

Supplementary Material
for

***N*-Heterocyclic carbene catalysed Mukaiyama-Michael reaction and
Mukaiyama-aldol/Mukaiyama-Michael three component coupling reaction.**

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I General experimental

Proton (^1H) and carbon (^{13}C) NMR spectra were recorded using a Bruker DRX300 spectrometer (operating at 300 MHz for proton nuclei and 75 MHz for carbon nuclei) or a Bruker DRX400 spectrometer (operating at 400 MHz for proton nuclei and 100 MHz for carbon nuclei), as solutions in deuterated chloroform (CDCl_3) or dimethyl sulfoxide (DMSO-d_6). ^1H NMR data are assigned according to the following convention: chemical shift (δ) in parts per million (ppm) [multiplicity, coupling constant(s) (J in Hz), relative integral]. The chemical shifts (δ) are reported relative to the residual chloroform or dimethyl sulfoxide peaks. Multiplicities are denoted as singlet (s), doublet (d), triplet (t), quartet (q), pentet (p), sextet, septet, multiplet (m), or a combination of the above, and a prefix broad (br) where necessary. Proton-decoupled ^{13}C -NMR data are assigned according to the following convention: chemical shift (δ) in parts per million (ppm).

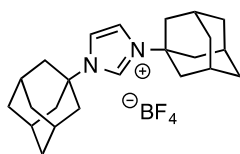
Analytical chiral HPLC was performed with a Perkin Elmer Series 200 HPLC using a Chiralpak AD-H obtained from Daicel Chemical Industries, Ltd. with visualization at 238 nm.

Infrared spectra (ν_{max}) were recorded using an Agilent Technologies Cary 630 FTIR Spectrometer. Samples were analyzed neat for both oils and solids. Analytical chiral HPLC was performed with a Perkin Elmer Series 200 HPLC using a Chiralpak® AD-H column (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd. with visualization at 254 nm. Low resolution mass spectrometry (LRMS) (ESI) was recorded using an Agilent Technologies 6120 Quadrupole LC/MS. High resolution mass spectrometry (HRMS) (ESI) was recorded using an Agilent Technologies 6540 UHD Accurate-Mass Q-TOF LC/MS.

Flash column chromatography was performed on silica gel (Davisil LC60A, 40-63 μm silica media) using compressed air. Thin layer chromatography (TLC) was performed using aluminium-backed plates coated with 0.2 mm silica (Merck, DC-Platten, Kiesegel; 60 F₂₅₄ plates). Eluted plates were visualized using a 254 nm UV lamp and/or treatment with a suitable stain followed by heating. These stains included permanganate (2 g, KMnO_4 , 20 g K_2CO_3 , 5 mL NaOH (5% w/v H_2O) and 300 mL H_2O), *p*-anisaldehyde (15 mL *p*-anisaldehyde, 6.2 mL acetic acid, 20.5 mL conc. H_2SO_4 , 28 mL H_2O and 530 mL EtOH) and vanillin (1.7 g vanillin, 33 mL acetic acid, 17 mL conc. H_2SO_4 and 300 mL H_2O). Concentration under reduced pressure was performed using a rotary evaporator with the water bath temperature not exceeding 50 °C.

Starting materials were purchased from Sigma-Aldrich, Alfa-Aesar, Merck or Oakwood Chemicals and were used as supplied, or in the case of some liquids, distilled. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium benzophenone ketyl. Toluene and benzene were dried by passing over activated alumina.

1,3-Bis(adamantan-1-yl)-1*H*-imidazol-3-ium tetrafluoroborate ($\text{A1}\cdot\text{HBF}_4$)^[1]

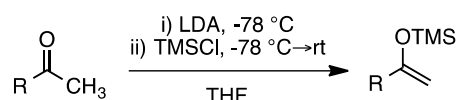


To an oven-dried round-bottom flask containing an atmosphere of argon, was added paraformaldehyde (0.33 g, 11 mmol) and toluene (4 mL). The flask was cooled to 0 °C with an ice bath before 1-adamantyl amine (3.03 g, 20 mmol) was added to the suspension in two separate portions with a 30 minute interval between additions.

The resultant thick suspension was stirred at room temperature for 20 minutes, then cooled with an ice bath before addition of HCl (2.5 mL of a 4 M solution in dioxane, 10 mmol), resulting in the generation

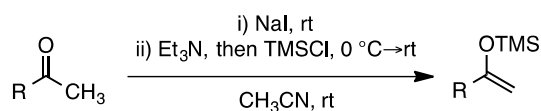
of a copious amount of white solid. Glyoxal (1.15 mL of a 40% w/v aqueous solution, 10 mmol) was subsequently added, and the thick paste stirred for 14 h. The flask was subsequently sealed and heated at 105 °C (oil bath temperature) until the solution turned brown. Solvent was removed *in vacuo*, and water (100 mL) added. The resulting suspension was filtered, and the filtrate neutralized with NaHCO₃. Tetrafluoroboric acid (1.96 mL of a 48% w/v aqueous solution, 15 mmol) was added, giving a white precipitate. The solid was triturated with CH₂Cl₂ (3 x 40 mL), and the combined organic layers concentrated *in vacuo* until solids began to form. Precipitation was completed by the addition of pentane (10 mL). The precipitate was collected, and dried overnight at 65 °C under high vacuum to yield IAd•HBF₄ as a white powder (2.45 g, 5.8 mmol, 58%). All spectroscopic data was consistent with literature.^[1] ¹H NMR (400 MHz, CDCl₃) δ 1.74-1.84 (m, 12H), 2.18-2.24 (m, 12H), 2.32 (br s, 6H), 7.44 (d, *J* = 1.5 Hz, 2H), 8.87 (t, *J* = 1.5 Hz, 1H). ¹³C NMR (100 MHz, DMSO-d₆) δ 28.9, 34.9, 41.5, 59.4, 119.4, 131.3. IR (neat) ν_{max} 3168, 2911, 2857, 1549, 1311, 1158, 1058, 1018 cm⁻¹.

II General procedure A for the synthesis of TMS enol ethers^[2]



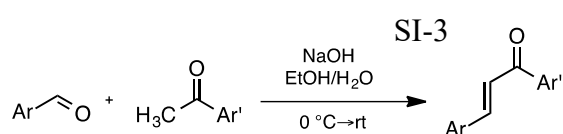
To a flame-dried round-bottom flask equipped with magnetic stirrer bar under nitrogen atmosphere was added anhydrous THF (10 mL) and diisopropylamine (12 mmol) before being cooled to -78 °C. *n*-Butyllithium (6 mL of a 2.0 M solution in cyclohexane, 12 mmol) was then added slowly. The cold bath was removed, and the solution allowed to warm to room temperature with stirring. Following this, the solution was cooled to -78 °C, and acetophenone (10 mmol in 2 mL anhydrous THF) was added dropwise. The resulting mixture stirred for 30 minutes at -78 °C before chlorotrimethylsilane (12 mmol) was added slowly, followed by removal of the cold bath. After stirring for 14 h, the solvent was removed *in vacuo* and the residue purified by short-path distillation under high vacuum to yield pure silyl enol ether.

III General procedure B for the synthesis of TMS enol ethers^[3]



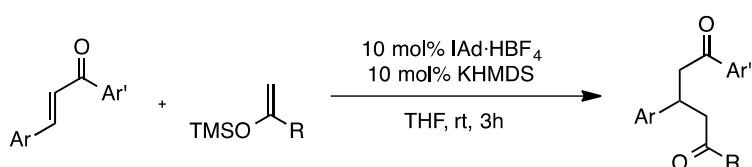
A flame-dried flask equipped with stirrer bar under argon was charged with sodium iodide (12 mmol) and ketone (10 mmol). Acetonitrile (10 mL) was added and the mixture stirred until all solids dissolved. The resultant solution was cooled to 0 °C and triethylamine (12 mmol) added dropwise, generating a thick white suspension. This was followed by the slow addition of chlorotrimethylsilane (12 mmol). The ice bath was removed and the mixture allowed to stir at room temperature for 14 h, then poured into ice water. The aqueous layer was subsequently extracted with pentane (4 x 10 mL). The combined organics were washed rapidly with cold HCl (20 mL of a 1 M aqueous solution), cold water (20 mL) and brine (20 mL), then dried with sodium sulfate. The solvent was removed *in vacuo* and the residue purified by short-path distillation under high vacuum to yield pure silyl enol ether.

IV General procedure for the synthesis of chalcones^[4]



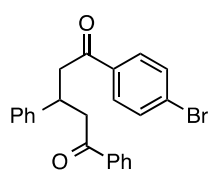
To a conical flask equipped with a magnetic stirrer bar was added ethanol (10 mL), benzaldehyde (10 mmol) and acetophenone (10 mmol), and the resulting mixture cooled to 0 °C with an ice bath. The resultant homogeneous solution was treated with NaOH (10 mL of a 8% w/v aqueous solution, 20 mmol) in a drop-wise fashion. Precipitate typically evolved prior to complete addition of the NaOH. The ice bath was subsequently removed and the mixture stirred at room temperature for 14 h. The resultant precipitate was collected *via* filtration and washed with a cold ethanol/water solution (20 mL, 1:1 v/v). The solid was further purified by recrystallization from warm or hot ethanol.

V General procedure for the NHC-catalyzed Mukaiyama-Michael addition reaction



To a flame-dried round-bottom flask equipped with a magnetic stirrer bar under nitrogen was added 1,3-bis(1-adamantyl)imidazolium tetrafluoroborate **A1•HBF₄** (0.02 mmol). Anhydrous THF (2 mL) was added to the flask, followed by potassium hexamethyldisilazide (0.04 mL of a 0.5 M solution in toluene, 0.02 mmol). The mixture was stirred at room temperature for 30 minutes. A second flame-dried round bottom flask equipped with a magnetic stirrer bar under nitrogen was charged with the α,β -unsaturated carbonyl compound (0.2 mmol). Anhydrous THF (10 mL) was added, followed by the TMS enol ether (0.26 mmol). After stirring this mixture, the solution containing the generated carbene was transferred to this flask *via* airtight syringe. The reaction was monitored by TLC and allowed to stir for approximately 3 h, or until no further conversion of the α,β -unsaturated carbonyl compound was observed. Upon completion, the reaction was opened to air and HCl (0.26 mL of 1 M aq. solution) was added and the resultant mixture stirred for 1 h. After transferring to a separating funnel, brine (10 mL) was added and the organic layers separated. The aqueous layer was extracted with ethyl acetate (2 x 5 mL), the combined organic layers dried with MgSO₄, and solvent removed *in vacuo*. The crude residue was purified by flash column chromatography to yield the desired Michael adduct.

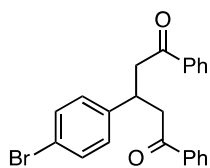
1-(4-Bromophenyl)-3,5-diphenylpentane-1,5-dione (7ab/7ea)



Following the general procedure *p*-bromoacetophenone TMS enol ether **2b** and chalcone **1a** were combined to afford the title compound (**3ab**, 64 mg, 0.16 mmol, 79%) as a yellow solid. The title compound was also synthesized (**3ea**, 34 mg, 0.08 mmol, 42%) from acetophenone TMS enol ether **1a** and chalcone **2e**. Eluted with 1:9 v/v EtOAc:hexanes. R_f = 0.3 (1:9 v/v EtOAc:hexanes). ¹H NMR (400 MHz, CDCl₃) δ 3.26-3.51 (m, 4H), 4.04 (m, 1H), 7.16-7.21 (m, 1H), 7.24-7.29 (m, 4H), 7.42-7.48 (m, 2H), 7.53-7.56 (m, 1H), 7.56-7.61 (m, 2H), 7.78-7.83 (m, 2H), 7.92-7.97 (m, 2H). ¹³C NMR (100 MHz, CDCl₃) δ 37.3, 44.9, 45.0, 126.9, 127.5, 128.3, 128.4, 128.7, 128.8, 129.8, 132.0, 133.3, 135.7, 137.0, 143.7, 197.7, 198.6. IR

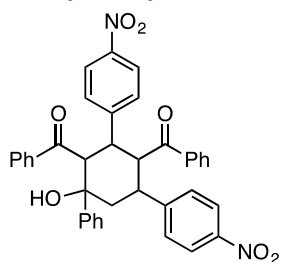
(neat) ν_{\max} 3066, 3062, 3030, 2924, 1685, 1598, 1587, 1451, 1398, 1073 cm^{-1} . **HRMS** calc'd for $\text{C}_{23}\text{H}_{19}^{81}\text{BrO}_2$ $[\text{M}+\text{H}]^+$ 409.0621, found 409.0620.

3-(4-Bromophenyl)-1,5-diphenylpentane-1,5-dione (7ca)



Following the general procedure, acetophenone TMS enol ether **1a** and the chalcone **2c** were combined to afford **3ca** (32 mg, 0.08 mmol, 39%) as a yellow solid. Eluted with 1:9 v/v EtOAc:hexanes. $R_f = 0.3$ (1:9 v/v EtOAc:hexanes). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 3.32 (AB dd, $J = 17.0, 6.8$ Hz, 2H), 3.48 (AB dd, $J = 17.0, 6.8$ Hz, 2H), 4.05 (p, $J = 6.8$ Hz, 1H), 7.15-7.20 (m, 2H), 7.37-7.41 (m, 2H), 7.42-7.48 (m, 4H), 7.53-7.59 (m, 2H), 7.91-7.96 (m, 4H). $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 36.7, 44.8, 120.6, 128.2, 128.8, 129.4, 131.8, 133.3, 136.9, 143.0, 198.3. **IR** (neat) ν_{\max} 3060, 2924, 1685, 1598, 1492, 1451, 1013 cm^{-1} . **HRMS** calc'd for $\text{C}_{23}\text{H}_{19}^{81}\text{BrO}_2$ $[\text{M}+\text{H}]^+$ 409.0621, found 409.0621.

(4-Hydroxy-2,6-bis(4-nitrophenyl)-4-phenylcyclohexane-1,3-diyl)bis(phenylmethanone) (10)



Compound **10** was obtained as a single diastereoisomer with relative stereochemistry undetermined. $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 2.08 (d, $J = 13.0$ Hz, 1H), 3.40 (dd, $J = 13.0, 3.2$ Hz, 1H), 4.28-4.48 (m, 3H), 5.06 (br s, 1H), 5.72 (d, $J = 11.7$ Hz, 1H), 7.02-7.09 (m, 2H), 7.11-7.18 (m, 5H), 7.23-7.32 (m, 6H), 7.36-7.39 (m, 2H), 7.44-7.47 (m, 2H), 7.69-7.76 (m, 4H), 7.92-7.98 (m, 2H). $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 38.1, 42.2, 47.8, 49.8, 50.9, 75.7, 123.5, 123.7, 125.1, 127.5, 127.6, 128.3, 128.3, 128.5, 128.6, 128.8, 129.8, 133.5, 133.8, 137.8, 139.0, 145.8, 146.6, 146.9, 147.0, 149.0, 204.8, 207.1. **IR** (neat) ν_{\max} 1699, 1701, 1672, 1019 cm^{-1} . **HRMS** calc'd for $\text{C}_{38}\text{H}_{30}\text{N}_2\text{O}_7$ $[\text{M}+\text{H}]^+$ 627.2126, found 627.2123.

VI General procedure for the Mukaiyama aldol/Mukaiyama-Michael addition cascade

To a flame-dried round-bottom flask equipped with a magnetic stirrer bar under nitrogen was added 1,3-bis(1-adamantyl)imidazolium tetrafluoroborate **A1**•**HBF₄** (0.02 mmol). Anhydrous THF (2 mL) was added to the flask, followed by potassium hexamethyldisilazide (0.04 mL of a 0.5 M solution in toluene, 0.02 mmol). The mixture was stirred at room temperature for 30 minutes. A second flame-dried round bottom flask containing activated 4Å powdered molecular sieves and equipped with a magnetic stirrer bar was fitted with a reflux condenser and flushed with nitrogen. Aldehyde (0.2 mmol) and TMS enol ether (0.46 mmol) were added through the condenser, followed by anhydrous THF (10 mL). This mixture was stirred for 15 minutes before being treated with the solution containing the generated carbene, added through the condenser by airtight syringe. The resultant mixture was immediately heated to reflux, and the reaction was monitored by TLC until all starting material was consumed or no more product was formed after 2 h. After completion, the reaction was opened to air and HCl (0.46 mL of a 1 M aq. solution) was added and the resultant mixture stirred for 1 h. After transferring to a separating funnel, brine (10 mL) was added and the organic layer separated. The aqueous layer was extracted with ethyl acetate (2 x 5 mL), the combined organic layers dried with MgSO_4 , and solvent removed *in vacuo*. The crude residue was purified by flash column chromatography to yield the desired Michael adducts.

Using this general procedure, Michael adducts **7aa** (60%), **7ea** (62%), **7fa** (50%) and **3ha** (29%) were prepared from the appropriate aldehydes.

VII Procedure for the three component Mukaiyama aldol/Michael addition cascade

To a flame-dried round-bottom flask equipped with a magnetic stirrer bar under nitrogen was added 1,3-bis(1-adamantyl)imidazolium tetrafluoroborate **A1•HBF₄** (0.02 mmol). Anhydrous THF (2 mL) was added to the flask, followed by potassium hexamethyldisilazide (0.04 mL of a 0.5 M solution in toluene, 0.02 mmol). The mixture was stirred at room temperature for 30 minutes. A second flame-dried round bottom flask containing activated 4Å powdered molecular sieves and equipped with a magnetic stirrer under nitrogen was charged with benzaldehyde (0.2 mmol), the TMS enol ether of acetophenone **9a** (0.22 mmol), and THF (5 mL). This mixture was stirred for a period of time before being cooled to -78 °C by an acetone/dry ice cold bath, and subsequently treated with the solution containing the generated carbene by airtight syringe. The cold bath was then removed, the reaction allowed to warm slowly to room temperature, by which time it was stirred for a further 30 minutes. The mixture was then treated with a mixture of the TMS enol ether of *p*-bromoacetophenone **9b** (0.26 mmol) in THF (5 mL) at room temperature, followed by stirring for another 2 hours. Upon completion, the reaction was opened to air and HCl (0.48 mL of a 1 M aq. solution) was added and the resultant mixture stirred for 1 h. After transferring to a separating funnel, brine (10 mL) was added and the organic layer separated. The aqueous layer was extracted with ethyl acetate (2 x 5 mL), the combined organic layers dried with MgSO₄, and solvent removed *in vacuo*. The crude residue was purified by flash column chromatography (1:9, v/v ethyl acetate:hexanes) to yield the desired Michael adduct **7b** in 56% yield.

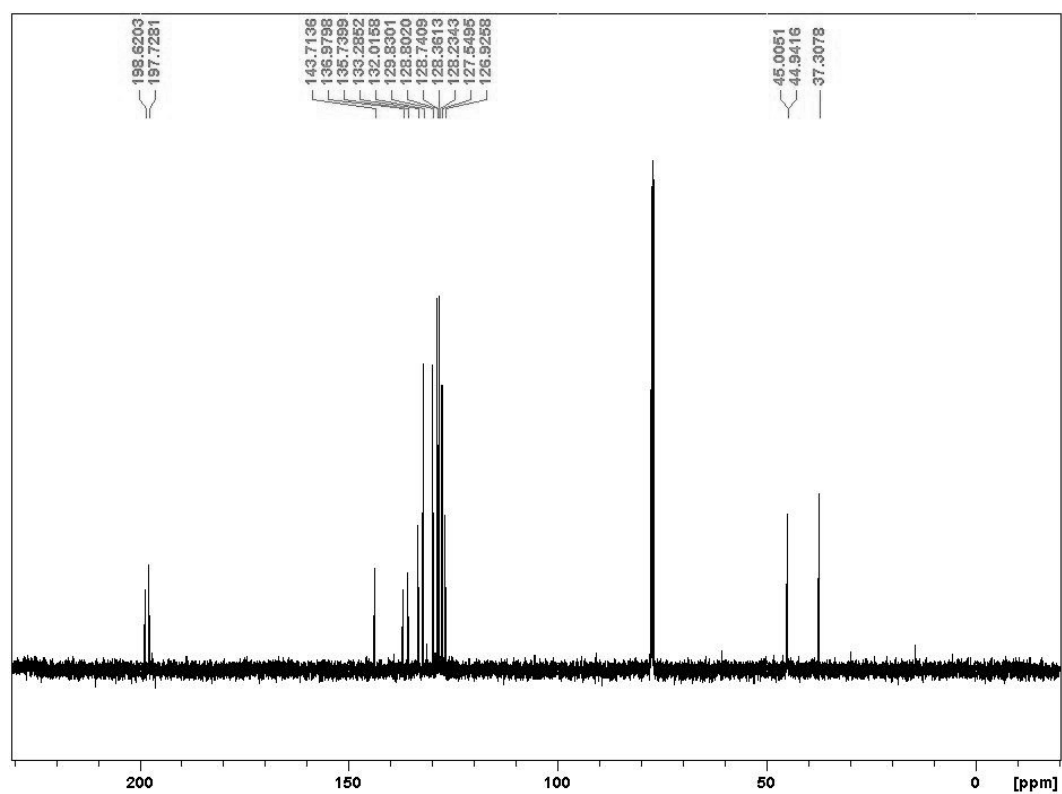
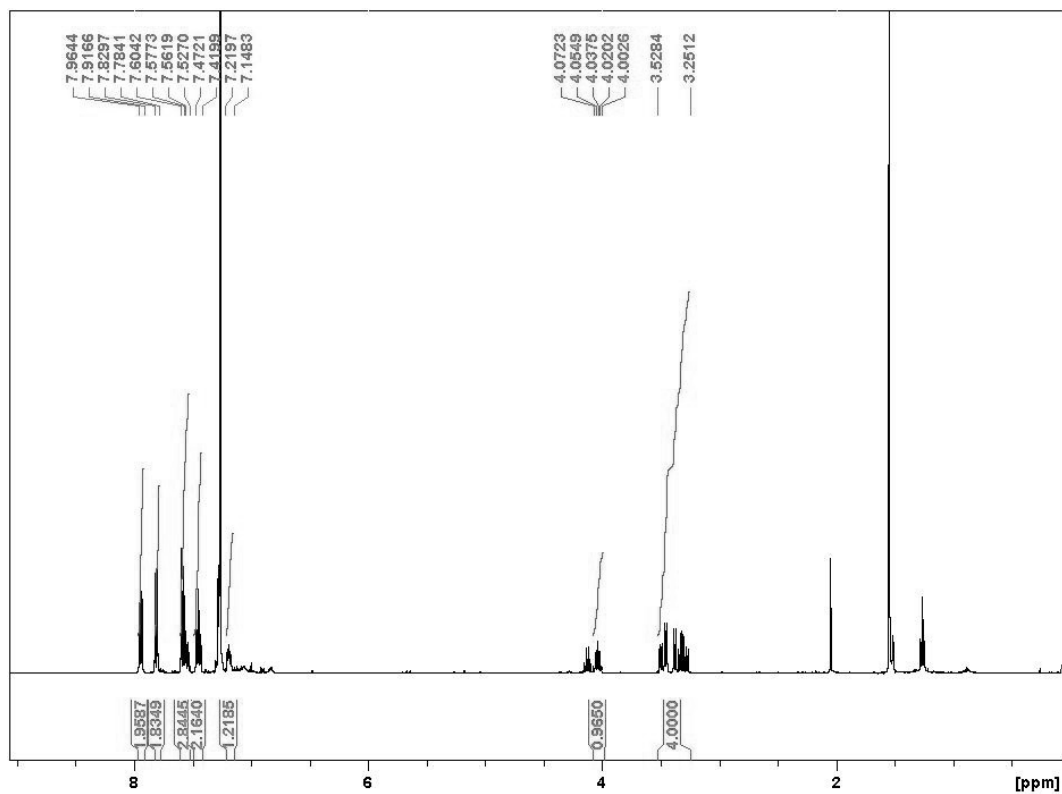
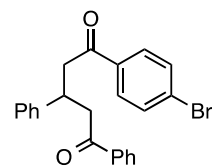
General procedure for the attempted enantioselective Mukaiyama-Michael addition

To a flame-dried round-bottom flask equipped with a magnetic stirrer bar under nitrogen was added the triazolium precursor salt (0.01 mmol). Anhydrous THF (1mL) was added to the flask, followed by potassium hexamethyldisilazide (0.02 mL of a 0.5 M solution in toluene, 0.01 mmol). The mixture was stirred at room temperature for 1 hour. A second flame-dried round bottom flask fitted containing a magnetic stirrer bar under nitrogen was charged with chalcone (0.1mmol) and the TMS enol ether of *p*-bromoacetophenone (0.13 mmol), followed by anhydrous THF (10 mL). This mixture was stirred for a period of time before being cooled to 0 °C, and subsequently treated with the solution containing the generated carbene by airtight syringe. The resultant mixture was stirred for 4 h at this temperature before being opened to air and treated with 0.13 mL of a 1 M aqueous solution of HCl and allowed to warm to room temperature. After being stirred for 1 h, the resultant mixture was transferred to a separating funnel, whereupon brine (10 mL) was added and the organic layer separated. The aqueous layer was extracted with ethyl acetate (2 x 5 mL), the combined organic layers dried with MgSO₄, and solvent removed *in vacuo*. The crude residue was purified by flash column chromatography to yield the desired Michael adducts. Enantiomeric ratio was determined using an analytical HPLC with chiral stationary phase (Daicel AD-H); hexane:*i*PrOH 70:30, 1.0 mL/min, fraction *t*₁ = 17.97 min, *t*₂ = 20.02 min.

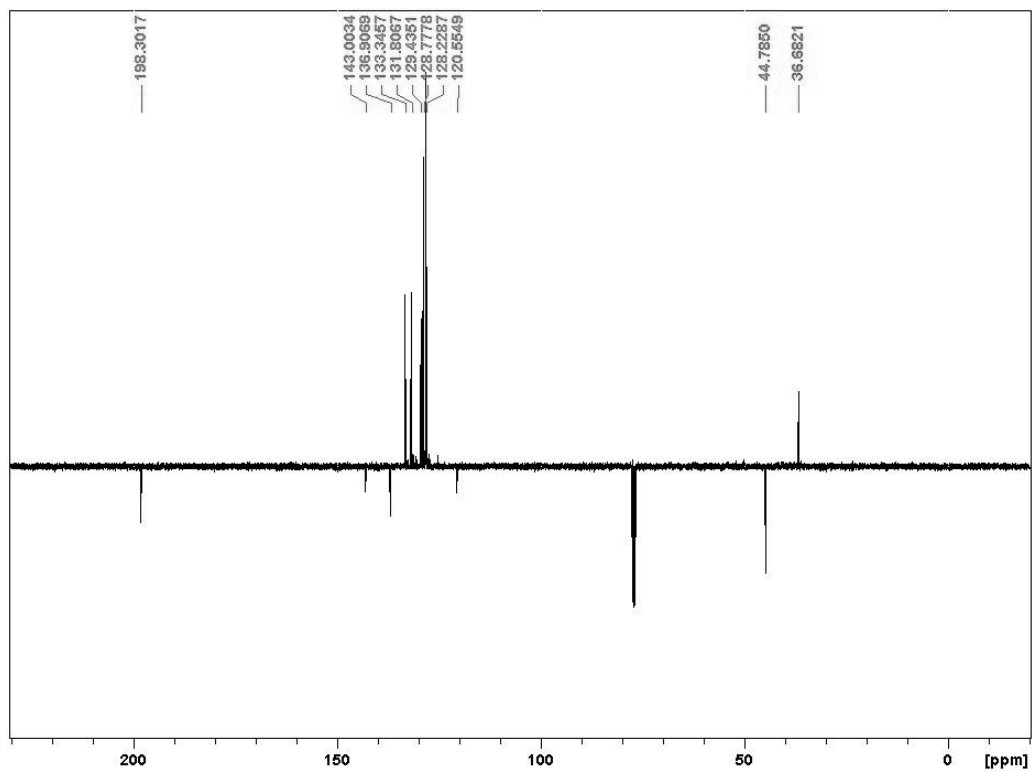
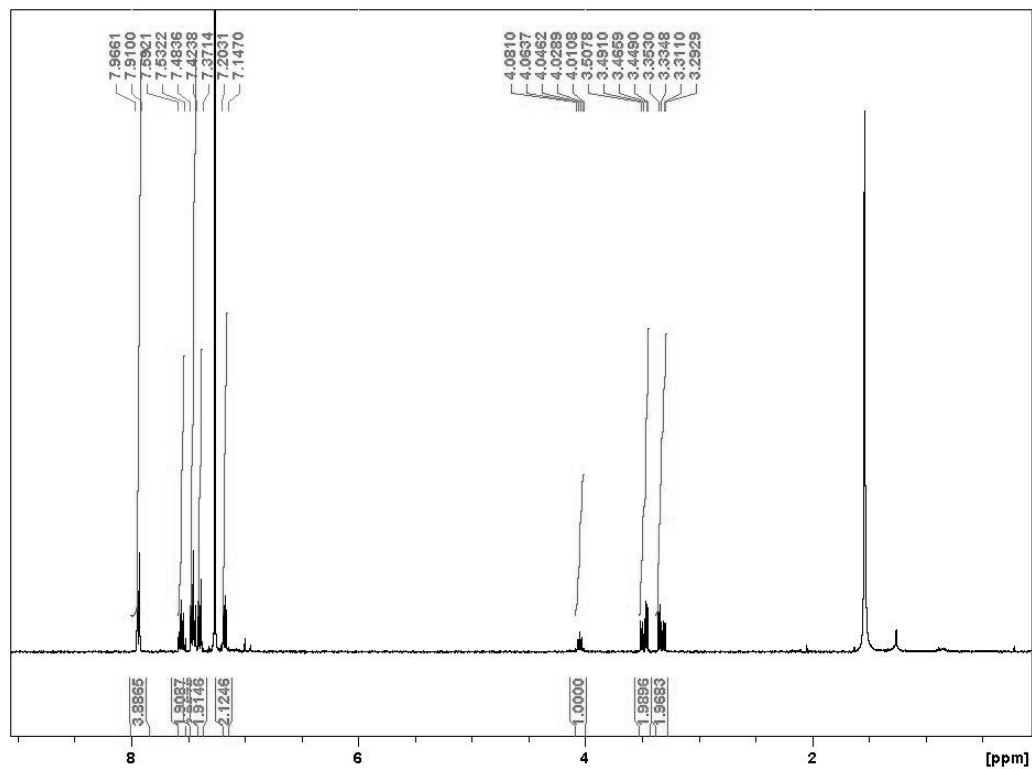
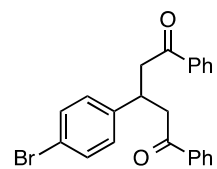
References

- [1] H. Richter, H. Schwertfeger, P. Schreiner, R. Fröhlich, F. Glorius *Synlett* **2009**, 193.
- [2] A. G. Smith, J. S. Johnson, *Org. Lett.* **2010**, *12*, 1784.
- [3] S. Wei, H. Du, *J. Am. Chem. Soc.* **2014**, *136*, 12261.
- [4] J. Kumar, G. Chawla, U. Kumar, K. Sahu, *Med. Chem. Res.* **2014**, *23*, 3929.

1-(4-Bromophenyl)-3,5-diphenylpentane-1,5-dione (7ab/7ea)
obtained in $CDCl_3$ at 400 MHz (1H -NMR) and 100 MHz (^{13}C -NMR)



(3-(4-Bromophenyl)-1,5-diphenylpentane-1,5-dione (7ca)
obtained in $CDCl_3$ at 400 MHz (1H -NMR) and 100 MHz (^{13}C -NMR)



(4-Hydroxy-2,6-bis(4-nitrophenyl)-4-phenylcyclohexane-1,3-diyl)bis(phenylmethanone) (10)

obtained in $CDCl_3$ at 400 MHz (1H -NMR) and 100 MHz (^{13}C -NMR)

