DOI: 10.1002/ejoc.200801146

Cyclic 2:1 and 1:2 Aldehyde-to-Acetone Byproduct Adducts in Aldol Reactions Promoted by Supported Proline-Incorporated Catalysts

Lital Tuchman-Shukron,[a] Tzofit Kehat,[a] and Moshe Portnoy*[a]

Keywords: Supported catalysts / Organocatalysis / Domino reactions / Aldol reactions / Cyclizations

Significant amounts of cyclic byproducts of aldol addition with stoichiometry deviating from a regular 1:1 addition pattern were formed when the reaction of acetone with aromatic aldehydes was promoted by polymer-supported proline-incorporated catalysts. These adducts, unprecedented in the context of the aldol reaction, are most probably formed via a multistep domino mechanism.

Introduction

Over the past decade a considerable number of experimental work investigated the catalytic properties of proline and proline-derived compounds in a variety of asymmetric organic transformations, particularly the aldol addition.[1] The majority of the catalytic studies were carried out with soluble catalysts, whereas only a few involved heterogeneous proline-based moieties.[2] Despite the questionable economic profitability of developing a successful immobilized proline catalyst, because of the low price of this amino acid and the possibility of its easy recovery from homogeneous reaction mixtures, proline and related molecules provide excellent models for organocatalyst immobilization studies as a result of their simplicity and the ready availability of various derivatives. Moreover, immobilization frequently provides catalysts with an altered reactivity profile that can lead to products different from those obtained in solution and provide valuable mechanistic information. For instance, the major focus of the investigation of the aldol reaction of aldehydes and ketones was on the aldol adduct formed with the 1:1 stoichiometry of the addition. Yet, these aldol products usually possess additional nucleophilic or electrophilic sites and can participate in the formation of adducts of higher stoichiometric ratios. For instance, three aldehyde molecules can combine into a carbohydrate-like cyclic structure.[3] Linear 2:1 aldehyde/acetone adducts were obtained when the reaction was promoted by pyrrolidine or prolinethioamide in neat acetone.[4]

In this article we report the formation of a significant amount of 2:1 and 1:2 cyclic adduct byproducts in the reaction of aromatic aldehydes and acetone catalyzed by two new polymer-supported proline-related catalytic systems. To the best of our knowledge, cyclic adducts of stoichiometry deviating from a 1:1 ratio have never been observed in the proline-catalyzed ketone addition to aldehydes.

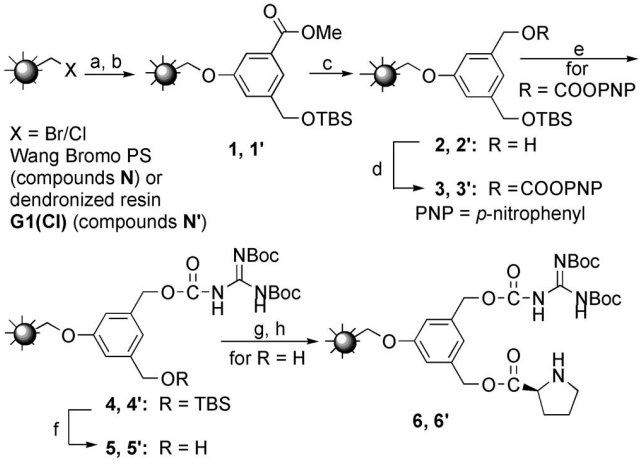
Results and Discussion

In the past we demonstrated that *trans*-4-hydroxyproline could be immobilized on a dendronized solid support through the hydroxy function, whereas the carboxylic and amino functional groups are available for catalysis. These supported dendritic catalysts promoted the asymmetric aldol addition of acetone to aromatic aldehydes with the yield and selectivity comparable (or even slightly better) than those displayed by L-proline catalysts in solution.[5] An alternative catalytic design involved immobilization of the proline unit through the carboxylate moiety, while providing a replacement for the electrophile activator (formerly the COOH group) in the form of remotely attached potentially double hydrogen-bond-donating trisalkoxycarbonyl guanidine unit. The synthesis of the potential catalyst **G0(Pro, Gua-Boc$_2$)** (**6**) is depicted in Scheme 1. It is based on the immobilization of the heteroarm branching unit, methyl 3-hydroxy-5-hydroxymethylbenzoate,[6] on its conversion into monoprotected diol **2**, and on the stepwise assembly of the arms: first the trisalkoxycarbonyl guanidine arm and then the proline arm.

Though we hoped that the carboxylic acid could be replaced by the double hydrogen-bond-donor moiety of **6**, the model reaction of acetone with benzaldehyde in the presence of **6** (30 mol-%) yielded only trace amounts of the aldol product. When a more active electrophile, such as 4-nitrobenzaldehyde, was employed, the reaction yielded 33% of a low optical purity aldol product (7%*ee*), but also an additional compound in 20% yield (Scheme 2). The com-

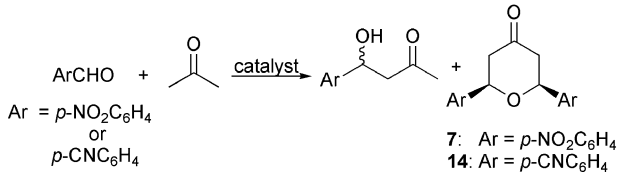
[a] School of Chemistry, Raymond and Beverly Sackler Faculty of Exact Sciences, Tel Aviv University,
Tel Aviv, 69978, Israel
Fax: +972-3-6409293
E-mail: portnoy@post.tau.ac.il

Supporting information for this article is available on the WWW under http://www.eurjoc.org or from the author.



Scheme 1. Synthesis of bifunctional catalysts **6** and **6′**. Reagents and conditions: (a) methyl 3-hydroxy-5-hydroxymethylbenzoate, LiH, TBAI, DMF, 60 °C, overnight; (b) TBSCl, Et_3N, DMAP, DCM, room temp., 3 h; (c) $LiBH_4$, $B(OMe)_3$, THF, 60 °C, overnight; (d) *p*-nitrophenyl chloroformate, DIPEA, pyridine, THF, room temp., 2 h; (e) bis(Boc)guanidine, HOBt, DMF, 50 °C, 24 h; (f) TBAF, THF, room temp., 4 h; (g) Fmoc-Pro-OH, diisopropylcarbodiimide (DIC), DMAP, DMF, room temp., 6 h; (h) piperidine/DMF (2:8), room temp., 2–3 min.

pound is significantly less polar than the aldol product and could be purified chromatographically. On the basis of NMR spectroscopic data and its comparison to literature sources,[7] in addition to mass spectrometric data, the compound was identified as *cis*-2,6-bis(4-nitrophenyl)tetrahydro-4*H*-pyran-4-one (**7**). Particularly, there was an excellent correlation of the aliphatic carbon signals of **7** with the *meso* (*cis*) isomer of 2,6-diphenyltetrahydro-4*H*-pyran-4-one.[7a] During the preparation of the manuscript an independent synthesis of *cis*-2,6-bis(4-nitrophenyl)tetrahydro-4*H*-pyran-4-one was reported with spectroscopic data completely matching that of **7**.[8] The *meso* isomer is, according to the literature, the more thermodynamically stable isomer.[7b] Formation of **7** without any visible trace of its *trans* isomer may thus point to thermodynamic control of the reaction sequence leading to the formation of the cyclic adduct.



Scheme 2. The reaction of aldehyde with acetone leading to 2:1 adducts.

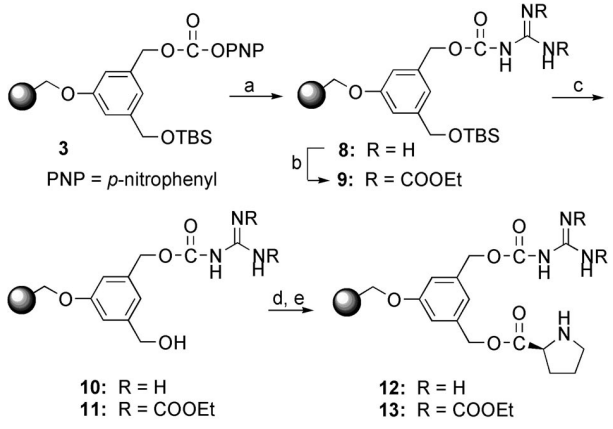
In an attempt to improve the chemoselectivity of the reaction toward **7**, we changed a number of reaction parameters and prepared two new catalysts related to **6** (Table 1). Thus, a decrease in the amount of the catalyst from 30 to 15% led to a decrease in the overall conversion of the aldehyde, but improved the chemoselectivity significantly. In contrast, the replacement of DMSO by DMF or THF had the opposite effect. The addition of water (5 equiv.) or a fivefold increase in the concentration of the aldehyde also led to a decrease in the chemoselectivity with a concomitant increase in the conversion. Whereas facilitation of the reaction kinetics upon an increase in the concentration of the reactants is hardly surprising, the decrease in the selectivity toward the formation of the more "aldehyde-rich" adduct under these conditions is less comprehensible and we will subsequently provide a possible explanation.

Table 1. The reaction of aldehyde with acetone leading to 2:1 adducts.[a]

Entry	Catalyst	Yield of aldol product [%][b]	Yield of **7** [%][b]	Chemoselectivity [%, **7**/(aldol + **7**)]
1	**6**	32	20	38
2[c]	**6**	15	18	55
3[d]	**6**	47	trace	<4
4[e]	**6**	44	6	12
5[f]	**6**	82	16	16
6[g]	**6**	72	28	28
7	**13**	35	30	46
8	**6′**	76	24	24
9[g]	**6′**	86	14	14
10[h]	**6**	39	26	40

[a] Reaction conditions: *p*-nitrobenzaldehyde (1 mmol) and resin-supported catalyst (0.3 mmol) in DMSO/acetone (4:1, 2 mL per 0.2 g of resin) at room temp. for 48 h. [b] Yield determined by NMR spectroscopy. [c] Resin-supported catalyst (0.15 mmol). [d] DMF instead of DMSO was used. [e] THF instead of DMSO was used. [f] H_2O (5 mmol) was added. [g] Aldehyde (5 mmol). [h] *p*-Cyanobenzaldehyde instead of *p*-nitrobenzaldehyde was used.

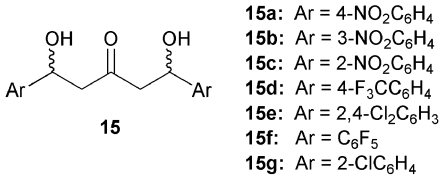
Catalyst **13**, related to catalyst **6**, was prepared as depicted in Scheme 3. The use of catalyst **13** in the model reaction led to a slight improvement in the conversion and a notable increase in the chemoselectivity towards **7**. In contrast, **6′**, a catalyst analogous to **6** but prepared on first-generation dendronized chloromethyl-terminated resin (vs. Wang Bromo PS, Scheme 1),[9] displayed significantly higher activity, but much lower selectivity toward **7**. *p*-Cya-



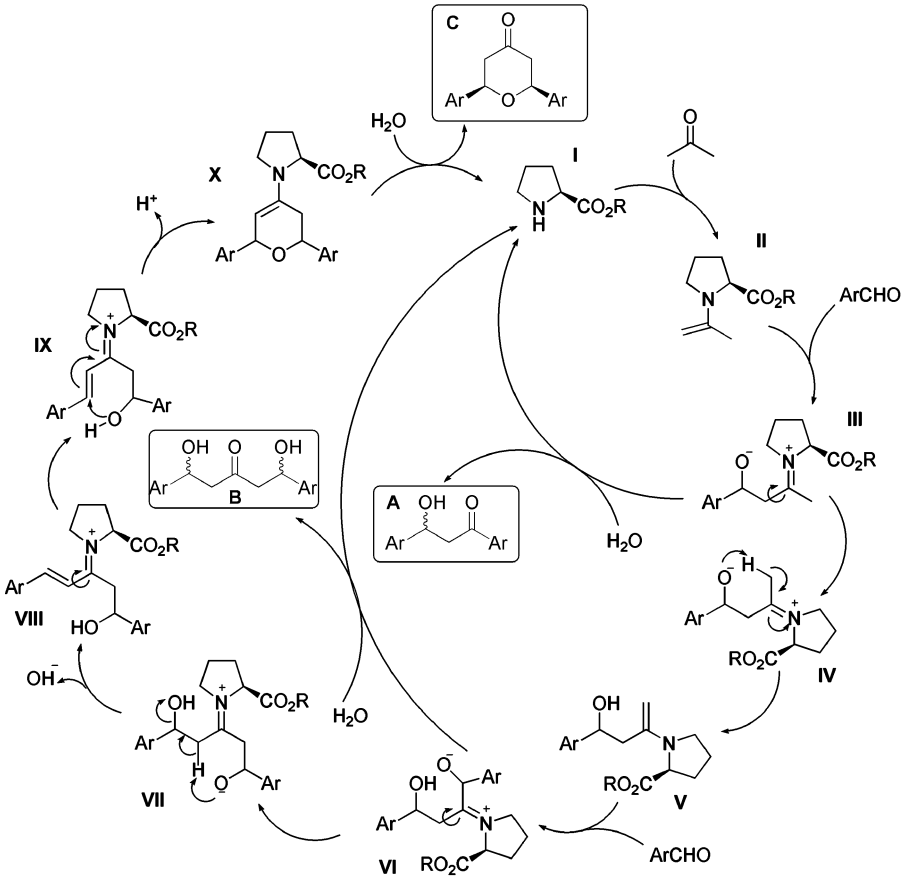
Scheme 3. Synthesis of catalysts **12** and **13**. Reagents and conditions: (a) guanidine hydrochloride, DIPEA, DMF, 50 °C, 24 h; (b) ethyl chloroformate, DIPEA, pyridine, THF, room temp., 2 h; (c) TBAF, THF, room temp., 4 h; (d) Fmoc-Pro-OH, DIC, DMAP, DMF, room temp., 6 h; (e) piperidine/DMF (2:8), room temp., 2–3 min.

nobenzaldehyde (replacing *p*-nitrobenzaldehyde) reacted similarly with acetone in the presence of **6** to form cyclic byproduct **14** along with the main aldol adduct.

As to the possible mechanism for the formation of **7**, a few important points described in the literature are worth emphasizing. Compound **15**, the product of the double aldol addition of aldehydes to acetone under aldol reaction conditions, was observed on two occasions: with pyrrolidine or prolinethioamide catalysts.[4] These acyclic 2:1 aldehyde/acetone adducts were formed with electron-poor aromatic aldehydes only. In the case of pyrrolidine catalysis, a substantial amount of the byproduct (up to 50%) could be obtained, but its formation was suppressed by acidic additive/water addition.[4a,4b] In the case of prolinethioamide catalysis, a 2:1 stoichiometric ratio of the aldehyde to acetone should be used to reach a 40% yield of the double aldol addition product.[4c] It should be noted that *trace amounts* of **15a** were also observed by us in the model reaction. Formation of acyclic double addition product **15e** was also achieved by treating the regular aldol product with the corresponding aldehyde.[4b] Moreover, in the report that appeared whilst this article was in preparation, pyrrolidine was established as an effective catalyst for the stepwise oxa-Diels–Alder-like reaction of acyclic β-aryl-α,β-unsaturated ketones with aldehyde.[8] As aforementioned, this reaction produces 2,6-disubstituted tetrahydro-4*H*-pyran-4-ones, such as **7**.



The proposed mechanism for the multistep transformation in our case is depicted in Scheme 4. Contrary to one of the examples in ref.[4b] and the reaction in ref.[8] it is highly unlikely that the reaction takes place stepwise with the formation of the aldol (**A**) and linear double aldol (**B**) adducts as intermediates. In other words, the catalyst does not undergo detachment and reattachment to the carbonyl group along the route to **7**. Rather, these two acyclic products **A** and **B** are "byproducts" en-route to **7** that are formed by "shortcuts" when the proline-containing intermediates undergo hydrolysis "too early" before the full catalytic cycle is complete. Thus, reaction of 4-nitrobenzaldehyde with acetone in the presence of the aldol adduct of benzaldehyde and acetone (**A** with Ar = Ph) did not lead to 2-(4-nitrophenyl)-6-phenyltetrahydro-4*H*-pyran-4-one. Only **7** and the two aldol products were detected at the end of the reaction. The addition of water helps to "shortcut" the cycle through hydrolysis of intermediate **III**, which forms aldol **A** and restores the catalyst, thus facilitating the rate



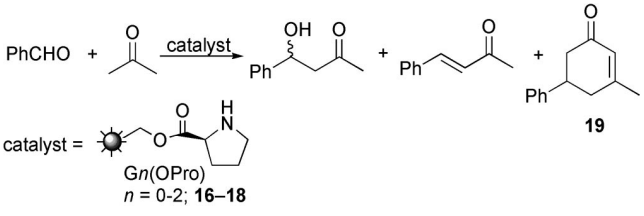
Scheme 4. Proposed mechanism for the formation of 2:1 aldehyde/acetone adducts.

of the reaction in general but lowering the chemoselectivity toward **C** (**7** in our case).

The rate of consumption of the aldehyde is also higher and the chemoselectivity toward **7** is lower when the reaction is promoted by **6′** (the first generation dendron) or when the initial concentration of the aldehyde is increased fivefold. In contrast, the reduced reaction rate upon a decrease in the catalyst loading is associated with the increased selectivity toward **7**. This connection between the activity of the catalyst and its chemoselectivity can originate from two factors. First, it is possible that the formed aldol (**A**) facilitates the hydrolysis of the iminium cation, enables a "shortcut" of the more extended cycle, and promotes its own formation. Second, it is also possible that the hydroxy group of the aldol disrupts the interaction of the trisalkoxycarbonyl guanidine with the intermediates, which increases the preference for the shorter route leading to **A** at the expense of the cycles leading to higher adducts.

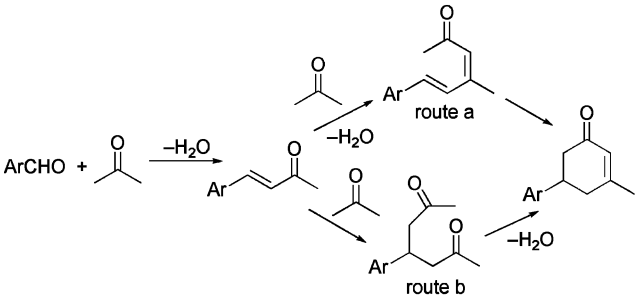
Although guanidine unit itself does not promote the reaction, the crucial role of the potential double hydrogen-bond donor site for the formation of the 2:1 cyclic adduct is evidenced by two experimental observations. Lowering the steric hindrance of the group (ethoxycarbonyl vs. *tert*-butoxycarbonyl on the nitrogen atoms) has a positive influence on the chemoselectivity by raising it from 38 to 46%. Secondly, catalysts without the trisalkoxycarbonyl guanidine unit, that is, those decorated with proline ester and benzyloxycarbonyl guanidine (**12**, Scheme 3) or with proline esters only (**16**–**18**), do not promote the formation of **7** or analogous byproducts.

The synthesis of the **G*n*(OPro)** catalysts (*n* = 0–2; **16**–**18**) as well as the detailed investigation of their catalytic activity in the aldol reaction will be reported elsewhere.[10] However, as mentioned above, linear or cyclic 2:1 aldehyde/acetone adducts have never been observed in the relevant reactions with these catalysts. Interestingly, another cyclic byproduct adduct, **19**, with the opposite stoichiometry of the components (1:2, aldehyde/acetone) was always observed with these catalytic systems in the reaction of benzaldehyde with acetone (Scheme 5). Although the nondendritic and dendritic first-generation catalysts (**16** and **17**) provided the byproduct in only 3–5% yield, the yield reached a remarkable 30% when the reaction was carried out with second-generation catalyst **18**.[11] Similar yields were obtained in DMF and chloroform. The spectroscopic data (^{1}H and ^{13}C NMR) of the byproduct matched that reported in the literature for the compound.[12]



Scheme 5. The reaction of aldehyde with acetone leading to a 1:2 adduct.

Two plausible routes to byproduct **19** can be envisioned. These are shown schematically in Scheme 6. Although both routes are three-step transformations (two aldol condensations and one Michael addition, one of them being an intramolecular ring-closing step), this does not necessarily mean that the catalyst is detached from the intermediate after each step. Rather, the routes are depicted in this way for simplicity. It is noteworthy that path b, the intramolecular aldol cyclization of the 1,5-dione, is a well-documented reaction and can also be promoted by proline.[13] The preceding step, however, that is, the formation of the 1,5-dicarbonyl intermediate by Michel addition of the nonactivated carbonyl compound (acetone) to the nonactivated Michael acceptor (enone), is unprecedented in organocatalysis.[14] Although highly speculative, route a cannot be ruled out at this stage.[15]



Scheme 6. Proposed mechanisms for the formation of a 1:2 aldehyde/acetone adduct.

Conclusions

We demonstrated that complex multistep transformations could be promoted by proline-derived heterogeneous catalysts. Although formed as byproducts with only up to 30% yield, the cyclic adducts described here expose the potential of relatively simple organocatalytic systems to form, in a one-pot reaction, products of high complexity that could be valuable intermediates for many synthetic targets.[13d] The mere demonstration of such reactivity (unprecedented before), will provide strong encouragement for catalytic chemists to seek systems that can perform these transformations in a more high-yielding and selective way.

Experimental Section

General: The loading of the catalytic resins was determined by acidolytic cleavage on the basis of the ^{1}H NMR spectra of the cleavage solution (TFA/$CDCl_3$, 1:1) with 11 mM C_6H_6 as an internal standard.

General Procedure for the Aldol Reaction: The catalytic resin (0.3 mmol, 0.3 equiv.) was added to a mixture of DMSO/acetone (4:1, 8 mL:2 mL). The suspension was stirred for 5 min at room temperature and then the aldehyde (1 mmol, 1 equiv.) was added. The suspension was mixed at room temperature for 48 h. The resin was separated from the solution by filtration and washed with ethyl acetate. Water (10 mL) and saturated aqueous NH_4Cl solution

(10 mL) were added to the combined filtrate. The mixture was extracted with ethyl acetate (3 × 10 mL). The organic phase was dried on $MgSO_4$. The solvent was evaporated, and the crude material was analyzed to determine conversion and yield, and then chromatographed on a silica gel column (EtOAc/hexanes, 1:9, up to EtOAc/hexanes, 3:7) to yield the pure adducts.

7: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.29 (d, J = 8.6 Hz, 4 H), 7.63 (d, J = 8.6 Hz, 4 H), 4.99 (dd, J = 2.1, 11.8 Hz, 2 H), 2.84–2.80 (dd, J = 2.1, 16.0 Hz, 2 H), 2.69–2.62 (dd, J = 11.8, 16.0 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 203.1, 147.8, 146.9, 126.3, 124.1, 77.9, 49.0 ppm. MS (FAB): m/z = 343.1 $[M + H]^+$.

19: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27–7.34 (m, 2 H), 7.20–7.24 (m, 3 H), 5.95 (s, 1 H), 3.26–3.34 (m, 1 H), 2.45–2.65 (m, 4 H), 1.98 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.8, 162.3, 144.0, 129.5, 127.7, 127.4, 127.3, 44.6, 41.5, 39.7, 25.1 ppm.

Supporting Information (see footnote on the first page of this article): Experimental procedures and characterization data of the polymer-bound intermediates and catalysts.

Acknowledgments

This research was supported by The Israel Science Foundation (Grant No. 960/06).

[1] a) B. List, *Tetrahedron* **2002**, *58*, 5573–5590; b) G. Guillena, C. Nájera, D. J. Ramón, *Tetrahedron: Asymmetry* **2007**, *18*, 2249–2293.
[2] M. Gruttadauria, F. Giacalone, R. Noto, *Chem. Soc. Rev.* **2008**, *37*, 1666–1688 and references cited therein.
[3] I. Ibrahem, W. Zou, Y. Xu, A. Córdova, *Adv. Synth. Catal.* **2006**, *348*, 211–222.
[4] a) C. Ji, Y. Peng, C. Huang, N. Wang, Y. Jiang, *Synlett* **2005**, 986–990; b) C. Ji, Y. Peng, C. Huang, N. Wang, Z. Luo, Y. Jiang, *J. Mol. Catal. A* **2006**, *246*, 136–139; c) D. Gryko, R. Lipinski, *Eur. J. Org. Chem.* **2006**, 3864–3876.
[5] T. Kehat, M. Portnoy, *Chem. Commun.* **2007**, 2823–2825.
[6] K. Goren, T. Kehat, M. Portnoy, *Adv. Synth. Catal.*, accepted.
[7] a) K. Ramalingan, K. D. Berlin, N. Satyamurthy, R. Sivakumar, *J. Org. Chem.* **1979**, *44*, 471–477; b) C. A. R. Baxter, D. A. Whiting, *J. Chem. Soc. C* **1968**, 1174–1178.
[8] L.-Q. Lu, X.-N. Xing, X.-F. Wang, Z.-H. Ming, H.-M. Wang, *Tetrahedron Lett.* **2008**, *49*, 1631–1635.
[9] A. Mansour, T. Kehat, M. Portnoy, *Org. Biomol. Chem.* **2008**, *6*, 3382–3387.
[10] T. Kehat, unpublished results.
[11] This byproduct was obtained with low optical purity (<10%*ee*).
[12] A. Buzas, F. Gagosz, *J. Am. Chem. Soc.* **2006**, *128*, 12614–12615.
[13] a) C. Agami, H. Sevestre, *J. Chem. Soc., Chem. Commun.* **1984**, 1385–1386; b) C. Agami, N. Platzer, H. Sevestre, *Bull. Soc. Chim. Fr.* **1987**, *2*, 358–360; c) B. List, R. A. Lerner, C. F. Barbas III, *Org. Lett.* **1999**, *1*, 59–61; d) J. Zhou, V. Wakchaure, P. Kraft, B. List, *Angew. Chem.* **2008**, *120*, 7768–7771; *Angew. Chem. Int. Ed.* **2008**, *47*, 7656–7658.
[14] H. Pellisier, *Tetrahedron* **2007**, *63*, 9267–9331.
[15] For this route, both steps 2 and 3 are unprecedented.

Received: November 18, 2008
Published Online: January 16, 2009

