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Organocatalytic transformation of 1,3-diketones into optically active cyclohexanones

Dorota Gryko*

Institute of Organic Chemistry of the Polish Academy of Science, Kasprzaka 44/52, 01-224 Warsaw, Poland

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Abstract—The domino Michael-aldol reaction of 1,3-diketones with MVK in the presence of L-proline furnished highly substituted cyclohexanones in a regio- and stereocontrolled manner. When the reaction was performed in NMP, high yields (up to 93%) and enantioselectivities up to 80% were observed.

1. Introduction

The usual procedure for the synthesis of organic compounds is the stepwise formation of the individual bonds in a target molecule. However, it would be much more efficient if several bonds could be formed in one sequence without isolating the intermediates. This type of transformation called a domino reaction.[1] Among them the domino Michael-aldol reaction is one of the simplest methods for the preparation of highly substituted cyclohexane derivatives in a diastereo- and enantioselective manner.[2] This transformation is related to the proline catalyzed Robinson annulation studied by the Parrish and Wiechert groups[3] and further investigated by Bui and Barbas.[4] As it was subsequently discovered, proline itself can be an effective organocatalyst of many other asymmetric transformations, such as the aldol,[5] Mannich,[5a,b,6] Michael[5a,b,7] reactions, the direct electrophilic α-amination,[8] aminoxylation,[9] and several others.[5a,f]

The objective herein was to develop an efficient, enantioselective protocol for the synthesis of 3-hydroxycyclohexanones via a domino Michael-aldol reaction of acyclic 1,3-diketones with simple α,β-unsaturated ketones. We envisioned that both steps can be catalyzed by L-proline or an analogous catalyst. Until very recently, it was known that chiral amines could catalyze only the first step of such Michael-aldol tandem sequence.[10] On the other hand, the use of DMSO as a solvent for such types of process led to the subsequent elimination after the aldol reaction as recently reported.[4] While this paper was in preparation, the related subject was described by Jørgensen et al.[2e,f] They demonstrated that the addition of α,β-unsaturated ketones to β-ketoesters in the presence of an imidazolidine catalyst–phenylalanine derivatives, gave highly substituted cyclohexanones containing 3–4 stereogenic centers in a diastereo- and enantioselective manner. The same authors widely studied the reactions of α,β-unsaturated enones with malonates and 4-hydroxycumarins.[11]

2. Results and discussion

The reaction of 1,3-bisphenyl-propane-1,3-dione **1** with methyl vinyl ketone (MVK) in DMSO catalyzed by L-proline has been chosen as a model system for the optimization studies (Scheme 1).

The results of the initial screening experiments showed that only L-proline, among catalysts studied [*trans*-4-hydroxy-L-proline, (*R*)-(−)-thiazolidine-4-carboxylic acid, MacMillan catalyst], gave the cyclic product. It was found that the use of less polar solvents than DMSO gave very poor yields of the desired cyclohexanone derivative **3a** (Table 1, entries 2–5). The reactions in CH_2Cl_2, CH_3CN, or dioxane, even, when performed at high pressure (10.5 kbar) only gave traces of **3a**. Using EtOH as a solvent, Michael adduct **2a** was obtained in 50% yield, accompanied by only traces of **3a** (Table 1, entry 7). It should be pointed out that EtOH was the solvent of choice for the domino Michael-aldol reaction catalyzed by imidazolidine-type catalyst giving

* Tel.: +48 22 3432129; fax: +48 22 6326681; e-mail: dgryko@icho.edu.pl

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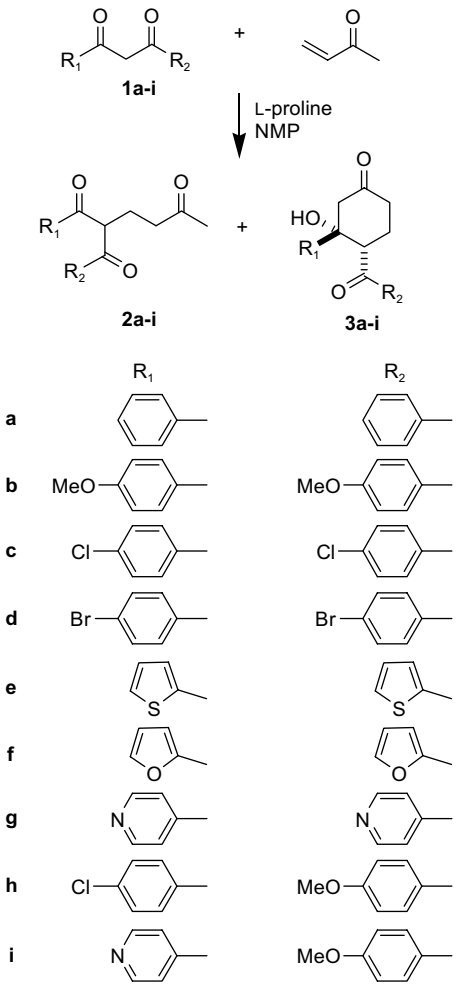


Scheme 1. The domino Michael-aldol reaction of 1,3-diketones **1a**–**i** with MVK catalyzed by L-proline.

Table 1. Solvent screening for the domino Michael-aldol reaction of **1a** with MVK

Entry	Solvent	Yield[a] of **2a** (%)	Yield[a] of **3a** (%)	Ee[b] of **3a** [%]
1	DMSO	17	46	56
2	CH_2Cl_2	56	6	45
3	$CHCl_3$	37	0	—
4	CH_3CN	52	27	60
5	THF	24	0	—
6	MeOH	11	2	46
7	EtOH	50	Trace	nd
8	DMF	44	12	11
9	NMP	14	61	58

[a] Isolated yield after column chromatography.
[b] Enantiomeric excesses were determined by chiral HPLC analysis in comparison with racemic material.

cyclohexanone derivatives as described by Jørgensen's group.[2e,f] Furthermore, it was observed that the yield, as well as the enantiomeric excess, could be improved by using 1-methyl-2-pyrrolidinone (NMP) as a solvent (Table 1, entry 9). With the defined optimal conditions, a series of 1,3-diketones **1b**–**i** was examined in order to establish the scope of the reaction (Table 2). These compounds were synthesized using the Claisen condensation described by Franek.[12] This procedure was selected due to its simplicity and robustness (purification did not require column chromatography since the product was isolated as the sodium enolate salt). The use of other methods lead to an unseparable mixture of products. The procedure was suitable also for the preparation of non-symmetrical diketones **1h** and **1i**. The reaction of 1,3-diaroylmethanes **1a**–**d** with MVK gave cyclohexanones **3a**–**d** as single diastereoisomers in good yields and moderate enantioselectivities (Table 2, entries 1–4). An increase in the electronegativity of the functional group in the *para*-position resulted in an increase in the yield of the cyclic product, reaching 85% for the bromo substituent (Table 2, entry 4). The reaction proceeded well also for 1,3-diketones bearing heteroaromatic substituents: 2-furan, 2-thiophen and 4-pyridine (Table 2, entries 5–7). The highly reactive diketone **1g** gave only cyclohexanone derivative **3g** in 81% yield and 80% ee as a sole product. We have also tried the reaction of MVK with nonsymmetrical 1,3-diketones **1h** and **1j**. The difference in the reactivity of the carbonyl group strongly influences the course of the domino Michael-aldol reaction. In the reaction of **1h** with MVK, two regioisomeric cyclohexanones were obtained in a ratio 15 (**3h**): 1 (Table 2, entry 8). They were separated on column chromatography and the location of substituents unambiguously elucidated using ^{13}C–^{1}H GHSQC and ^{13}C–^{1}H GHMBC NMR techniques. When the *p*-chlorophenyl group was replaced by the more electron withdrawing 4-pyridine substituent only **3i** was isolated in 93% yield (Table 2, entry 9).

Table 2. The enantioselective domino Michael-aldol reaction of 1,3-diketones **1a**–**i** with MVK in the presence of L-proline in NMP

Entry	**1**	Recovery of **1** (%)	Yield[a] of **2** (%)	Yield[a] of **3** (%)	Ee[b] of **3**
1	**1a**	11	14	63	58
2	**1b**	39	39	39	43
3	**1c**	12	7	82	53
4	**1d**	8	7	85	63
5	**1e**	2	52	47	67
6	**1f**	16	35	52	47
7	**1g**	0	0	81	80
8	**1h**	21	26	57 +4	67
9	**1i**	0	0	93	50

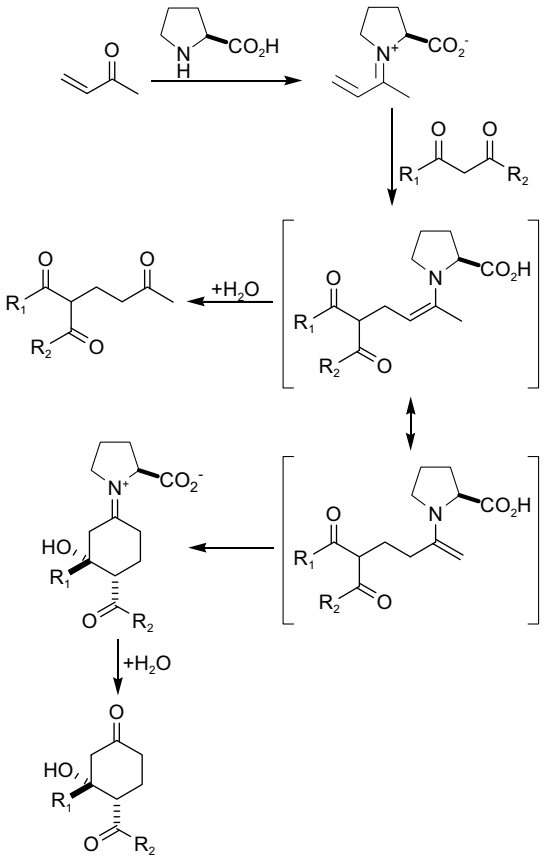
[a] Isolated yield after column chromatography.
[b] Enantiomeric excesses were determined by chiral HPLC analysis in comparison with racemic material.

In all cases of the domino Michael-aldol reaction, only a single diastereoisomer was formed. The reaction proceeds through the initial formation of the Michael product, which epimerizes in the reaction mixture because the pro-stereogenic or the stereogenic carbon center bears two ketone substituents. Subsequent intramolecular aldol reaction catalyzed by L-proline proceeds with high diastereoselectivity but with moderate enantioselectivity. This is intriguing because Jørgensen and co-workers[2e] postulated that the diastereoselectivity in the similar Michael-aldol reaction catalyzed by the imidazolidine derivative is controlled by the stable stereogenic

center formed in the initial Michael reaction. This is not the case when MVK is used as a starting material since there is no stable stereogenic center in the Michael adduct **2**. On the other hand, Christoffers[13] reported that the reaction of benzylidene acetone with β-ketoesters catalyzed by inorganic bases gave regioisomeric mixture of cyclic products.

Furthermore, the reaction of 1,3-bisphenyl-propane-1,3-dione **1** with MVK in the presence of simple organic base, pyrrolidine, only gave the Michael adduct (with low yield). Consequently, contrary to Jørgensen and co-workers[2e,f] in the domino Michael-aldol reaction presented in these papers, the intramolecular aldol reaction is catalyzed by the chiral molecule, L-proline. We believe that the catalyst: (a) activates the Michael acceptor by iminium-ion formation, (b) deprotonates the 1,3-diketone, and (c) activates the donor by the enamine formation in the intramolecular aldol reaction. Furthermore, it activates the acceptor by the formation of the hydrogen bond (through carboxylic group), since the reaction in the presence of pyrrolidine stopped at the Michael adduct (Scheme 2).

The assignment of the relative stereochemistries of cyclohexanones is based on X-ray crystallographic studies (Fig. 1, Supporting Information) of **3i**. The OH group is *cis* to *p*-MeOPhCO. The same configuration was assigned for the remaining adducts **3a**–**h** by comparison of their NMR spectra and by analogy to **3i**.



Scheme 2. The domino Michael-aldol reaction catalyzed by L-proline.

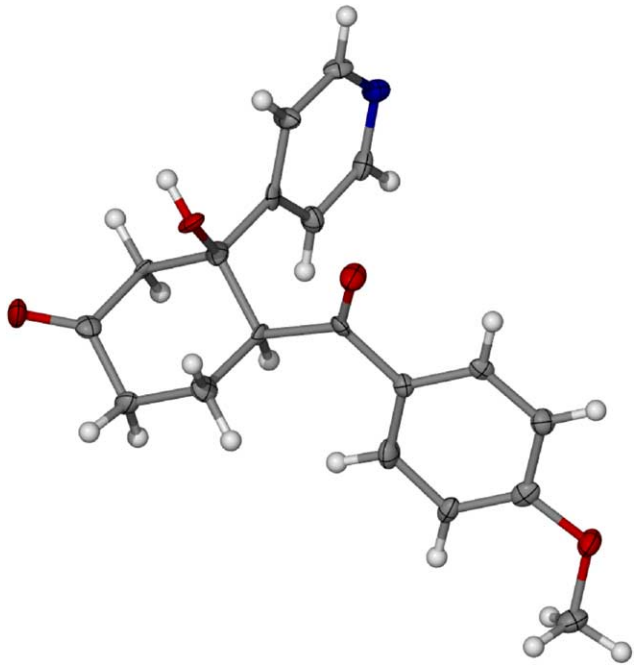


Figure 1. X-ray structure of **3i**. Thermal ellipsoids are at 50% probability level.

3. Conclusion

In summary, we have developed the L-proline catalyzed domino Michael-aldol reaction that provides cyclohexanone derivatives with new type of substitution pattern in a highly diastereoselective manner and with good enantioselectivity. The described method is complementary to the Jørgensen procedure,[2e,f] which does not work for MVK. We have demonstrated that the reaction is also highly regioselective when the non-symmetrical 1,3-diketones were used. The regioselectivity of this process increases with an increase in the difference in reactivity of carbonyl groups. It is believed that the subsequent intramolecular aldol reaction proceeds through an enamine mechanism and that the chirality transfer takes place at this stage. These results are not only of theoretical significance in that they provide insight into factors influencing the course of the reaction of 1,3-diketones with MVK, but they may also open the door to practical applications of new cyclohexanone derivatives.

4. Experimental

4.1. General experimental

All chemicals were used as received unless otherwise noted. Reagent grade solvents (CH_2Cl_2, hexanes) were distilled prior use. All reported ^1H NMR spectra were collected on a Bruker spectrometer at 500 (^1H NMR) and 125 (^{13}C NMR) MHz or a Varian Gemini spectrometer at 200 (^1H NMR) and 50 (^{13}C NMR) MHz. Chemical shifts are reported as δ values relative to the TMS signal defined at $\delta = 0.00$ (^1H NMR) or $\delta = 0.0$ (^{13}C NMR). IR spectra were obtained on a

Perkin–Elmer 1640 FTIR unit. Mass spectra were obtained on an AMD-604 Intectra instrument using the EI or on a Mariner PerSeptive Biosystem instrument using the ESI technique. Chromatography was performed on silica (Kieselgel 60, 200–400 mesh). Melting points were determined using a Kofler hot-stage apparatus and are uncorrected. The following ketones were obtained according to the literature:[12] **1a**–**h**.

4.2. Synthesis of 1,3-diketones

A solution of methyl pyridine-4-carboxylate (1.90 mL, 16.3 mmol) and 4-methoxy-acetophenone (2.20 g, 14.8 mmol) in a mixture of THF (3.0 mL) and DMSO (2.0 mL) was added within 1 h under vigorous magnetic stirring to a cooling (0–10 °C) suspension of NaH (0.66 g, 60% suspension in a mineral oil) in a mixture of THF (2.6 mL) and DMSO (2.5 mL). After the addition, stirring was continued and the temperature raised to 20 °C within 30 min. Finally the reaction mixture was stirred at 30 °C for 50 min. The solvents were then removed in vacuo (water bath 40 °C). A dark-brown fluid formed, which was then dissolved in water and washed three times with Et_2O. The aqueous layer was acidified with 10% AcOH. During the acid addition, dark brown color was disappearing and at the same time a yellowish precipitate was forming. The precipitate was filtered off and washed with water. Analytically pure compound **1i** was obtained and recrystallized from EtOH (yellow needles, 2.8 g, 75%). mp 132–133 °C (EtOH). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 3.86 (s, 3H), 6.82 (s, 1H), 6.98 (AA′BB′/2, J = 9.0 Hz, 2H), 7.76 (AA′BB′/2, J = 6.2 Hz, 2H), 7.99 (AA′BB′/2, J = 9.0 Hz, 2H), 8.78 (AA′BB′/2, J = 6.2 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 55.5, 93.4, 114.1, 120.3, 127.8, 129.7, 142.4, 150.6, 163.7, 179.5, 188.2. IR (KBr): 3035, 2973, 2844, 1607, 1590, 1543, 1518, 1497, 1312, 1267, 1240, 1190, 1181, 1024, 840, 788, 698, 633, 584 cm^{-1}. ESI-MS: obsd: 256.0974 $[M+H]^+$; calcd exact mass: 256.0968. Anal. Calcd for $C_{15}H_{13}NO_3$: C, 70.47; H, 5.10; N, 5.48. Found: C, 70.47; H, 4.99; N, 5.48.

4.3. General procedure for the addition of MVK to diketones

To a solution of diketone (1.0 mmol) and L-proline (0.2 mmol) in NMP (2.5 mL), MVK (1.0 mmol, 98 μL) was added at room temperature. The resulting mixture was stirred for 72 h and then diluted with an aqueous solution of NH_4F. The resulting solution was extracted with AcOEt three times. The organic layer was washed with water and dried over Na_2SO_4. Column chromatography (mixture of hexanes/AcOEt) gave three fractions: the recovered substrate, the Michael adduct and the cyclic derivative in the order of elution.

4.3.1. Compound 2a. Crystallization from AcOEt/hexanes gave white solid (77 mg, 15%). mp 64–65 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.12 (s, 3H), 2.32 (dd, J = 13.1 Hz, J = 6.5 Hz, 2H), 2.69 (t, J = 6.4 Hz, 2H), 5.48 (t, J = 6.7 Hz, 1H), 7.46 (t, J = 7.7 Hz, 4H), 7.57 (t, J = 7.4 Hz, 2H), 8.03 (d, J = 7.6 Hz, 4H). ^{13}C NMR ($CDCl_3$, 125 MHz), δ = 23.2, 30.0, 40.8, 54.8, 128.7, 128.9, 133.6, 135.9, 196.3, 208.6. IR (KBr): 3065, 2946, 1700, 1667, 1596, 1449, 1328, 1292, 1252, 1211, 1200, 1180, 1003, 757, 707, 691, 643, 600 cm^{-1}. ESI-MS: obsd: 317.1152 $[M+Na]^+$; calcd exact mass: 317.1148. Anal. Calcd for $C_{19}H_{18}O_3$: C, 77.53; H, 6.16. Found: C, 77.44; H, 6.18.

4.3.2. Compound 3a. Column chromatography gave a white solid (204 mg, 64%). mp 127–128 °C (AcOEt/hexanes). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.2–2.3 (m, 1H), 2.47 (ddd, J = 25.5 Hz, J = 12.6 Hz, J = 4.9 Hz, 1H), 2.54–2.74 (m, 4H), 4.48 (dd, J = 12.3 Hz, J = 3.8 Hz, 1H), 4.92 (d, J = 2.8 Hz, 1H), 7.15 (t, J = 7.3 Hz, 1H), 7.25 (t, J = 7.8 Hz, 2H), 7.45 (m, 4H), 7.58 (t, J = 7.4 Hz, 1H), 7.87 (d, J = 7.5 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 26.439.9, 49.1, 55.1, 78.4, 124.3, 127.3, 128.2, 128.5, 128.9, 134.1, 135.9, 145.4, 205.0, 207.0. IR (KBr): 3360, 3056, 2962, 2934, 1707, 1678, 1448, 1379, 1342, 1298, 1253,1235, 1105, 970, 950, 758, 701 cm^{-1}. ESI-MS: obsd: 317.1164 $[M+Na]^+$; calcd exact mass: 317.1148. Anal. Calcd for $C_{19}H_{18}O_3$: C, 77.53; H, 6.16. Found: C, 77.47; H, 6.27. ee = 58% determined by HPLC: Chiracel OD-H, hexane/*i*-PrOH, 8:2, flow rate: 0.5 mL/min, λ = 225 nm; t_1(major) = 20.80, t_2(minor) = 22.83.

4.3.3. Compound 2b. Column chromatography gave a white solid (210 mg, 59%). mp 96–97 °C (AcOEt/cyclohexane). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.12 (s, 3H), 2.31 (dd, J = 13.2 Hz, J = 6.5 Hz, 2H), 2.67 (t, J = 6.5 Hz, 2H), 3.85 (s, 6H), 5.32 (t, J = 6.8 Hz, 1H), 6.92 (m, 4H), 8.02 (m, 4H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 23.3, 30.0, 40.9, 54.7, 55.5, 114.1, 129.0, 131.0, 163.8, 194.9, 208.8. IR (KBr) : 3425, 2960, 2937, 2839, 1716, 1652, 1599, 1572, 1512, 1345, 1301, 1254, 1238, 1171, 1117, 1093, 1030, 965, 840, 735, 608, 583, 564 cm^{-1}. ESI-MS: obsd: 354.14592 $[M]^+$; calcd exact mass: 354.14672. Anal. Calcd for $C_{21}H_{22}O_5$: C, 71.17; H, 6.26. Found: C, 71.22; H, 6.16.

4.3.4. Compound 3b. Column chromatography gave a white solid (97 mg, 27%). mp 123–124 °C (AcOEt/cyclohexane). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.2–2.25 (m, 1H), 2.44 (ddd, J = 25.3 Hz, J = 12.6 Hz, J = 5.2 Hz, 1H), 2.5–2.7 (m, 4H), 3.71 (s, 3H), 3.86 (s, 3H), 4.39 (dd, J = 12.3 Hz, J = 3.8 Hz, 1H), 5.09 (s, 1H), 6.76 (AA′BB′/2, J = 8.9 Hz, 2H), 6.92 (AA′BB′/2, J = 8.9 Hz, 2H), 7.36 (AA′BB′/2, J = 8.8 Hz, 2H), 7.88 (AA′BB′/2, J = 8.9 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 26.4, 39.9, 48.5, 55.1, 55.4, 55.5, 78.2, 113.8, 114.1, 125.5, 128.8, 130.6, 137.8, 158.5, 164.4, 203.4, 207.3. IR (KBr): 3425, 2960, 2937, 2839, 1716, 1652, 1599, 1572, 1512, 1345, 1301, 1254, 1238, 1171, 1117, 1093, 1030, 965, 840, 735, 608, 583, 564 cm^{-1}. Anal. Calcd for $C_{21}H_{22}O_5$: C, 71.17; H, 6.26. Found: C, 71.15; H, 6.09. Ee = 43% determined by HPLC: Chiracel OD-H, hexane/*i*-PrOH, 1:1, flow rate: 0.8 mL/min, λ = 285 nm; t_1(major) = 8.83, t_2(minor) = 11.07.

4.3.5. Compound 2c. Column chromatography gave a white solid (24 mg, 7%). mp 73–74 °C (AcOEt/pentane). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.13 (s, 3H), 2.2–2.3 (m, 2H), 2.70 (t, J = 6.2 Hz, 2H), 5.37 (t, J = 6.8 Hz,

1H), 7.44 (m, 4H), 7.97 (m, 4H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 23.1, 30.1, 40.6, 54.9, 129.3, 130.0, 134.0, 140.4, 195.0, 208.7. IR (KBr): 2928, 2913, 1711, 1693, 1665, 1588, 1401, 1288, 1252, 1209, 1159, 1089, 1003, 979, 923, 843, 825 cm^{-1}. ESI-MS: obsd: 363.0544 $[M]^+$; calcd exact mass: 363.0549. Anal. Calcd for $C_{19}H_{16}O_3Cl_2$: C, 62.83; H, 4.44; Cl, 19.52. Found: C, 63.09; H, 4.40; Cl, 19.63.

4.3.6. Compound 3c. Column chromatography gave a white solid (297 mg, 82%). mp 137–139 °C (AcOEt–pentane). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.2–2.3 (m, 1H), 2.45 (ddd, J = 25.7 Hz, J = 12.8 Hz, J = 4.6 Hz, 1H), 2.5–2.7 (m, 4H), 4.37 (dd, J = 12.3 Hz, J = 3.8 Hz, 1H), 4.86 (br s, 1H), 7.22 (AA′BB′/2, J = 8.6 Hz, 2H), 7.37 (AA′BB′/2, J = 8.6 Hz, 2H), 7.44 (AA′BB′/2, J = 8.6 Hz, 2H), 7.82 (AA′BB′/2, J = 8.6 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 26.3, 39.8, 49.0, 54.9, 78.1, 125.8, 128.8, 129.4, 129.6, 133.3, 133.9, 141.1, 143.8, 203.5, 206.2. IR (KBr): 3353, 2957, 2934, 1712, 1681, 1587, 1490, 1403, 1300, 1231, 1094, 1012, 968, 862, 842, 827, 742, 625, 542 cm^{-1}. EI-MS: obsd: 362.04681 $[M]^+$; calcd exact mass: 362.04765. Anal. Calcd for $C_{19}H_{16}O_3Cl_2$: C, 62.83; H, 4.44; Cl, 19.52. Found: C, 62.88; H, 4.54; Cl, 19.37. Ee = 53% determined by HPLC: Chiracel OD-H, hexane/*i*-PrOH, 75:15, flow rate: 1 mL/min, λ = 225 nm; t_1(major) = 12.67, t_2(minor) = 16.27.

4.3.7. Compound 2d. Column chromatography gave a white solid (34 mg, 8%). mp 99–100 °C (MeOH). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.13 (s, 3H), 2.29 (dd, J = 12.7 Hz, J = 6.4 Hz, 2H), 2.69 (t, J = 6.2 Hz, 2H), 5.36 (t, J = 6.7 Hz, 1H), 7.61 (AA′BB′/2, J = 8.6 Hz, 4H), 7.89 (AA′BB′/2, J = 8.6 Hz, 4H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 23.0, 30.1, 40.6, 54.8, 129.1, 130.1, 132.3, 134.4, 195.2, 208.7. IR (KBr) : 2927, 2910, 1710, 1695, 1664, 1583, 1430, 1395, 1287, 1252, 1208, 1159, 1067, 1002, 978, 841, 822, 727, 604 cm^{-1}. ESI-MS: obsd: 472.9381 $[M+Na]^+$; calcd exact mass: 472.9358. Anal. Calcd for $C_{19}H_{16}O_3Br_2$: C, 50.47; H, 3.57; Br, 35.35. Found: C, 50.48; H, 3.65; Br, 35.40.

4.3.8. Compound 3d. Column chromatography gave a white solid (297 mg, 82%). mp 148–149 °C (MeOH). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.2–2.3 (m, 1H), 2.43 (ddd, J = 25.7 Hz, J = 12.8 Hz, J = 5.0 Hz, 1H), 2.53 (m, 1H), 2.6–2.7 (m, 3H), 4.38 (dd, J = 12.4 Hz, J = 3.7 Hz, 1H), 4.86 (br s, 1H), 7.32 (AA′BB′/2, J = 8.6 Hz, 2H), 7.38 (AA′BB′/2, J = 8.6 Hz, 2H), 7.62 (AA′BB′/2, J = 8.6 Hz, 2H), 7.75 (AA′BB′/2, J = 8.6 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 26.2, 39.7, 48.9, 54.8, 78.1, 121.4, 126.1, 129.6, 129.9, 131.7, 132.4, 134.3, 144.3, 203.7, 206.2. IR (KBr): 3428, 2958, 1720, 1655, 1580, 1484, 1397, 1305, 1230, 1210, 1091, 1070, 1008, 959, 839, 782, 741, 589, 562 cm^{-1}. ESI-MS: obsd: 472.9384 $[M+Na]^+$; calcd exact mass: 472.9385. Anal. Calcd for $C_{19}H_{16}O_3Br_2$: C, 50.47; H, 3.57; Br, 35.35. Found: C, 50.49; H, 3.48; Br, 35.44. Ee = 63% determined by HPLC: Chiracel OD-H, hexane/*i*-PrOH, 8:2, flow rate: 0.8 mL/min, λ = 225 nm; t_1(major) = 11.52 min, t_2(minor) = 14.00 min.

4.3.9. Compound 2e. Column chromatography gave a white solid (158 mg, 52%). mp 96–97 °C (AcOEt/pentane). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.12 (s, 3H), 2.36 (dd, J = 13.0 Hz, J = 6.6 Hz, 2H), 2.68 (t, J = 6.4 Hz, 2H), 5.09 (t, J = 7.0 Hz, 1H), 7.12 (dd, J = 4.9 Hz, J = 3.9 Hz, 2H), 7.67 (dd, J = 5.1 Hz, J = 1.1 Hz, 2H), 7.90 (dd, J = 3.9 Hz, J = 1.1 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 23.7, 30.1, 40.6, 58.1, 128.5, 133.2, 134.9, 143.2, 188.2, 208.3. IR (KBr): 3122, 3087, 2921, 1710, 1668, 1634, 1516, 1412, 1352, 1278, 1240, 1198, 1160, 1063, 958, 855, 744, 732, 612 cm^{-1}. ESI-MS: obsd: 329.0280 $[M+Na]^+$; calcd exact mass: 329.0277. Anal. Calcd for $C_{15}H_{14}O_3S_2$: C, 58.80; H, 4.61; S, 20.93. Found: C, 58.84; H, 4.52; S, 20.74.

4.3.10. Compound 3e. Column chromatography gave a white solid (144 mg, 47%). mp 134–136 °C (AcOEt/pentane). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.27 (m, 1H), 2.51 (m, 2H), 2.61 (m, 1H), 2.71 (d, J = 14.9 Hz, 1H), 2.83 (dd, J = 14.9 Hz, J = 2.0 Hz, 1H), 4.15 (m, 1H), 5.23 (br s, 1H), 6.84 (dd, J = 5.2 Hz, J = 3.6 Hz, 1H), 6.94 (dd, J = 3.6 Hz, J = 1.1 Hz, 1H), 7.11 (dd, J = 5.0 Hz, J = 1.1 Hz, 1H), 7.18 (dd, J = 4.9 Hz, J = 3.9 Hz, 1H), 7.73 (dd, J = 4.9 Hz, J = 1.0 Hz, 1H), 7.84 (dd, J = 3.9 Hz, J = 1.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 26.4, 39.7, 52.3, 56.0, 77.3, 122.7, 124.4, 127.0, 128.6, 133.1, 135.7, 143.0, 150.7, 196.8, 205.9. IR (KBr): 3361, 3105, 2953, 1717, 1628, 1513, 1409, 1389, 1300, 1249, 1200, 1096, 1086, 1049, 946, 849, 807, 745, 720, 654, 634, 608 cm^{-1}. ESI-MS: obsd: 329.0281 $[M+Na]^+$; calcd exact mass: 329.0277. Anal. Calcd for $C_{15}H_{14}O_3S_2$: C, 58.80; H, 4.61; S, 20.93. Found: C, 58.82; H, 4.60; S, 20.78. Ee = 67% determined by HPLC: Diacel Chiralpak OJ, hexane/*i*-PrOH, 1:1, flow rate: 0.5;mL/min, λ = 245 nm; t_1(minor) = 28.41, t_2(major) = 31.41.

4.3.11. Compound 2f. Column chromatography gave a white solid (95 mg, 35%). mp 47–48 °C (Et_2O/pentane). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.11 (s, 3H), 2.31 (dd, J = 13.8 Hz, J = 6.9 Hz, 2H), 2.60 (t, J = 6.9 Hz, 2H), 4.94 (t, J = 7.0 Hz, 1H), 6.54 (dd, J = 3.6 Hz, J = 1.7 Hz, 2H), 7.34 (d, J = 3.6 Hz, 2H), 7.57 (d, J = 1.7 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 22.5, 29.9, 40.6, 56.0, 112.6, 118.7, 147.0, 151.8, 184.1, 207.9. ESI-MS: obsd: 297.0748 $[M+Na]^+$; calcd exact mass: 297.0748. Anal. Calcd for $C_{15}H_{14}O_5$: C, 65.69; H, 5.14. Found: C, 65.66; H, 5.14.

4.3.12. Compound 3f. Column chromatography (very slow) gave a white solid (146 mg, 52%). mp. 143–144 (Et_2O/pentane) ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.16 (m, 1H), 2.42 (ddd, J = 25.4 Hz, J = 12.7 Hz, J = 4.7 Hz, 1H), 2.52 (d, J = 6.3 Hz, 1H), 2.60–266 (m, 1H), 2.71 (dd, J = 14.9 Hz, J = 2.7 Hz, 1H), 2.83 (d, J = 14.92 Hz, 1H), 4.41 (dd, J = 12.2 Hz, J = 3.9 Hz, 1H), 4.68 (br s, 1H), 6.22 (dd, J = 3.3 Hz, J = 1.8 Hz, 1H), 6.25 (d, J = 3.2 Hz, 1H), 6.57 (dd, J = 3.6 Hz, J = 1.7 Hz, 1H), 7.21 (d, J = 1.0 Hz, 1H), 7.28 (d, J = 3.6 Hz, 1H), 7.64 (d, J = 1.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 24.9, 39.6, 48.4, 52.1, 75.5, 105.8, 110.5, 112.8, 119.1, 141.7, 147.7, 151.6, 157.1,

192.3, 206.4. IR (KBr): 3360, 2963, 2922, 1710, 1673, 1562, 1468, 1400, 1306, 1264, 1150, 1110, 1090, 989, 882, 781, 732, 594 cm^{-1}. ESI-MS: obsd: 297.0736 $[M+Na]^+$; calcd exact mass: 297.0733. Anal. Calcd for $C_{15}H_{14}O_5$: C, 65.69; H, 5.14. Found: C, 65.60; H, 5.27. Ee = 47% determined by HPLC: Diacel Chiralpak OJ, hexane/*i*-PrOH, 1:1, flow rate: 0.5 mL/min, λ = 285 nm; t_1(minor) = 20.32, t_2(major) = 22.16.

4.3.13. Compound 3g. Column chromatography (silica, CH_2Cl_2/MeOH) gave a white solid (241 mg, 81%). mp 179–181 °C (MeOH/CH_2Cl_2). ^{1}H NMR (DMSO-d_6, 500 MHz): δ = 2.04–2.21 (m, 3H), 2.25–2.4 (m, 3H), 2.7–2.8 (m, 1H), 3.17 (d, J = 14.3 Hz, 1H), 4.73 (dd, J = 11.8 Hz, J = 3.56 Hz, 1H), 5.47 (s, 1H), 7.45 (m, 2H), 7.60 (m, 2H), 8.35 (m, 2H), 8.66 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 24.5, 39.0, 49.9, 53.7, 76.8, 120.1, 120.9, 142.8, 149.3, 150.5, 154.0, 201.8, 207.4. IR (KBr): 3417, 3163, 2972, 2935, 1708, 1694, 1597, 1556, 1411, 1370, 1343, 1300, 1230, 1207, 1110, 1063, 957, 948, 822, 658, 605, 577 cm^{-1}. ESI-MS: obsd: 297.1245 $[M+H]^+$; calcd exact mass: 297.1234. Anal. Calcd for $C_{17}H_{16}N_2O_3$: C, 68.91; H, 5.44; N, 9.45. Found: C, 68.79; H, 5.36; N, 9.40. Ee = 80% determined by HPLC: Chiracel ODH, hexane/*i*-PrOH, 1:1, flow rate: 0.5 mL/min, λ = 225 nm; t_1(major) = 14.91, t_2(minor) = 20.40.

4.3.14. Compound 2h. Column chromatography (very slow) gave a white solid (94 mg, 26%). mp 81–82 °C (AcOEt/cyclohexane). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.12 (s, 3H), 2.30 (dd, J = 13.0 Hz, J = 6.5 Hz, 2H), 2.68 (t, J = 6.4 Hz, 2H), 3.86 (s, 3H), 5.35 (t, J = 6.8 Hz, 1H), 6.95 (AA′BB′/2, J = 7.0 Hz, 2H), 7.41 (AA′BB′/2, J = 7.4 Hz, 2H), 7.95 (AA′BB′/2, J = 7.9 Hz, 2H), 8.03 (AA′BB′/2, J = 8.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 23.2, 30.0, 40.7, 54.8, 55.5, 114.2, 128.7, 129.2, 130.0, 131.1, 134.3, 140.0, 164.1, 194.6, 195.2, 208.7. IR (KBr): 2950, 1714, 1691, 1651, 1600, 1571, 1421, 1397, 1351, 1318, 1266, 1206, 1180, 1171, 1032, 1011, 998, 854, 842, 580, 542 cm^{-1}. ESI-MS: obsd: 381.0879 $[M]^+$; calcd exact mass: 381.0888. Anal. Calcd for $C_{22}H_{18}O_4Cl$: C, 66.95; H, 5.34; Cl, 9.86. Found: C, 67.20; H, 5.38; Cl, 9.86.

4.3.15. Compound 3h. Column chromatography (very slow) gave a white solid (203 mg, 57%). mp 117–118 °C (AcOEt/cyclohexane). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.2–2.3 (m, 1H), 2.45 (m, 1H), 2.51–2.65 (m, 4H), 3.87 (s, 3H), 4.37 (dd, J = 12.4 Hz, J = 3.7 Hz, 1H), 5.15 (br s, 1H), 6.93 (m, 2H), 7.21 (m, 2H), 7.39 (m, 2H), 7.87 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 26.5, 39.9, 48.3, 55.0, 55.6, 78.1, 114.2, 125.9, 128.5, 128.6, 129.1, 130.7, 133.1, 144.2, 164.6, 203.0, 206.6. IR (KBr): 3419, 3359, 2956, 2937, 1719, 1644, 1599, 1573, 1422, 1384, 1267, 1237, 1170, 1092, 1014, 840, 602, 566 cm^{-1}. ESI-MS: obsd: 381.0885 $[M+Na]^+$; calcd exact mass: 381.0864. Anal. Calcd for $C_{20}H_{19}O_4Cl$: C, 66.95; H, 5.34; Cl, 9.88. Found: C, 66.93; H, 5.50; Cl, 9.63. Ee = 67% determined by Chiracel OD-H, hexane/*i*-PrOH, 8:2, flow rate: 1 mL/min, λ = 285nm; t_1(major) = 10.33 min, t_2(minor) = 15.20 min.

4.3.16. Regioisomer of 3h. Column chromatography (very slow) gave a white solid (33 mg, 4%). mp 124–126 °C (AcOEt/cyclohexane).^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.1–2.2 (m, 1H), 2.44 (ddd, J = 25.4 Hz, J = 12.8 Hz, J = 4.5 Hz, 1H), 2.54 (dt, J = 14.0 Hz, J = 6.3 Hz, 1H), 2.60–266 (m, 3H), 3.82 (s, 3H), 4.22 (dd, J = 12.2 Hz, J = 3.7 Hz, 1H), 4.76 (br s, 1H), 6.77 (AA′BB′/2, J = 8.9 Hz, 2H), 7.33 (AA′BB′/2, J = 8.9 Hz, 2H), 7.43 (AA′BB′/2, J = 8.9 Hz, 2H), 7.81 (AA′BB′/2, J = 8.9 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 26.2, 39.8, 49.3, 55.2, 55.3, 78.1, 113.9, 125.5, 129.3, 129.6, 134.2, 137.4, 140.8, 158.7, 203.9, 209.8. IR (KBr): 3334, 2958, 2931, 1710, 1681, 1612, 1589, 1513, 1400, 1369, 1298, 1257, 1236, 1179, 1096, 1031, 1013, 957, 831, 753, 685, 585 cm^{-1}. ESI-MS: obsd: 381.0883 $[M+Na]^+$; calcd exact mass: 381.0864. Anal. Calcd for $C_{20}H_{19}O_4Cl$: C, 66.95; H, 5.34. Found: C, 66.81; H, 5.21. Ee = 47% determined by HPLC: Chiracel OD-H, hexane/*i*-PrOH, 8:2, flow rate: 0.5 mL/min, λ = 225 nm; t_1(major) = 19.95 min, t_2(minor) = 22.11 min.

4.3.17. Compound 3i. Column chromatography (CH_2Cl_2/Et_2O then CH_2Cl_2/MeOH, 5%) gave white crystals (303 mg, 93%) suitable for X-ray analysis. mp 142–144 °C (CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.25–2.32 (m, 1H), 2.48 (ddd, J = 25.6 Hz, J = 12.4 Hz, J = 5.8 Hz, 1H), 2.6–2.7 (m, 4H), 3.88 (s, 3H), 4.40 (dd, J = 12.4 Hz, J = 3.8 Hz, 1H), 5.26 (br s, 1H), 6.93 (AA′BB′/2, J = 8.9 Hz, 2H), 7.43 (d, J = 6.0 Hz, 2H), 7.88 (AA′BB′/2, J = 8.9 Hz, 2H), 8.51 (d, J = 4.4s Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 26.4, 39.9, 48.0, 54.0, 55.6, 77.7, 114.3, 119.8, 128.2, 130.7, 149.5, 155.0, 164.8, 202.5, 205.8. IR (KBr): 3371, 2961, 2932, 1707, 1668, 1599, 1574, 1411, 1258, 1238, 1173, 1024, 866, 818, 598, 576 cm^{-1}. ESI-MS: obsd: 326.1370 $[M]^+$; calcd exact mass: 326.1387. Anal. Calcd for $C_{19}H_{20}NO_4$: C, 70.14; H, 5.89; N, 4.31. Found: C, 70.10; H, 5.71; N, 4.22. Ee = 50% determined by HPLC: Chiracel OD-H, hexane/*i*-PrOH, 8:2, flow rate: 1.0 mL/min, λ = 260 nm; t_1(major) = 18.91 min, t_2(minor) = 26.77 min.

5. Crystallographic data of X-ray structure of 3i

Measurement of the crystal structure was performed on a Kuma KM4CCD κ-axis diffractometer with graphite-monochromated MoKα radiation. The crystal was positioned at 65 mm from the KM4CCD camera. One thousand two hundred and four frames were measured at 1.0° intervals with a counting time of 20 s. The data were corrected for Lorentz and polarization effects. None absorption correction was applied. Data reduction and analysis were carried out with the Kuma Diffraction (Wrocław) programs.

The structure was solved by direct methods[14] and refined using SHELXL.[15] The refinement was based on F^2 for all reflections except those with very negative F^2 weighted R factors wR and all goodness-of-fit S values are based on F^2. Conventional R factors are based on F with F set to zero for negative F^2. The $F_0^2 > 2s(F_0^2)$

criterion was used only for calculating R factors and is not relevant to the choice of reflections for the refinement. The R factors based on F^2 are about twice as large as those based on F. All hydrogen atoms were located in idealized averaged geometrical positions, allowed to ride at the heavy atoms. Scattering factors were taken from Tables 6.1.1.4 and 4.2.4.2.[16]

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References

1. Tietze, L. F.. *Chem. Rev.* **1996**, *96*, 115–136.
2. (a) Rodriguez, J. *Synlett* **1999**, 505–518; (b) Schneider, C.; Reese, O. *Angew. Chem., Int. Ed.* **2000**, *39*, 2948–2950; (c) Surya Prakash Rao, H.; Jeyalakshmi, K.; Senthilkumar, S. P. *Tetrahedron* **2002**, *58*, 2189–2199; (d) Surya Prakash Rao, H.; Senthilkumar, S. P. *J. Org. Chem.* **2004**, *69*, 2591–2594; (e) Halland, N.; Aburel, P. S.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 1272–1277; (f) Pulkkinen, J.; Aburel, P. S.; Halland, N.; Jørgensen, K. A. *Adv. Synth. Catal.* **2004**, *346*, 1077–1080.
3. (a) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem., Int. Ed.* **1971**, *83*, 496–497; (b) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615–1621.
4. Bui, T.; Barbas, C., III. *Tetrahedron Lett.* **2000**, *41*, 6951–6954.
5. (a) List, B. *Tetrahedron* **2002**, *58*, 5573–5590; (b) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 3726–3748; (c) Palomo, C.; Oiarbide, M.; Garcia, J. M. *Chem. Soc. Rev.* **2004**, *33*, 65–75; (d) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138–5175; (e) List, B. In Mahrwald, R., Ed.; Modern Aldol Reactions; Wiley-Interscience: Weinheim, 2004; Vol. 1, pp 161–200; (f) Berkessel, A.; Gröger, H. *Asymmetric Organocatalysis*; Wiley-Interscience, 2005.
6. Córdova, A. *Chem. Eur. J.* **2004**, *10*, 1987–1997.
7. (a) Kotrusz, P.; Toma, S.; Schmalz, H.-G.; Adler, A. *Eur. J. Org. Chem.* **2004**, 1577–1583; (b) Mase, N.; Thayumanavan, R.; Tanaka, F.; Barbas, C. F., III. *Org. Lett.* **2004**, *6*, 2527–2530, and references cited therein.
8. (a) List, B. *J. Am. Chem. Soc.* **2002**, *124*, 5656–5657; (b) Kumaragurubaran, N.; Juhl, K.; Zhuang, W.; Bøgevig, A.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2002**, *124*, 6254–6255; (c) Bøgevig, A.; Juhl, K.; Kumaragurubaran, N.; Zhuang, W.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1790–1793.
9. (a) Merino, P.; Tejero, T. *Angew. Chem., Int. Ed.* **2004**, *43*, 2995–2997; (b) Brown, S. P.; Brochu, M. P.; Sinz, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 10808–10809; (c) Bøgevig, A.; Sundéen, H.; Córdova, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 1109–1112; (d) Hayashi, Y.; Yamaguchi, J.; Suniya, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 1112–1115.
10. (a) Melchiorre, P.; Jørgensen, K. A. *J. Org. Chem.* **2003**, *68*, 4151–4157; (b) Bella, M.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 5672–5673.
11. (a) Halland, N.; Aburel, P. S.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 661–664; (b) Halland, N.; Hansen, T.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4955–4957.
12. Franek, W. *Monatsh. Chem.* **1996**, *127*, 895–907.
13. Christoffers, J. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3141–3148.
14. Sheldrick, G. M. *Acta Crystallogr.* **1990**, *A46*, 467–473.
15. Sheldrick, G. M. SHELXL93. *Program for the Refinement of Crystal Structures*, Univ. of Göttingen, Germany.
16. *International Tables for Crystallography*; Wilson, A. J. C., Ed.; Kluwer: Dordrecht, 1992; Vol. C.
17. CCDC number: 253670.