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Thermal Effects in the Organocatalytic Asymmetric α-Amination of Disubstituted Aldehydes with Azodicarboxylates: A High-Temperature Organocatalysis

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This article describes the thermally accelerated organocatalytic α-amination of disubstituted aldehydes with azodicarboxylates under microwave conditions. Compared to the results previously obtained at room temperature, both yield and enantioselectivity could be significantly increased. Employing microwave irradiation resulted in a considerably reduced reaction time. Therefore, this improved protocol allows the fast and efficient synthesis of α,α-disubstituted amino aldehydes and provided the best results for the α-amination of disubstituted aldehydes to date.

Introduction

The amino functionality is ubiquitous and of great importance as a building block in organic synthesis.[1] Formation of carbon–nitrogen bonds is usually achieved by attack of a nucleophilic nitrogen on an electrophilic carbon centre bearing a leaving group, via an S_N2-type reaction. Using the 'umpolung' methodology, increased attention has been given to the development of electrophilic reagents for the amination of carbon nucleophiles.[2] Since most nitrogen-containing natural products possess at least one stereogenic centre, it is of general interest to develop stereoselective transformations for their preparation in enantiomerically enriched form.[3] Asymmetric versions of electrophilic amination have been investigated using chiral aminating reagents, chiral catalysts, or chiral carbanions.[4] Recently discovered by List and Jørgensen, the asymmetric proline-catalyzed α-amination of achiral linear aldehydes and ketones with azodicarboxylates provides the corresponding aminated carbonyl compounds in good yield and excellent enantioselectivities.[5,6] This concept of enamine catalysis which refers to the formation of nucleophilic enamine intermediates from aldehydes or ketones with the chiral organocatalyst has been extended to aldol,[7,8] Mannich,[9] and Michael-type reactions,[10] as well as to α-functionalizations such as alkylations,[11] hydroxylations[12,13] and halogenations.[14,15]

Based on the protocol developed by List and Jørgensen, we have been able to show that this strategy could also be transferred to α-branched aldehydes, resulting in α,α-disubstituted amino aldehydes in up to 86% *ee*.[16] While the enantioselectivities, especially for aromatic aldehydes, were remarkably high, two other major aspects of this asymmetric amination reaction were more critical and therefore of more concern: first, the overall reaction times were long (1 h to several days, indicated by the disappearance of the yellow colour of the azodicarboxylate), and second, the catalyst loading was generally high (10–50 mol-%). In the reaction of 2-phenylpropionaldehyde with diethyl azodicarboxylate in dichloromethane, a minimum of 50 mol-% L-proline was required for a maximum yield of 60% and the highest stereoselectivity of 80% *ee*.[16] This sub-stoichiometric use of the catalyst is most likely due to the rather poor solubility of proline in many solvents.

Based on our successful use of microwave heating in the α-amination of aldehydes with chloramine-T,[17] we decided to investigate the influence of various reaction parameters on yield and enantioselectivity in the formation of the α-aminated product. Furthermore, Bolm could recently show a positive thermal effect in the organocatalytic asymmetric Mannich reaction, indicating a high-temperature tolerance for that specific reaction type.[18] Further examples include aldol reactions, conjugated additions, and Diels–Alder reactions, in which both reaction time and the amount of catalyst could be significantly lowered without affecting reactivity and selectivity.[19] For us, the challenge and goal was to develop an optimized protocol by improving the aforementioned critical factors: reduction in reaction time and catalyst load.

Results and Discussion

With the notion in mind that common organic solvents have been categorized as high, medium, and low absorbers

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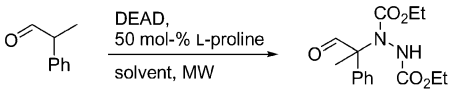
under microwave conditions,[20] we examined the influence of all three classes. In our previously published results at room temperature, dichloromethane was found to perform best in terms of stereoselectivity and therefore it was used in subsequent studies, although 1,4-dioxane gave a maximum yield of 87%, yet with a lower enantioselectivity of 67%. The screening of different solvents in the microwave-assisted reaction of 2-phenylpropionaldehyde with diethyl azodicarboxylate and 50 mol-% L-proline is summarized in Table 1.

Table 1. Solvent screening in the microwave-assisted α-amination of 2-phenylpropionaldehyde with diethyl azodicarboxylate.[a]



Solvent	Time [min]	Power [W][b]	Temp. [°C][c]	Yield [%][d]	*ee* [%][e]
DMSO[f]	60	200	70	51	62
Ethanol[f]	60	200	60	62	14
Acetonitrile[g]	60	200	60	99	84
1,2-Dichloroethane[g]	60	200	60	71	72
Chloroform[h]	60	200	60	49	73
THF[h]	60	200	60	24	70
1,4-Dioxane[h]	30	200	80	13	69
1,4-Dioxane[h]	60	200	80	26	56
1,4-Dioxane[h]	120	200	80	30	48

[a] Reaction conditions: 1.0 equiv. aldehyde, 0.5 equiv. L-proline, 1.5 equiv. DEAD. [b] Application of constant microwave power. [c] For cooling, compressed air with a constant pressure of 0.7 bar (10 psi) was used during the entire experiment. [d] Isolated yields. [e] Determined by HPLC analysis using a chiral column (Chiracel AD); see General Procedure for details. [f] High absorbance level. [g] Medium absorbance level. [h] Low absorbance level.

We initially started the reaction in 1,4-dioxane, as this solvent turned out to be the best with respect to yield at room temperature. To our delight, using microwave heating at 80 °C and 200 W power, a moderate level of selectivity of 69% *ee* could be detected, indicating a high-temperature tolerance for this reaction. However, a disappointing low yield of only 13% was achieved after 30 min (the conversion was controlled by GC as well as by TLC).

Extending the reaction time to one hour had little influence on both yield and enantioselectivity. However, the selectivity further decreased to 48% *ee* when the reaction time was extended to 120 min. After that time, all starting material was consumed, but only 30% of the desired product could be isolated. Other low absorbing solvents such as THF or chloroform did not show any significant difference; the most promising results were obtained using the medium absorbing solvent 1,2-dichloroethane, in which the aminated product was isolated in 71% yield and moderate selectivity of 72% *ee*. Contrary to the findings obtained at room temperature, acetonitrile was found to deliver the best results in terms of both yield and stereoselectivity. This medium absorbing solvent did not only provide the α-aminated product in quantitative yield after 60 min at 60 °C and 200 W power, but also, and even more importantly, increased the enantioselectivity up to 84% *ee*. To the best of our knowledge, this is the first report of a thermal accelerating effect in the asymmetric α-amination of aldehydes with azodicarboxylates.

As a remarkable result, the absorbance level of the tested solvents seemed to play a crucial role in this reaction, with the best outcome on both yield and enantioselectivity from medium absorbing solvents. Although extension of the reaction time did affect the yield positively, the selectivity was considerably decreased. Surprisingly, the protic solvent ethanol could only deliver the product as an almost racemic mixture, indicating a reduced capability for the formation of hydrogen bridging bonds in the transition state.

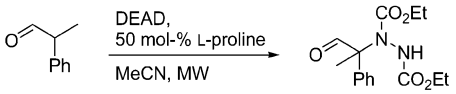
All further studies were performed in acetonitrile, with the influence of both catalyst loading and reaction time being examined. Since the reaction still required 50 mol-% of the catalyst, we next tried to reduce the amount of L-proline. With 0.4 equiv. organocatalyst, the yield of isolated product dropped to 50%, while selectivity was slightly increased. Additional experiments with 25 and 10 mol-% confirmed the decrease in yield with only very little differences in selectivity. By further lowering the catalyst loading down to 5%, the aminated aldehyde could only be obtained in traces. Surprisingly, the selectivity fell to 72% *ee*, indicating a background reaction without participation of the catalyst. This was most likely due to formation of the conjugated enol, which non-selectively attacked the azodicarboxylate. Consequently, the required minimum amount of L-proline was found to be 50 mol-% and could not further decreased without affecting both yield and enantioselectivity. Although the catalyst loading may still not reach quite satisfactory levels, the inexpensiveness and good availability of L-proline and the possibility of reusing the catalyst renders this amination reaction highly attractive and provided the best results for the α-amination of disubstituted aldehydes to date.

To determine the influence of reaction temperature, time, and applied microwave power, we next performed studies varying these three parameters. The results are given in Table 2.

Reducing the reaction time to 30 min at 200 W showed no difference in yield whatsoever, but a slight increase in selectivity. As expected, raising the temperature to 80 °C resulted in a lower yield of 65%, indicating the thermal upper limit, whereas stereoselectivity remained almost the same (82% *ee* vs. 84% *ee*).[21] Lowering the irradiating power to 150 W did not significantly affect the yield or the stereoselectivity. Neither after 60 min nor after 30 min could considerable differences be observed. In further decrease of the applied power to 100 W, a noticeable decline in yield was found. After 60 min, only 83% of the aminated product could be isolated, with an even lower yield of 78% obtained after 30 min, whereas selectivity was slightly increased.

These results suggested a very fast reaction rate, which is influenced more by the irradiating microwave power rather than by temperature or reaction time. Above a critical point, a significant drop in yield was observed, whereas selectivity was surprisingly found to remain virtually the

Table 2. Variation of temperature, time and power in the microwave-assisted α-amination of 2-phenylpropionaldehyde with diethyl azodicarboxylate.[a]



Entry	Time [min]	Power [W][b]	Temp. [°C][c]	Yield [%][d]	*ee* [%][e]
1	60	200	60	99	84
2	30	200	60	97	89
3	30	200	80	65	82
4	60	150	60	98	84
5	30	150	60	97	86
6	60	100	60	83	89
7	30	100	60	78	89
9	60	(o.b.)	80	62	83
10	60	(o.b.)	60	79	90
11	120	(o.b.)	60	84	89
12	360	(o.b.)	60	93	88

[a] Reaction conditions: 1.0 equiv. aldehyde, 0.5 equiv. L-proline, 1.5 equiv. DEAD. [b] Application of constant microwave power; o.b.: oil bath. [c] For cooling, compressed air with a constant pressure of 0.7 bar (10 psi) was used during the entire experiment. [d] Isolated yields. [e] Determined by HPLC analysis using a chiral column (Chiracel AD); see General Procedure for details.

same. Interestingly, extending the reaction time to 3 hours while simultaneously lowering the applied power to 100 W and reducing the temperature to only 40 °C gave the product in quantitative yield and constant selectivity of 88% *ee*. To determine the real impact and evaluate the beneficial effect of microwave irradiation, we performed comparative experiments using conventional oil bath heating. Applying the standard conditions, a decrease in yield could be observed after 60 min, while the selectivity was surprisingly improved (79% and 90% *ee*). Extention of the reaction time to 2 h afforded the product in a slightly increased yield of 84% with the same selectivity of 89% *ee*. For achieving comparable conversion and yield, the required reaction time had to be extended to 6 h, yet still not accomplishing quantitative outcome. Similar to the microwave assisted studies, when heating beyond a critical temperature, a drop in yield was noticed, together with a significantly decrease of the enantioselectivity. Thus, the main difference to the microwave experiments was found to be the reaction time, which had to be considerably increased, while no discrepancy with respect to temperature and yield could be measured. The observed rate enhancement is thought to be a consequence of the instantaneous heating of the reaction mixture when irradiated in a microwave field, and most likely not attributed to a specific microwave effect.[22] Since the first step in the catalytic cycle comprises of a nucleophilic attack of the proline nitrogen to give intermediate dipolar adducts, the beneficial effect of microwave irradiation may be further associated with the dehydration step in formation of the imine-enamine system from an incipient tetrahedral precursor.

Therefore, this organocatalysed direct asymmetric α-amination has been proven to be thermally accelerated. Using microwave irradiation, the reaction time could be significantly reduced, to date with high catalyst loading. In combination with simultaneous cooling, applying a medium microwave power opens a well-balanced reaction window, in which both a high reaction rate and very good enantioselectivities can be achieved.

Although L-proline was proved to be an excellent catalyst not only for amination reactions, but furthermore turned out to be efficient for various aldol, Michael, and Mannich-type reactions, several analogous were found to give even better results in terms of yield and stereoselectivity. Thus, we screened a wide range of proline-derivatives for their catalytic activity in the microwave-assisted α-amination of 2-phenylpropionaldehyde with diethyl azodicarboxylate (Figure 1). The results are summarized in Table 3.

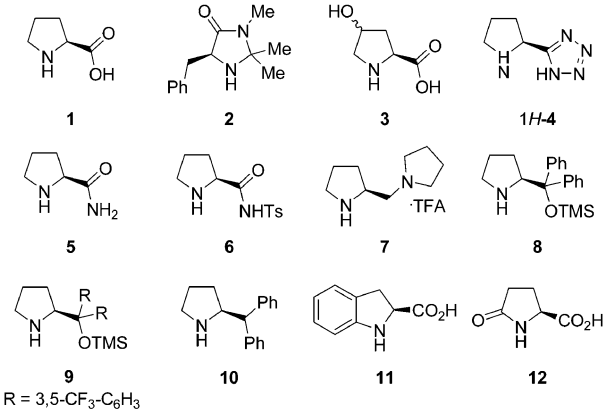
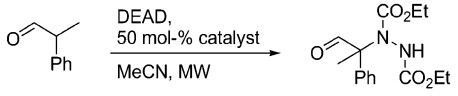


Figure 1. Pyrrolidine-based catalysts for the α-amination of 2-phenylpropionaldehyde.

Table 3. Screening of proline-derived catalysts in the microwave-assisted α-amination of 2-phenylpropionaldehyde with diethyl azodicarboxylate.[a]



Catalyst	Time [min]	Power [W][b]	Temp. [°C][c]	Yield [%][d]	*ee* [%][e]
L-proline **1**	60	200	60	99	84
2	60	200	60	n. r.	–
3	60	200	60	< 10	60
4	60	200	60	75	91
5	60	200	60	36	73
6	60	200	60	10	37
7	60	200	60	< 5	n. d.
8	60	200	60	17	75
9	60	200	60	15	79
10	60	200	60	20	38[f]
11	60	200	60	12	72
12	60	200	60	n. r.	–

[a] Reaction conditions: 1.0 equiv. aldehyde, 0.5 equiv. catalyst, 1.5 equiv. DEAD. [b] Application of constant microwave power. [c] For cooling, compressed air with a constant pressure of 0.7 bar (10 psi) was used during the entire experiment. [d] Isolated yields. [e] Determined by HPLC analysis using a chiral column (Chiracel AD); see General Procedure for details. [f] Other enantiomer.

With the exception of the tetrazole derivative **4**, reported simultaneously and independently by Ley, Saito/Yamamoto, and Arvidsson,[23] which delivered the product with an improved selectivity of 91% *ee*, none of the tested catalysts could reach the efficiency of L-proline. In all cases, a significant drop in yield was observed which is probably due to the decomposition of the catalysts used.

While in most cases the aldehyde was completely consumed, the formation of various side products could be detected on TLC, thus lowering the yield of α-aminated product. As expected, no reaction whatsoever could be indicated when pyroglutamic acid **12** was used, most likely as a result of the decreased nucleophilicity of the amide nitrogen. Similarly, the same outcome was observed for MacMillan's catalyst **2**, which was found to deliver excellent results in various organocatalytic C–C and C–N bond formation reactions.[24] Both L-proline amide derivatives **5** and **6** gave the aminated product with disappointingly low yields (36 and 10%, respectively), probably as a consequence of the lower acidity of the amide proton, which is transferred onto the azodicarboxylate nitrogen atom. Improving this acidity by substituting one proton with a tosyl residue had only little effect on the yield, but resulted in an increased enantioselectivity of 73% *ee*, still not matching with L-proline.

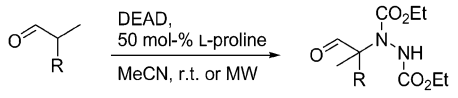
The absolute configuration of the α-aminated product was assigned to be (*R*) through transformation to the corresponding oxazolidinones by comparison with known optical rotation values.[25]

Interestingly, when using (*S*)-2-diphenylmethylpyrrolidine **10**,[26] without the possibility of active electronic interactions, the other enantiomer was formed in moderate selectivity, due to the steric shielding of the Re-face of the enamine carbon atom, thus forcing an approach of the azodicarboxylate from the opposite site of the chiral substituent. The poor yield obtained for this catalyst and its OTMS-protected methanol derivatives **8** and **9** is most likely a result of the heterolytic cleavage of the methyl and hydroxyl group, respectively, and subsequent rearrangement of the generated stabilized double benzylic cation. In summary, none of these tested catalysts was found to improve or even reach the efficiency of L-proline, probably as a consequence of thermal liability or decreased nucleophilicity.

Variation of the ester residue of the azodicarboxylate did not show any significant differences compared to the ethyl derivative. Applying the standard conditions to dibenzyl azodicarboxylate delivered the aminated aldehyde in quantitative yield, yet with a slightly lower enantioselectivity of 72% *ee*. The influence of the size of the residue was further examined using the diisopropyl and di-*tert*-butyl derivative. In both cases, decomposition of the electrophile was observed indicated by a drastic increase of the pressure in the reaction vessel. This was most likely a consequence of the steric demanding of the residue, thus preventing the attack of the enamine. Consequently, only a poor yield of 33% was obtained for both diisopropyl and di-*tert*-butyl azodicarboxylate, together with a disappointingly low selectivity of only 14% *ee* in the case of the diisopropyl derivative. Thus, the size of the residue was found to be mandatory both for effective conversion as well as for a high level of stereoselectivity.

Once the optimum reaction conditions had been established, the scope and limitation of this catalytic α-amination, with respect to the substrates, were tested (Table 4). As a consequence of the poor reactivity and selectivity of 2-phenylpropionaldehydes bearing electron-withdrawing substituents like the fluoro-, nitro- or trifluoromethyl group at room temperature conditions, more attention was concentrated on such starting materials.

Table 4. Microwave-assisted α-amination of α,α-disubstituted aldehydes with diethyl azodicarboxylate.[a]



Ald.	R	Room temperature			Microwave[b]	
		Time [d]	Yield [%][c]	*ee* [%][d]	Yield [%][c]	*ee* [%][d]
a	H	3	62	80	97	89
b	2-naphthyl	2	54	84	76	90
c	4-OMe-C_6H_4	5	85	75	85	88
d	4-CO_2Me-C_6H_4	5	52	82	58	68
e	4-F-C_6H_4	5	26	68	91	89
f	3-CF_3-C_6H_4	4	6	73	54	72
g	4-CF_3-C_6H_4	5	19	24	63	56
h	4-NO_2-C_6H_4	2	85	36	86	52

[a] Reaction conditions: 1.0 equiv. aldehyde, 0.5 equiv. L-proline, 1.5 equiv. DEAD. [b] Application of constant microwave power (200 W, 30 min, 60 °C; for cooling, compressed air with a constant pressure of 0.7 bar (10 psi) was used during the entire experiment). [c] Isolated yields. [d] Determined by HPLC analysis using a chiral column (Chiracel AD); see General Procedure for details.

Thus, when applying microwave irradiation, similar to the unsubstituted 2-phenylpropionaldehyde, a considerable increase in yield as well as selectivity could be noticed, which was reflected in the dramatic rise from 26% yield at room temperature up to 91% yield in case of the fluoro substituent. Since, furthermore, the enantiomeric excess was significantly enhanced to 89%, remarkable improvements could be obtained for normally unreactive starting materials by using microwave irradiation. Aside, the presence of either a nitro- or trifluoromethyl moiety resulted in an notable increase in yield (63% vs. 19% for CF_3) as well as selectivity (52% *ee* vs. 36% *ee* for NO_2) compared to experiments carried out at room temperature. In particular, the values obtained for the nitro substituent indicate a strong decrease of the amount of unselective reacting, through electron-withdrawing substituents stabilized enolates in favour of the formation of chiral enamines, which can preferentially stereoselectively attack the azodicarboxylate. In addition, comparative experiments using electron-rich aromatic ring systems could round out the substitution pattern and demonstrate a positive influence of microwave irradiation on reaction time, yield, and selectivity for these species as well. While the use of the naphthyl derivative resulted in an increase of the yield of 22% and slight enhancement of

the enantiomeric excess to 90%, the *p*-methoxy compound was found to deliver the corresponding product with constantly high yield and rise in selectivity up to 88% *ee*.

Conclusions

The thermally accelerated organocatalytic α-amination of disubstituted aldehydes with azodicarboxylates under microwave conditions has been presented. Compared to the results previously obtained at room temperature, a positive influence of microwave irradiation on reaction time was observed, while both yield and enantioselectivity could be significantly increased. Although the catalyst loading may still not reach quite satisfactory levels, this improved protocol allows the fast and efficient synthesis of α,α-disubstituted amino aldehydes and provided the best results for the α-amination of α-branched aldehydes to date. Further experiments towards the scope and limitations of this organocatalytic reaction will be part of future work in our research group.

Experimental Section

General: All chemicals were purchased and used without further purification. The products were purified by flash chromatography[27] using silica gel 60 from SDS (0.035–0.070 mm) or Merck (0.040–0.063 mm) and sea sand (purified with acid and calcined) from Merck. The solvents were purified by distillation and were determined by volume. The microwave-assisted reactions were conducted using a focused microwave unit (Discover® Reactor from CEM Corporation). The instrument consists of a continuous focused microwave power delivery system with operator-selectable power output from 0–300 W. In all experiments, the microwave power was held constant to ensure reproducibility. Reactions were performed in 10-mL glass vessels, which were sealed with a septum and locked into a pressure device, which controlled the pressure in the reaction vessel (maximum 10 bar). The specified reaction time corresponds to the total irradiation time. The temperature was monitored by an infrared temperature sensor positioned below the reaction vessel. The indicated temperature corresponds to the maximum temperature reached during each experiment.

General Procedure for the Proline-Catalyzed α-Amination under Microwave Irradiation. Preparation of (+)-*N*,*N*′-Bis(ethoxycarbonyl)-2-hydrazino-2-phenylpropionaldehyde as a Detailed Representative Example: In a 10 mL vessel was placed 2-phenylpropionaldehyde (0.134 g, 1.00 mmol, 1.0 equiv.), L-proline (0.058 g, 0.50 mmol, 0.5 equiv.), diethyl azodicarboxylate (0.261 g, 1.50 mmol, 1.5 equiv.), acetonitrile (5 mL), and a magnetic stir bar. The vessel was sealed with a septum, placed into the MW cavity, and locked with the pressure device. Constant microwave irradiation of 200 W as well as simultaneous air-cooling (0.7 bar, 10 psi) were used during the entire reaction time (60 min, 60 °C). After cooling to room temperature, the solvent was removed under reduced pressure, and the product was purified by column chromatography (silica gel, diethyl ether/pentane, 1:1) to afford the α-aminated aldehyde as a light yellow oil (0.305 g, 99%). R_f = 0.50 (diethyl ether/pentane, 1:1). $[\alpha]_D$ = +48.1 (*c* = 1.0, CH_3OH). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.12–1.36 (m, 6 H), 1.79 (s, 3 H), 4.07–4.29 (m, 4 H), 6.27, 6.46 (br. s, 1 H), 7.27–7.63 (m, 5 H), 9.60, 9.77 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.2, 14.4 (CH_3), 17.7 (CH_3), 62.4, 63.4 (CH_2), 73.2 (CR_4), 126.9 (CH_{ar}), 128.2 (CH_{ar}), 129.0 (CH_{ar}), 136.9 (C_q), 156.0, 156.3 (C_q), 192.8 (C_q) ppm. IR (KBr): $\tilde{\nu}$ = 3245 cm^{-1} (m, ν[NH]), 3041 (w, ν[CH_{ar}]), 2990 [m, ν[CH_3]), 2872, 2769 (w, w, ν[C(O)H]), 1752 (m, ν[CO]), 1699 [m, ν[CO]), 1533 (m), 1481, 1448 (w, w, δ_{as}[CH_3]), 1368 (w, δ_{sy}[CH_3]), 1253 [m, ν[C–O–C]) cm^{-1}. MS (FAB): *m*/*z* (%): 309 (100) [M^+ + 1], 279 (32) [M^+ – CHO], 242 (5), 235 (20) [$C_{12}H_{15}N_2O_3^+$], 207 (90) [$C_{11}H_{15}N_2O_2^+$], 177 (86) [$C_{10}H_{11}NO_2^+$]. $C_{15}H_{20}N_2O_5$ (308.33 g/mol): calcd. C 58.43, H 6.54, N 9.09; found C 58.36, H 6.74, N 8.58. The *ee* was determined by HPLC with chiral stationary phase using Chiralpak AS (*n*-heptane/*i*PrOH, 7:3): R_t(major) = 11.12 min, R_t(minor) = 13.71 min, 84% *ee*.

Supporting Information (see also the footnote on the first page of this article): General experimental procedure and NMR spectra for all compounds.

Acknowledgments

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