Organic & Biomolecular Chemistry

Cite this: *Org. Biomol. Chem.*, 2012, **10**, 8322

www.rsc.org/obc

PAPER

Highly enantioselective and recyclable organocatalytic Michael addition of malonates to α,β-unsaturated aldehydes in aqueous media†

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Received 30th June 2012, Accepted 29th August 2012
DOI: 10.1039/c2ob26248g

A new type of pyrrolidine-based organocatalyst, which was developed earlier in our lab, has been found to be very effective for the Michael addition reaction in aqueous solvents involving a wide range of α,β-unsaturated aldehydes and malonate derivatives. For the reactions studied, good to excellent yields (73%–96%) and high to excellent enantioselectivities (up to 97%) were obtained using this catalyst. In addition, the catalyst could be recycled up to four times with gradual reductions in yields and enantioselectivity observed after the second cycle.

Introduction

The organocatalytic asymmetric Michael addition represents one of the most powerful carbon–carbon and carbon–heteroatom bond forming reactions. Such reactions have been widely applied in the synthesis of biologically active compounds and natural products.[1,2] More recently, aqueous organocatalysis has become a very active field of research.[3] Much effort has also been devoted to the development of organocatalyzed Michael addition performed in aqueous media.[3,4] In addition to the ease of catalyst separation from the products, water, when used as the solvent, provides an environmentally and economically attractive medium for such transformations. Of the various organocatalysts used for asymmetric Michael additions, chiral secondary amines have proven to be very effective for the Michael addition of the substrate aldehyde to electron-deficient alkenes in an aqueous environment through the enamine mechanism.[4a–i] However, less success has been achieved in aqueous systems for the Michael addition when α,β-unsaturated aldehydes are employed as Michael acceptors through the formation of iminium species, which are typically not compatible with water.[4j,k] Therefore, the development of a water-compatible organocatalyst is very important from a green chemistry perspective.

The emphasis of our research is on the development of water-compatible and recyclable organocatalysts for asymmetric organic transformations, and we recently observed that the diarylprolinol silyl ether **1**, which can be protonated to form the ammonium salt in the presence of benzoic acid, serves as an efficient recyclable catalyst for Michael reactions and domino Michael–Henry reactions in aqueous media with high levels of enantio- and/or diastereoselectivity.[5] Based on these observations, we envisioned that the catalyst **1** in combination with benzoic acid would react with α,β-unsaturated aldehydes in aqueous media to form a chiral iminium intermediate, which could serve as a Michael acceptor in reactions with malonates (eqn (1), Fig. 1). Herein, we describe the results of the studies using catalyst **1** to promote highly enantioselective Michael addition reactions, as well as the studies of the recyclability of catalyst **1**.[6]

Results and discussion

To examine the performance of catalyst **1**, a model reaction of dimethyl malonate and 4-nitrocinnamaldehyde was examined using benzoic acid as an additive. Screening of solvents and the ratio of benzoic acid to catalyst were investigated to optimize the

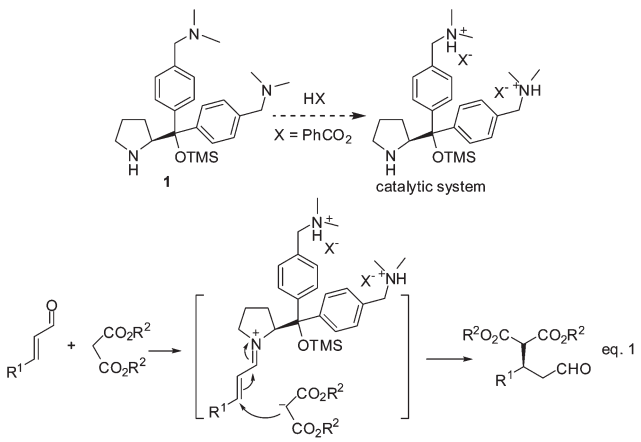

Fig. 1 Michael reaction of malonates with α,β-unsaturated aldehydes.

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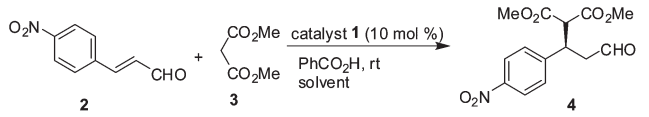
†Electronic supplementary information (ESI) available. See DOI: 10.1039/c2ob26248g

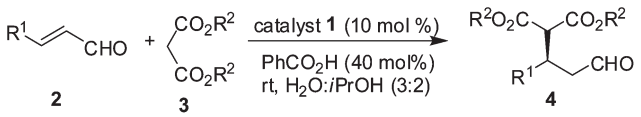
Table 1 Optimization of the reaction conditions of 4-nitro cinnamaldehyde with dimethyl malonate[a]



Entry	Solvent	$PhCO_2H$	*t* (h)	Yield[b] (%)	ee[c] (%)
1	H_2O	40 mol%	48	—	—
2	*i*PrOH	40 mol%	48	80	87
3	*i*PrOH	60 mol%	48	65	87
4	H_2O–*i*PrOH (1 : 1)	40 mol%	48	72	91
5	H_2O–*i*PrOH (2 : 1)	40 mol%	48	55	90
6	**H_2O–*i*PrOH (3 : 2)**	**40 mol%**	**48**	**86**	**91**
7	H_2O–*i*PrOH (3 : 2)	30 mol%	48	28	87
8	H_2O–*i*PrOH (3 : 2)	20 mol%	48	8	87

[a] Reactions performed on the 0.4 mmol scale using catalyst **1**, benzoic acid, 4-nitro cinnamaldehyde (1.3 equiv), and solvent (0.5 mL). [b] Isolated yield. [c] Determined by chiral HPLC of the product.

Table 2 Organocatalytic asymmetric Michael reaction using α,β-unsaturated aldehydes and dialkylmalonates[a]



Entry	R^1	R^2	Product	*t* (h)	Yield[b] (%)	ee[c] (%)
1	Ph	Me	**4a**	50	82	94[d]
2	4-FC_6H_4	Me	**4b**	60	85	95
3	4-$MeOC_6H_4$	Me	**4c**	60	88	91[d]
4	4-$NO_2C_6H_4$	Me	**4d**	48	86	91
5	2-Furanyl	Me	**4e**	50	91	89
6	Ph	Bn	**4f**	48	94	95[d]
7	4-BrC_6H_4	Bn	**4g**	60	73	91[d]
8	4-$NO_2C_6H_4$	Bn	**4h**	50	95	93
9	4-$MeOC_6H_4$	Bn	**4i**	60	92	95
10	Ph	Et	**4j**	60	96	97[d]
11	Me	Bn	**4k**	60	80	85

[a] Reactions performed on the 0.4 mmol scale using catalyst **1**, benzoic acid, α,β-unsaturated aldehydes (1.3 equiv), and solvent (0.5 mL). [b] Isolated yield. [c] Determined by chiral HPLC of the product. [d] Determined by chiral HPLC after oxidation to the corresponding methyl ester.

reaction conditions. The results are summarized in Table 1. Initially, the reaction was performed in pure water with 10 mol% of catalyst **1** in the presence of benzoic acid as an additive; product **4** was not observed after 48 h (entry 1). However, when the solvent *i*PrOH was used, the reaction proceeded smoothly at room temperature for 48 h and afforded the product **4** in 80% yield and high enantioselectivity 87% ee (entry 2). When the amount of benzoic acid was increased to 60 mol%, the yield was decreased to 65% with comparable enantioselectivity (entry 3). When mixture solvents H_2O–*i*PrOH at different ratios were examined, the desired product **4** was obtained in slightly improved enantioselectivities with various yields (entries 4–6). When the amount of benzoic acid was reduced from 40 mol% to 30 mol% and 20 mol%, the yields were dramatically decreased (entries 7–8). The optimal result was obtained by using a solvent mixture of water–*i*PrOH in the ratio 3 : 2, affording product **4** in 86% yield with 91% ee (entry 6). The absolute stereochemistry of product **4** was determined to be the (*R*) configuration, in comparison with that reported by Jørgensen.[7]

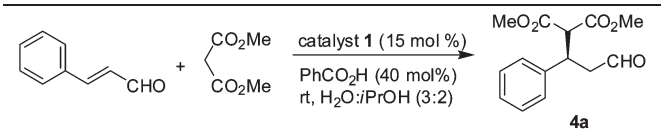
After the reaction conditions were optimized, the generality of the reaction was investigated, and good to excellent yields and excellent stereoselectivities were obtained for a variety of malonates and α,β-unsaturated aldehydes reacting at room temperature. The results are summarized in Table 2. As demonstrated in Table 2, the reactions proceeded smoothly for all malonate derivatives, which include methyl, ethyl, and benzyl esters. When the dimethyl malonate was used as a Michael donor, the electronic nature of the substituents at the aromatic ring of cinnamaldehyde had little influence on the reaction, and the Michael adducts **4a–d** were obtained in good yields 82–88% with very good enantioselectivities 91–95% ee (entries 1–4). The heteroaromatic α,β-unsaturated aldehyde was also a suitable substrate, affording the product **4e** in 91% yield with a slightly low enantioselectivity of 89% ee (entry 5). Aldehydes bearing both electron-deficient and electron-rich aromatic substituents are also excellent Michael acceptors that react with dibenzyl malonate, affording the Michael adducts **4f–i** in relatively improved yields up to 95% and enantioselectivities up to 95% ee (entries 1, 3–4 *vs.* entries 6, 8–9). In addition, diethyl malonate is found to be the best Michael donor, and reacts with cinnamaldehyde to afford the corresponding Michael product **4j** in excellent yield 96% and excellent enantioselectivity 97% ee (entry 10). Furthermore, catalyst **1** is also highly effective for Michael addition of dibenzyl malonate to aliphatic α,β-unsaturated aldehyde reacting at room temperature for 60 h, providing product **4k** in good yield 80% and enantioselectivity 85% ee (entry 11). The high to excellent ee obtained for these reactions utilizing catalyst **1** is due to the steric bulk brought about by the two benzyl dimethylammonium ions, combined with the bulky OTMS group, which serve to direct the incoming nucleophile to one face of the iminium intermediate.

The recyclability of the catalytic system (15 mol% of catalyst **1**) was studied using the reaction of dimethyl malonate with cinnamaldehyde under standard reaction conditions. As soon as the reaction was completed, the product was extracted with Et_2O–hexane mixture (1 : 6). The recovered aqueous phase was reused for the next cycle by adding 0.2 mL *i*PrOH, benzoic acid and the two substrates, dimethyl malonate and cinnamaldehyde, and the results are shown in Table 3. The catalyst could be recycled at least four times with an observed gradual reduction in yield; for cycles 2–4 there was a reduction in enantioselectivity. The gradual decrease in activity and enantioselectivity that was observed in the recycling of the catalytic system was probably due to the catalyst leaching out to the *i*PrOH and Et_2O–hexane layer during the phase-separation of each cycle.

Conclusion

In conclusion, a new type of pyrrolidine-based organocatalyst in combination with benzoic acid as water-compatible catalytic system, has been developed and found to be very effective for the Michael addition reaction in aqueous media. For the reaction

Table 3 Recyclability studies of the **1**-catalyzed reaction of dimethyl malonate with cinnamaldehyde[a]



4a

Cycle	*t* (h)	Yield[b] (%)	ee[c] (%)
1	38	95	94
2	50	88	94
3	65	70	86
4	80	44	76

[a] Reactions performed on 0.4 mmol scale using catalyst **1**, benzoic acid, cinnamaldehyde (1.3 equiv), and solvent (0.5 mL). [b] Isolated yield. [c] Determined by chiral HPLC after oxidation to the corresponding methyl ester.

involving various malonate derivatives and α,β-unsaturated aldehydes, good to excellent yields and enantioselectivities were obtained, and the catalytic system could be recycled four times with a gradual decreased reactivity and enantioselectivity observed.

Experimental

General information

Commercial reagents were used as received, unless otherwise stated. Merck 60 silica gel was used for chromatography, and Whatman silica gel plates with fluorescence UV254 were used for thin-layer chromatography (TLC) analysis. ^{1}H and ^{13}C-NMR spectra were recorded on a Bruker Avance 400. All the compounds synthesized in the manuscript are known compounds.[4l,6,7] Their data were determined by comparison with the known ^{1}H and ^{13}C-NMR and chiral HPLC analysis.

General procedure for Michael addition of dialkyl malonate to α,β-unsaturated aldehydes (Table 2). To a mixed solution of H_2O–*i*PrOH = 3 : 2 (v/v, 0.5 mL) was added α,β-unsaturated aldehyde (0.26 mmol), dialkyl malonate (0.2 mmol), catalyst (0.02 mmol) and benzoic acid (0.08 mmol). The reaction mixture was stirred at room temperature for the time indicated in Table 2. The products were extracted with Et_2O–hexane = 1 : 6 (v/v). The combined organic phase was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel to yield the desired addition product **4**.

(1) Dimethyl 2-((*R*)-2-formyl-1-phenylethyl)malonate 4a.[7] Yield = 82%; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 9.60 (d, J = 1.2 Hz, 1H), 7.31–7.22 (m, 5H), 4.03 (dt, J = 9.2 and 5.6 Hz, 1H), 3.76–3.74 (m, 4H), 3.50 (s, 3H), 2.94–2.90 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 199.9, 168.4, 167.8, 139.7, 128.8, 128.5, 128.0, 127.6, 57.3, 52.8, 52.7, 52.5, 47.2, 39.5; HPLC (Diacel Chiralpak AD, *i*PrOH–hexanes = 20 : 80, flow rate = 0.5 mL min^{-1}, λ = 254 nm): t_{major} = 14.51 min, t_{minor} = 16.48 min, ee = 94%.[8]

(2) Dimethyl 2-((*R*)-1-(4-fluorophenyl)-2-formylethyl)malonate 4b.[6] Yield = 85%; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 9.60 (s, 1H), 7.24–7.20 (m, 2H), 6.99 (t, J = 8.4 Hz, 2H), 4.02 (dt, J = 9.6 Hz and 5.2 Hz, 1H), 3.74–3.69 (m, 4H), 3.52 (s, 3H), 2.94–2.89 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 199.5, 168.2, 167.7, 162.0 (d, J_{C-F} = 245.0 Hz), 135.5 (d, J_{C-F} = 3.3 Hz); 129.7 (d, J_{C-F} = 8.2 Hz), 115.6 (d, J_{C-F} = 21.4 Hz), 57.2, 52.79, 52.77, 52.53, 52.51, 47.3, 38.7; HPLC (Chiralcel® OJ–H, *i*PrOH–hexanes = 30 : 70, flow rate = 1 mL min^{-1}, λ = 220 nm): t_{major} = 32.14 min, t_{minor} = 36.58 min, ee = 95%.

(3) Dimethyl 2-((*R*)-2-formyl-1-(4-methoxyphenyl)ethyl)malonate 4c.[7] Yield = 88%; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 9.60 (t, J = 2.0 Hz, 1H), 7.15 (dd, J = 6.8 and 2.0 Hz, 2H), 6.82 (dd, J = 6.8 and 2.0 Hz, 2H), 4.00 (dt, J = 9.6 and 5.6 Hz, 1H), 3.77 (s, 3H), 3.74–3.69 (m, 4H), 3.52 (s, 3H), 2.90–2.86 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 200.1, 168.4, 167.9, 158.9, 131.5, 129.0, 114.1, 57.5, 55.18, 55.16, 52.7, 52.48, 52.46, 47.3, 38.8; HPLC (Diacel Chiralpak AD, *i*PrOH–hexanes = 20 : 80, flow rate = 0.5 mL min^{-1}, λ = 254 nm): t_{major} = 18.65 min, t_{minor} = 24.79 min, ee = 91%.[8]

(4) Dimethyl 2-((*R*)-2-formyl-1-(4-nitrophenyl)ethyl)malonate 4d.[4l] Yield = 86%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 9.64 (s, 1H), 8.17 (d, J = 8.8 Hz, 2H), 7.45 (d, J = 8.4 Hz, 2H), 4.15 (dt, J = 9.2 and 4.8 Hz, 1H), 3.80 (d, J = 9.6 Hz, 2H), 3.76 (s, 3H), 3.55 (s, 3H), 3.10–2.96 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 198.4, 167.9, 167.4, 147.6, 129.2, 123.9, 56.3, 53.0, 52.8, 47.0, 38.8; HPLC (Chiralpak AD-H, *i*PrOH–hexanes = 30 : 70, flow rate = 0.7 mL min^{-1}, λ = 254 nm): t_{major} = 17.98 min, t_{minor} = 19.46 min, ee = 91%.

(5) Dimethyl 2-((*R*)-2-formyl-1-(furan-2-yl)ethyl)malonate 4e.[4l] Yield = 91%; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 9.68 (s, 1H), 7.31 (m, 1H), 6.27 (m, 1H), 6.13 (d, J = 2.4 Hz, 2H), 4.18–4.12 (m, 1H), 3.84 (d, J = 8.4 Hz, 1H), 3.74 (s, 3H), 3.65 (s, 3H), 2.96–2.88 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 199.5, 168.0, 167.9, 152.6, 142.1, 110.3, 107.3, 54.7, 52.7, 44.6, 33.0; HPLC (Chiralpak AD-H, *i*PrOH–hexanes = 30 : 70, flow rate = 0.7 mL min^{-1}, λ = 254 nm): t_{major} = 28.49 min, t_{minor} = 23.72 min, ee = 89%.

(6) Dibenzyl 2-((*R*)-2-formyl-1-phenylethyl)malonate 4f.[7] Yield = 94%; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 9.54 (t, J = 1.6 Hz, 1H), 7.33–7.18 (m, 13H), 7.06–7.04 (m, 2H), 5.14 (m, 2H), 4.89 (dd, J = 15.6 and 12.4 Hz, 2H), 4.07–4.01 (m, 1H), 3.83 (d, J = 10.0 Hz, 1H), 2.88–2.85 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 199.8, 167.6, 167.1, 139.6, 135.0, 134.9, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.5, 67.4, 67.2, 57.4, 47.2, 39.5; HPLC (Daicel Chiralpak AD, *i*PrOH–hexanes = 20 : 80, flow rate = 1 mL min^{-1}, λ = 254 nm): t_{major} = 7.03 min, t_{minor} = 7.99 min, ee = 95%.[8]

(7) Dibenzyl 2-((*R*)-1-(4-bromophenyl)-2-formylethyl)malonate 4g.[7] Yield = 73%; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 9.56 (s, 1H), 7.35–7.25 (m, 11H), 7.06–7.03 (m, 3H), 5.14 (m, 2H), 4.9 (s, 2H), 4.00 (dt, J = 9.2 and 5.2 Hz, 1H), 3.79 (d, J = 10.0 Hz, 1H), 2.87–2.83 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 199.2, 167.4, 167.0, 138.6, 134.9, 134.8, 131.8, 129.8, 128.6, 128.5, 128.4, 128.3, 121.5, 67.6, 67.4, 57.1, 47.1, 38.8; HPLC (Daicel Chiralpak AD, *i*PrOH–hexanes = 20 : 80, flow rate = 0.7 mL

min^{-1}, λ = 254 nm): t_{major} = 45.43 min, t_{minor} = 37.25 min, ee = 91%.[8]

(8) Dibenzyl 2-((*R*)-2-formyl-1-(4-nitrophenyl)ethyl)malonate 4h.[6] Yield = 95%; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 9.54 (s, 1H), 7.96 (d, J = 8.8 Hz, 2H), 7.35–7.21 (m, 10H), 7.06 (d, J = 7.2 Hz, 2H), 5.16 (s, 2H), 4.93 (dd, J = 14.0 and 12.4 Hz, 2H), 4.12 (dt, J = 9.2 and 4.8 Hz, 1H), 3.84 (d, J = 9.2 Hz, 1H), 3.0–2.87 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 199.4, 192.8, 167.1, 166.7, 148.9, 148.8, 147.2, 147.0, 139.9, 134.8, 134.5, 131.7, 129.1, 129.0, 128.7, 128.6, 128.6, 128.5, 128.4, 128.3, 128.2, 123.6, 67.7, 67.4, 56.5, 47.0, 38.8; HPLC (Chiralcel® OJ–H, *i*PrOH–hexanes = 30 : 70, flow rate = 1 mL min^{-1}, λ = 220 nm): t_{major} = 114.75 min, t_{minor} = 89.03 min, ee = 93%.

(9) Dibenzyl 2-((*R*)-2-formyl-1-(4-methoxyphenyl)ethyl)malonate 4i.[6] Yield = 92%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 9.52 (t, J = 2.0 Hz, 1H), 7.34–7.23 (m, 8H), 7.10–7.04 (m, 4H), 6.75 (d, J = 8.8 Hz, 2H), 5.15 (s, 2H), 4.91 (s, 2H), 3.99 (dt, J = 8.8 and 6.0 Hz, 1H), 3.79 (d, J = 10.0 Hz, 1H), 3.76 (s, 3H), 2.84–2.81 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 200.1, 167.7, 167.2, 158.8, 135.0, 131.4, 129.1, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 114.1, 67.4, 67.2, 57.7, 55.1, 47.3, 38.8; HPLC (Chiralcel® OJ–H, *i*PrOH–hexanes = 30 : 70, flow rate = 1 mL min^{-1}, λ = 220 nm): t_{major} = 75.67 min, t_{minor} = 68.65 min, ee = 95%.

(10) Diethyl 2-((*R*)-2-formyl-1-phenylethyl)malonate 4j.[6] Yield = 96%; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 9.60 (t, J = 1.6 Hz; 1H), 7.30–7.21 (m, 5H), 4.21 (q, J = 7.6 Hz, 2H), 4.02 (dt, J = 9.2 and 5.6 Hz, 1H), 3.95 (q, J = 7.2 Hz, 2H), 3.71 (d, J = 10.0 Hz, 1H), 2.93–2.88 (m, 2H), 1.26 (t, J = 7.2 Hz, 3H), 1.01 (t, J = 7.2 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 200.1, 168.0, 167.4, 139.8, 128.7, 128.1, 127.5, 61.8, 61.4, 57.5, 47.4, 39.5, 14.0, 13.7; HPLC (Chiralcel® OJ–H, *i*PrOH–hexanes = 30 : 70, flow rate = 0.5 mL min^{-1}, λ = 220 nm): t_{major} = 27.84 min, t_{minor} = 26.12 min, ee = 97%.[8]

(11) Dibenzyl 2-((*R*)-1-formylpropan-2-yl)malonate 4k.[4*l*] Yield = 80%; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 9.67–9.66 (m, 1H), 7.33–7.26 (m, 10H), 5.14 (s, 4H), 3.48 (d, J = 7.2 Hz, 1H), 2.89–2.86 (m, 1H), 2.64 (dd, J = 17.2 and 4.4 Hz, 1H), 2.39 (dq, J = 9.2 and 1.6 Hz, 1H), 1.04 (d, J = 6.8 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 200.6, 168.04, 168.01, 135.2, 128.6, 128.4, 128.3, 67.2, 56.3, 47.9, 28.0, 18.0; HPLC (Chiralpak AD-H, *i*PrOH–hexanes = 5 : 95, flow rate = 0.7 mL min^{-1}, λ = 254 nm): t_{major} = 24.73 min, t_{minor} = 23.70 min, ee = 85%.

Acknowledgements

We are grateful to the Robert A. Welch Foundation (T-1460) and National Science Foundation (CHE-1213287) for financial support for this research.

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