrozack, S.; Cripe, T. *J. Am. Chem. Soc*. **1988**, *110*, 8520–8525.
13. Bordwell, F. G.; McCallum, R. J.; Olmstead, W. N. *J. Org. Chem*. **1984**, *49*, 1424–1427.
14. Bordwell, F. G.; Algrim, D. J. *J. Am. Chem. Soc*. **1988**, *110*, 2964–2968.
15. Imai, M.; Hagihara, A.; Kawasaki, H.; Manabe, K.; Koga, K. *J. Am. Chem. Soc*. **1994**, *116*, 8829–8830.
16. For a discussion of the aggregate structure of enolates of similar type and the role of monomer in alkylation reactions see: Solladie-Cavallo, A.; Simon-Wermeister, M.; Schwarz, J. *Organometallics* **1993**, *12*, 3743–3747; Streitwieser, A.; Krom, J. A.; Kilway, K. V.; Abbotto, A. *J. Am. Chem. Soc*. **1998**, *120*, 10801–10806; Abbotto, A.; Leung, S. Sh.-W.; Streitwieser, A.; Kilway, K. V. *J. Am. Chem. Soc*. **1998**, *120*, 10807–10813.
17. Vyskocil, S.; Kocovsky P. manuscript in preparation. For the method, see: Weber, L. M. *J. Med. Chem*. **1963**, *6*, 637–646.