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Organocatalyzed Intramolecular Michael Addition of Morita–Baylis–Hillman Adducts of β-Arylnitroethylenes: An Entry to 3-Aryl-4-nitrocyclohexanones

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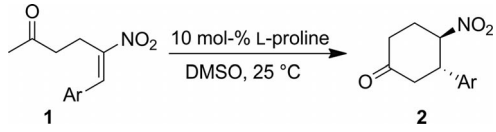
Keywords: Organocatalysis / Michael addition / Morita–Baylis–Hillman reaction / Nitroalkenes / Cyclohexanone / Epibatidine

The synthesis of 3-aryl-4-nitrocyclohexanones has been achieved from the Morita–Baylis–Hillman adducts of β-arylnitroethylenes. The strategy involves proline-catalyzed diastereoselective intramolecular Michael addition to obtain 3,4-*trans*-disubstituted cyclohexanones. This method provides a facile access to (±)-epibatidine analogues.

Introduction

The Morita–Baylis–Hillman (MBH) reaction, an organocatalyzed reaction of activated alkenes with carbon electrophiles, has appeared as one of the important carbon–carbon bond forming reactions.[1] Over the past three decades, adducts obtained from the MBH reaction have served as handy synthons for the synthesis of various heterocycles and carbocycles.[2] Furthermore, MBH adducts also emerged as potential bioactive compounds by showing various biological activities.[3] Although, several MBH products obtained from diverse activated alkenes have been employed as versatile building blocks, the utility of adducts of β-arylnitroethylenes has not been explored much. In 2006, Namboothri and co-workers reported the synthesis of MBH products from the reaction of β-arylnitroethylenes with methyl vinyl ketone (MVK) and acrylates.[4] Later, the utility of these adducts towards the synthesis of 1,2-disubstituted cyclopentenones through a one-pot reaction was also demonstrated.[5] Our interest in MBH chemistry has encouraged us to explore the efficacy of MBH adducts,[6] derived from β-arylnitroethylenes, to the synthesis of 3-aryl-4-nitrocyclohexanones.

3-Aryl-4-nitrocyclohexanones are valuable scaffolds because of their presence in natural as well as non-natural products with medicinal and therapeutic properties.[7] Furthermore, they can also be encountered as key intermediates in the synthesis of several bioactive compounds, such as epibatidine, a potent nicotinic acetylcholine receptor agonist.[8] Thus, 3-aryl-4-nitrocyclohexanones are interesting synthetic targets for chemists. Traditionally, the synthesis of these compounds is accomplished by Diels–Alder reactions between a diene and nitrostyrenes.[9] In addition, some enantioselective organocatalytic approaches including Michael–Michael, Michael–Mannich, and Michael–aldol reactions have also been developed.[10] In the majority of these methods, the reaction sequence involves the addition of the active methylene group of a carbonyl compound to nitrostyrene followed by the addition of the active methylene group adjacent to the nitro group. In contrast, we envisaged that the MBH reaction of β-nitrostyrene with an α,β-unsaturated enone would provide the corresponding adduct, which would be suitable for an intramolecular Michael addition reaction to give 3-aryl-4-nitrocyclohexanone. Herein, we describe the details of such an approach using MBH adducts of β-arylnitroethylenes (**1**) and the methodology that permits the synthesis of 3-aryl-4-nitrocyclohexanones (**2**, Scheme 1).



Scheme 1. Synthesis of 3-aryl-4-nitrocyclohexanone.

Results and Discussion

We began our investigation by studying the intramolecular Michael addition of (*E*)-5-nitro-6-phenylhex-5-en-2-one (**1a**), obtained from the MBH reaction of (*E*)-(2-nitrovinyl)-benzene with methyl vinyl ketone.[4] In the first case, the reaction was tested using L-proline (10 mol-%) in dimethyl sulfoxide (DMSO), and – gratifyingly – the starting material was consumed in 14 h to afford the expected product **2a** in 99% yield with excellent diastereoselectivity. The stereochemistry was determined as *trans*-**2a** from the ^{1}H

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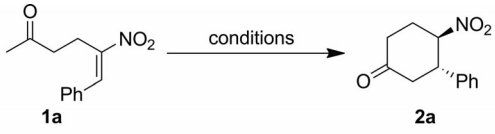
NMR spectrum of **2a**, in which the coupling constant between 3-H and 4-H was 10.6 Hz. However, the observed low enantioselectivity (20%*ee*, Table 1, Entry 1) directed us to study various reaction conditions. Accordingly, a series of organocatalysts were then screened for the above reaction (Table 1, Entries 2–6). Dipeptide **IV** and thiourea-based catalyst **V** provided the product **2a** in good yields with improved enantioselectivity (53%*ee* for **V**), though with longer reaction times. Notably, all the studied catalysts offered good yield of the product with excellent diastereoselectivity. Although we could not achieve the desired enantioselectivity, having established the optimal conditions for diastereoselective intramolecular Michael addition (10 mol-% L-proline, DMSO, room temp.), we next examined the effect of the substituent at the 6-position of the enone.

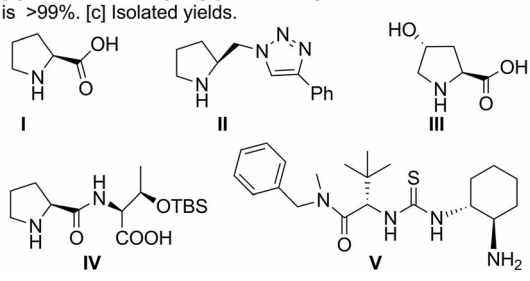
Table 1. Optimization of reaction conditions.



1a **2a**

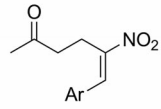
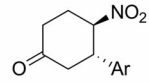
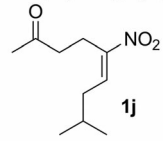
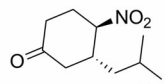
Entry	Catalyst[a]	Additive	Solvent	Time	*ee* [%]	Yield [%][b,c]
1	***I***	**–**	***DMSO***	***14 h***	***20***	***99***
2	**II**	PhCOOH	DMSO	7 d	23	84
3	**III**	–	DMSO	4 d	0	95
4	**IV**	–	DMSO	4 d	40	94
5	**V**	*p*TSA	DMSO	8 d	53	89
6	**V**	*p*TSA	DMF	7 d	53	65

[a] 10 mol-% catalyst. [b] With catalysts **I–V** diastereoselectivity is >99%. [c] Isolated yields.



A range of MBH adducts, obtained from β-arylnitrostyrenes, were tested for the present intramolecular Michael addition. Thiophenyl- and naphthyl-substituted nitro enones **1b** and **1c** successfully provided the corresponding 3-aryl-4-nitrocyclohexanones **2b** and **2c** in very good yields with excellent diastereoselectivity (Table 2, Entries 2 and 3). The substrates with electron-withdrawing substituents on the aryl group, **1d**–**1g**, participated in an intramolecular Michael addition to yield **2d**–**2g** (Table 2, Entries 4–7) with good diastereoselectivity. On the other hand, the reaction of MBH adducts with electron-donating substituents on the aryl group, **1h** and **1i**, provided the corresponding 3-aryl-4-nitrocyclohexanones **2h** and **2i** with low diastereoselectivity (Table 2, Entries 8 and 9). However, the MBH adduct with an aliphatic substitutent, **1j**, derived from β-alkylnitrostyrene, failed to undergo an intramolecular Michael addition (Table 2, Entry 10).

Table 2. Synthesis of 3-aryl-4-nitrocyclohexanones.[a]

Entry	MBH adduct **1**	Time [h]	Product **2**[b]	Yield [%][c,d]
1		14		
	Ar = Ph, **1a**		Ar = Ph, **2a**	99
2	Ar = 2-thiophenyl, **1b**	18	Ar = 2-thiophenyl, **2b**	96
3	Ar = 1-naphthyl, **1c**	20	Ar = 1-naphthyl, **2c**	76
4	Ar = 4-BrC_6H_4, **1d**	12	Ar = 4-BrC_6H_4, **2d**	88
5	Ar = 2-ClC_6H_4, **1e**	16	Ar = 2-ClC_6H_4, **2e**	98
6	Ar = 4-NCC_6H_4, **1f**	13	Ar = 4-NCC_6H_4, **2f**	79
7	Ar = 4-$O_2NC_6H_4$, **1g**	14	Ar = 4-$O_2NC_6H_4$, **2g**	95
8	Ar = 4-$MeOC_6H_4$, **1h**	22	Ar = $MeOC_6H_4$, **2h**	92[d]
9	Ar = 2,3-$(MeO)_2C_6H_3$, **1i**	20	Ar = 2,3-$(MeO)_2C_6H_3$, **2i**	96[d]
10		24		–
	1j		**2j**	

[a] Reaction conditions: MBH adduct (1 mmol), L-proline (10 mol-%), DMSO (5 mL), r.t. [b] All the products were characterized by ^1H and ^{13}C NMR, IR and mass spectra. [c] Isolated yield. [d] In all cases the diastereoselectivity is >99% except for **2h** (17:1) and **2i** (9:1), and the enantiomeric excess is <20%.

After the successful development of a new approach to *trans*-3-aryl-4-nitrocyclohexanones, we sought to apply this protocol towards the synthesis of an alkaloid, epibatidine (**3**, Figure 1), isolated from the Ecuadorian poison frog *Epipedobates tricolor*. Epibatidine is very potent and has remarkable analgesic properties (much more active than morphine) and has therefore received considerable attention from synthetic chemists.[11]

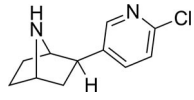


Figure 1. (±)-epibatidine **3**.

Here, we have explored a new synthesis of **3** through the above-developed methodology (Scheme 2). Thus, the desired MBH adduct **5** was obtained from the reaction of β-(chloropyridyl)nitrostyrene **4** with methyl vinyl ketone in 49% yield. The enone **5** was subjected to an intramolecular Michael addition with 10 mol-% DL-proline in DMSO to obtain the cyclohexanone **6** (86% yield), a handy precursor to (±)-epibatidine **3** through a three-step reaction sequence. Accordingly, nitrocyclohexanone **6** was subjected to sodium borohydride reduction in MeOH to obtain the alcohol **7**, which was mesylated to **8** in 87% yield (over two steps).

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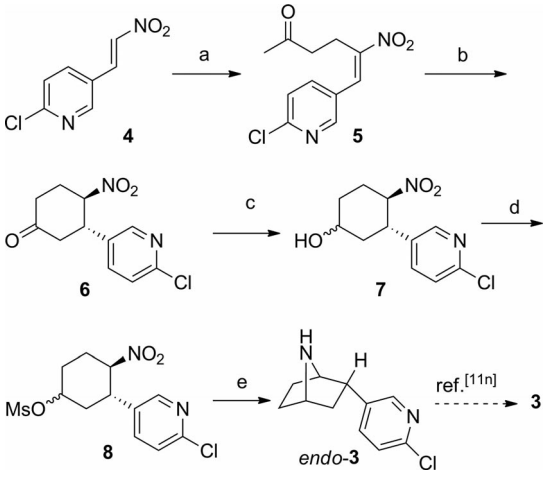
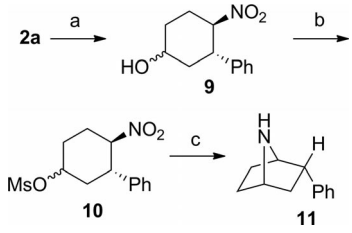
The reduction of the nitro group of **8** to an amine followed by reflux in chloroform provided the *endo* isomer of epibatidine (*endo*-**3**). The formation of the *endo* isomer of epibatidine further supports the *trans* selectivity of the developed intramolecular Michael addition reaction.[11n,11o] The conversion of the *endo* isomer to epibatidine (*exo* isomer) has already been reported.[11n]



Scheme 2. Synthesis of (±)-*endo*-**3**. Reagents and conditions: (a) MVK, imidazole, LiCl, tetrahydrofuran (THF), room temp., 18 h, 49%; (b) 10 mol-% DL-proline, DMSO, room temp., 16 h, 86%; (c) $NaBH_4$, MeOH, room temp., 1 h, 95%; (d) methanesulfonyl chloride (MsCl), Et_3N, 4-(dimethylamino)pyridine (DMAP), CH_2Cl_2, 0 °C, 2 h, 79%; (e) i) Zn, AcOH, THF, room temp.; 3 h, (ii) $CHCl_3$, 60 °C, 72 h, 75%.

A similar strategy was also used for the conversion of **2a** to the corresponding *endo*-bicyclic compound **11** (an analogue of epibatidine)[12] by the reduction of **2a** to **9** followed by mesylation of **9** to yield **10** (Scheme 3).



Scheme 3. Synthesis of **11**. Reagents and conditions: (a) $NaBH_4$, MeOH, room temp., 1 h, 95%; (b) MsCl, Et_3N, DMAP, CH_2Cl_2, 0 °C, 2 h, 80%; (c) (i) Zn, AcOH, THF, room temp., 3 h; (ii) $CHCl_3$, 60 °C, 72 h, 81%.

Conclusions

We have developed a novel proline-catalyzed intramolecular Michael addition reaction to provide 3-aryl-4-nitrocyclohexanones with excellent diastereoselectivity starting from MBH adducts obtained from the reaction of β-nitrostyrenes with MVK. The reaction exclusively provided *trans*-selective products under mild reaction conditions. Further, the methodology has been successfully utilized for the new synthesis of the *endo* isomer of epibatidine and an analogue.

Experimental Section

General: ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ with 300, 400, 500, or 75 MHz spectrometers at ambient temperature. The chemical shifts (δ) are reported in ppm on the scale downfield from tetramethylsilane (TMS) as an internal standard, and signal patterns are indicated as follows: s, singlet; d, doublet; dd, doublet of doublets; ddd, doublet of doublet of doublets; td, triplet of doublets; t, triplet; m, multiplet; br. s, broad singlet. Coupling constants J are in Hz. FTIR spectra were recorded as KBr thin films or neat. For low (MS) and high (HRMS) resolution, m/z ratios are reported as values in atomic mass units. All the reagents and solvents were reagent grade and used without further purification unless specified otherwise. Technical grade ethyl acetate and petroleum ether used for column chromatography were distilled prior to use. Column chromatography was performed with silica gel (60–120 mesh) packed in glass columns.

General Experimental Procedure for the MBH Reaction: To a stirred solution of nitroalkene (5 mmol) in THF (15 mL) was added imidazole (5 mmol) and lithium chloride (5 mmol), followed by MVK (15 mmol) at room temp., and the reaction mixture was stirred at the same temperature. After completion of the reaction (monitored by TLC), the mixture was diluted with water (40 mL) and acidified with 5 N HCl (40 mL). The aqueous layer was extracted with ethyl acetate (2 × 40 mL), the combined organic layers were washed with brine (20 mL), dried with anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (10% EtOAc/hexanes) to afford the pure product. The spectroscopic data of **1a**,**b**,**g**,**h** are in full agreement with the literature data.[4]

(*E*)-6-(Naphthalen-1-yl)-5-nitrohex-5-en-2-one (1c): Yield 46%; pale yellow solid; m.p. 88–90 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.62 (s, 1 H), 7.95–7.84 (m, 3 H), 7.62–7.49 (m, 3 H), 7.42–7.39 (m, 1 H), 3.01 (t, J = 8.3 Hz, 2 H), 2.75 (t, J = 8.3 Hz, 2 H), 2.10 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 205.8, 151.9, 133.2, 133.0, 131.1, 130.1, 129.1, 128.6, 126.9, 126.5, 126.3, 125.1, 123.8, 41.0, 29.5, 21.4 ppm. IR (KBr): $\tilde{\nu}$ = 3055, 2923, 1716, 1520, 1329, 1164, 1007, 805, 783 cm^{-1}. MS (ESI): m/z = 270 $[M + H]^+$. HRMS (ESI): calcd. for $C_{16}H_{15}NNaO_3$ $[M + Na]^+$ 292.0944; found 292.0936.

(*E*)-6-(4-Bromophenyl)-5-nitrohex-5-en-2-one (1d): Yield 39%; pale yellow solid; m.p. 100–101 °C. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.96 (s, 1 H), 7.59 (d, J = 7.9 Hz, 2 H), 7.30 (d, J = 7.9 Hz, 2 H), 3.07 (t, J = 7.9 Hz, 2 H), 2.77 (t, J = 7.9 Hz, 2 H), 2.18 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 205.9, 150.8, 133.2, 132.3, 131.0, 130.6, 124.7, 40.7, 29.7, 21.4 ppm. IR (KBr): $\tilde{\nu}$ = 2923, 1715, 1520, 1324, 1219, 1073, 772, 514 cm^{-1}. MS (ESI): m/z = 299 $[M + H]^+$.

(*E*)-6-(2-Chlorophenyl)-5-nitrohex-5-en-2-one (1e): Yield 51%; viscous liquid. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.10 (s, 1 H), 7.50–7.44 (m, 1 H), 7.40–7.31 (m, 3 H), 2.95 (t, J = 8.7 Hz, 2 H), 2.73 (t, J = 8.7 Hz, 2 H), 2.14 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 205.8, 151.9, 134.3, 131.6, 130.9, 130.7, 129.8, 129.5, 127.0, 40.7, 29.5, 21.1 ppm. IR (KBr): $\tilde{\nu}$ = 2930, 1718, 1525, 1435, 1332, 1164, 1055, 872, 769 cm^{-1}. MS (ESI): m/z = 254 $[M + H]^+$. HRMS (ESI): calcd. for $C_{12}H_{13}ClNO_3$ $[M + H]^+$ 254.0578; found 254.0554.

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(*E*)-4-(2-Nitro-5-oxohex-1-enyl)benzonitrile (1f): Yield 42%; pale yellow solid; m.p. 85–86 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.04 (s, 1 H), 7.76 (d, J = 8.3 Hz, 2 H), 7.54 (d, J = 8.3 Hz, 2 H), 3.07 (t, J = 7.9 Hz, 2 H), 2.80 (t, J = 7.9 Hz, 2 H), 2.19 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 205.7, 152.4, 136.3, 132.4, 132.0, 129.8, 117.8, 113.1, 40.4, 29.5, 21.1 ppm. IR (KBr): $\tilde{\nu}$ = 3065, 2924, 2228, 1713, 1522, 1412, 1328, 1219, 1163, 772 cm^{-1}. MS (ESI): m/z = 245 [M + H]$^+$. $C_{13}H_{12}N_2O_3$ (244.25): calcd. C 63.93, H 4.95, N 11.47; found C 63.76, H 4.91, N 11.35.

(*E*)-6-(2,3-Dimethoxyphenyl)-5-nitrohex-5-en-2-one (1i): Yield 62%; brown solid; m.p. 95–96 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.22 (s, 1 H), 7.10 (t, J = 8.0 Hz, 1 H), 6.99 (d, J = 8.0 Hz, 1 H), 6.80 (d, J = 7.0 Hz, 1 H), 3.89 (s, 3 H), 3.85 (s, 3 H), 3.03 (t, J = 7.0 Hz, 2 H), 2.76 (t, J = 7.0 Hz, 2 H), 2.16 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 206.2, 154.3, 151.0, 148.0, 130.5, 126.2, 124.3, 120.6, 114.2, 61.2, 55.7, 40.9, 29.6, 21.6 ppm. IR (KBr): $\tilde{\nu}$ = 2939, 1716, 1520, 1475, 1328, 1277, 1079, 1002, 751 cm^{-1}. MS (ESI): m/z = 280 [M + H]$^+$. HRMS (ESI): calcd. for $C_{14}H_{18}NO_5$ [M + H]$^+$ 280.1179; found 280.1160.

(*E*)-8-Methyl-5-nitronon-5-en-2-one (1j): Yield 45%; viscous liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.10 (t, J = 7.9 Hz, 1 H), 2.80 (t, J = 6.9 Hz, 2 H), 2.65 (t, J = 6.9 Hz, 2 H), 2.19 (t, J = 7.5 Hz, 2 H), 2.13 (s, 3 H), 1.90–1.74 (m, 1 H), 0.99 (s, 3 H), 0.97 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 206.3, 150.5, 136.7, 40.8, 36.6, 29.5, 27.9, 22.1, 20.3 ppm. IR (KBr): $\tilde{\nu}$ = 2960, 1718, 1520, 1464, 1334, 1165, 858, 725 cm^{-1}. MS (ESI): m/z = 200 [M + H]$^+$.

General Procedure for the Intramolecular Michael Addition Reaction: To a stirred solution of MBH adduct **1** (1 mmol) in DMSO (5 mL) was added L-proline (10 mol-%), and the reaction mixture was stirred at 25 °C. After completion of the reaction (monitored by TLC), the mixture was diluted with water (20 mL), and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine (20 mL), dried with anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (12% EtOAc/hexanes) to afford the pure product.

4-Nitro-3-phenylcyclohexanone (2a): White solid; m.p. 97–98 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.39–7.19 (m, 5 H), 5.06 (td, J = 10.6, 3.8 Hz, 1 H), 3.71 (ddd, J = 10.6, 6.8, 3.8 Hz, 1 H), 2.74–2.43 (m, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 205.6, 138.1, 129.2, 128.3, 127.0, 88.0, 46.9, 45.5, 38.0, 29.5 ppm. IR (KBr): $\tilde{\nu}$ = 2923, 1725, 1552, 1377, 1291, 1190, 1091, 766, 699, 546 cm^{-1}. MS (ESI): m/z = 242 [M + Na]$^+$. HRMS (ESI): calcd. for $C_{12}H_{14}NO_3$ [M + H]$^+$ 220.0968; found 220.0955.

4-Nitro-3-(thiophen-2-yl)cyclohexanone (2b): Brown solid; m.p. 148–149 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.22 (d, J = 5.3 Hz, 1 H), 6.93 (dd, J = 5.3, 3.2 Hz, 1 H), 6.87 (d, J = 3.2 Hz, 1 H), 4.89 (td, J = 8.3, 3.8 Hz, 1 H), 4.11 (ddd, J = 8.3, 5.3, 3.8 Hz, 1 H), 2.90–2.47 (m, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 204.7, 141.2, 127.2, 125.8, 125.2, 88.7, 45.8, 42.0, 37.7, 28.9 ppm. IR (KBr): $\tilde{\nu}$ = 2923, 1718, 1551, 1373, 1284, 705, 642 cm^{-1}. MS (ESI): m/z = 248 [M + Na]$^+$. HRMS (ESI): calcd. for $C_{10}H_{11}NNaO_3S$ [M + Na]$^+$ 248.0351; found 248.0351.

3-(Naphthalen-1-yl)-4-nitrocyclohexanone (2c): Brown solid; m.p. 192–193 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.11 (d, J = 8.5 Hz, 1 H), 7.95–7.78 (m, 2 H), 7.64–7.40 (m, 4 H), 5.29 (td, J = 8.3, 5.1 Hz, 1 H), 4.82 (ddd, J = 8.3, 5.8, 5.1 Hz, 1 H), 2.98–2.88 (m, 1 H), 2.82–2.478 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 206.4, 134.0, 129.6, 129.2, 128.7, 127.0, 126.1, 125.4, 124.2, 121.9, 120.5, 85.7, 44.7, 40.5, 37.5, 29.6 ppm. IR (KBr): $\tilde{\nu}$ = 2923, 2854, 1946, 1715, 1543, 1370. 1337, 1280, 1193, 1087, 769 cm^{-1}. MS (ESI): m/z = 270 [M + H]$^+$. HRMS (ESI): calcd. for $C_{16}H_{15}NNaO_3$ [M + Na]$^+$ 292.0944; found 292.0933.

3-(4-Bromophenyl)-4-nitrocyclohexanone (2d): Pale yellow solid; m.p. 169–170 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.49 (d, J = 9.0 Hz, 2 H), 7.11 (d, J = 9.0 Hz, 2 H), 5.02 (td, J = 10.6, 3.0 Hz, 1 H), 3.67 (ddd, J = 10.6, 5.3, 3.0 Hz, 1 H), 2.76–2.40 (m, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 204.9, 137.0, 132.3, 128.6, 122.2, 87.2, 46.3, 45.2, 37.8, 29.8 ppm. IR (KBr): $\tilde{\nu}$ = 2907, 1712, 1546, 1488, 1370, 1074, 824, 540 cm^{-1}. MS (ESI): m/z = 299 [M + H]$^+$.

3-(2-Chlorophenyl)-4-nitrocyclohexanone (2e): Brown solid; m.p.175–176 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.42–7.37 (m, 1 H), 7.29–7.18 (m, 3 H), 5.18 (td, J = 9.1, 3.8 Hz, 1 H), 4.34 (ddd, J = 9.1, 6.8, 3.8 Hz, 1 H), 2.87–2.79 (m, 1 H), 2.69–2.47 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 205.5, 135.7, 133.6, 130.7, 129.3, 127.8, 127.7, 85.1, 43.9, 43.1, 37.7, 28.9 ppm. IR (KBr): $\tilde{\nu}$ = 2965, 2922, 1722, 1545, 1482, 1287, 1036, 977, 746 cm^{-1}. MS (ESI): m/z = 276 [M + Na]$^+$. HRMS (ESI): calcd. for $C_{12}H_{12}ClNNaO_3$ [M + Na]$^+$ 276.0397; found 276.0394.

4-(2-Nitro-5-oxocyclohexyl)benzonitrile (2f): Pale yellow solid; m.p. 162–163 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.67 (d, J = 8.3 Hz, 2 H), 7.37 (d, J = 8.3 Hz, 2 H), 5.08 (td, J = 10.6, 3.8 Hz, 1 H), 3.77 (ddd, J = 10.6, 5.3, 3.8 Hz, 1 H), 2.76–2.43 (m, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 204.3, 143.2, 133.0, 127.9, 118.1, 112.3, 87.2, 46.7, 44.9, 37.8, 29.5 ppm. IR (KBr): $\tilde{\nu}$ = 2922, 2228, 1717, 1548, 1374, 1289, 840, 564 cm^{-1}. MS (ESI): m/z = 245 [M + H]$^+$. HRMS (ESI): calcd. for $C_{13}H_{13}N_2O_3$ [M + H]$^+$ 245.0920; found 245.0932.

4-Nitro-3-(4-nitrophenyl)cyclohexanone (2g): Pale yellow solid; m.p. 158–159 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.24 (d, J = 8.7 Hz, 2 H), 7.41 (d, J = 8.7 Hz, 2 H), 5.01 (td, J = 10.6, 5.5 Hz, 1 H), 3.83 (ddd, J = 10.6, 6.4, 5.5 Hz, 1 H), 2.76–2.45 (m, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 204.0, 145.1, 128.1, 124.5, 116.5, 87.3, 46.5, 45.0, 37.8, 29.6 ppm. IR (KBr): $\tilde{\nu}$ = 2924, 2884, 1711, 1549, 1519, 1348, 1246, 1113, 857, 697, 543 cm^{-1}. MS (ESI): m/z = 265 [M + H]$^+$. HRMS (ESI): calcd. for $C_{12}H_{13}N_2O_5$ [M + H]$^+$ 265.0819; found 265.0826.

3-(4-Methoxyphenyl)-4-nitrocyclohexanone (2h): Pale yellow solid; m.p. 167–168 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.10 (d, J = 8.7 Hz, 2 H), 6.82 (d, J = 8.7 Hz, 2 H), 4.91 (td, J = 10.2, 3.6 Hz, 1 H), 3.77 (s, 3 H), 3.64 (ddd, J = 10.2, 5.6, 3.6 Hz, 1 H), 2.73–2.41 (m, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 205.7,159.3, 130.0, 128.0, 114.5, 88.3, 55.2, 46.2, 45.6, 37.9, 29.4 ppm. IR (KBr): $\tilde{\nu}$ = 2966, 2836, 1712, 1545, 1516, 1264, 1180, 1032, 829, 546 cm^{-1}. MS (ESI): m/z = 272 [M + Na]$^+$. HRMS (ESI): calcd. for $C_{13}H_{16}NO_4$ [M + H]$^+$ 250.1074; found 250.1072.

3-(2,3-Dimethoxyphenyl)-4-nitrocyclohexanone (2i): Pale yellow solid; m.p. 191–193 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.02 (d, J = 8.1 Hz, 1 H), 6.86 (dd, J = 8.3, 1.3 Hz, 1 H), 6.75 (dd, J = 7.7, 1.3 Hz, 1 H), 5.27 (td, J = 10.0, 3.8 Hz, 1 H), 4.07 (ddd, J = 10.0, 6.4, 3.8 Hz, 1 H), 3.91 (s, 3 H), 3.86 (s, 3 H), 2.75–2.44 (m, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 206.0, 152.7, 146.8, 131.3, 124.3, 119.3, 112.2, 86.1, 60.7, 55.6, 44.5, 42.0, 37.8, 29.3 ppm. IR (KBr): $\tilde{\nu}$ = 2963, 2931, 1722, 1547, 1479, 1279, 1089, 1007, 748, 510 cm^{-1}. MS (ESI): m/z = 302 [M + Na]$^+$. HRMS (ESI): calcd. for $C_{14}H_{17}NNaO_5$ [M + Na]$^+$ 302.0998; found 302.0996.

(*E*)-6-(6-Chloropyridin-3-yl)-5-nitrohex-5-en-2-one (5): Starting from **4** and according to the same procedure as reported above for the MBH reaction. Yield 46%; brown solid; m.p. 95–96 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.46 (d, J = 2.1 Hz, 1 H), 7.99 (s, 1 H), 7.81 (dd, J = 8.5, 2.5 Hz, 1 H), 7.46 (d, J = 8.5 Hz, 1 H), 3.07

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(t, J = 7.5 Hz, 2 H), 2.82 (t, J = 7.5 Hz, 2 H), 2.19 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 205.7, 152.7, 152.3, 150.3, 138.8, 129.5, 126.9, 124.6, 40.5, 29.7, 21.3 ppm. IR (KBr): $\tilde{\nu}$ = 2921, 2851, 1715, 1581, 1522, 1462, 1331, 1165, 1105, 869, 729 cm^{-1}. MS (ESI): m/z = 277 [M + Na]$^+$. HRMS (ESI): calcd. for $C_{11}H_{11}ClN_2NaO_3$ [M + Na]$^+$ 277.0350; found: 277.0342.

3-(6-Chloropyridin-3-yl)-4-nitrocyclohexanone (6):[11e] The procedure followed that described for the intramolecular Michael addition reaction. Brown solid; m.p. 122–124 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.31 (d, J = 2.6 Hz, 1 H), 7.53 (dd, J = 8.3, 2.6 Hz, 1 H), 7.33 (d, J = 8.1 Hz, 1 H), 5.01 (td, J = 10.7, 4.0 Hz, 1 H), 3.73 (ddd, J = 10.7, 5.5, 2.0 Hz, 1 H), 2.75–2.44 (m, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 204.0, 151.5, 148.5, 137.3, 132.6, 124.8, 87.3, 44.9, 43.8, 37.8, 29.6 ppm. IR (KBr): $\tilde{\nu}$ = 1720, 1590, 1520, 1480, 1368, 1234, 1055, 924, 784 cm^{-1}. MS (ESI): m/z = 255 [M + H]$^+$. HRMS (ESI): calcd. for $C_{11}H_{12}ClN_2O_3$[M + H]$^+$ 255.0531; found 255.0552.

3-(6-Chloropyridin-3-yl)-4-nitrocyclohexanol (7): To a suspension of substituted cyclohexanone **6** (1 mmol) in MeOH (6 mL), $NaBH_4$ (1.5 mmol) was added in small portions (10 min), and the mixture was stirred at room temperature for 2 h. After completion of the reaction, the solvent was evaporated, and the residue was quenched with saturated aqueous solution of NH_4Cl. The aqueous layer was extracted with ethyl acetate (3 × 10 mL), the combined organic layers were washed with brine (20 mL), dried with anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (20% EtOAc/hexanes) to afford the pure product. Colorless amorphous solid; m.p. 148–149 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.25 (s, 1 H), 7.53 (dd, J = 7.9, 2.5 Hz, 1 H), 7.30 (d, J = 8.3 Hz, 1 H), 4.60 (td, J = 11.5, 3.8 Hz, 1 H), 3.97–3.84 (m, 1 H), 3.30 (t, J = 11.2 Hz, 1 H), 2.50–2.39 (m, 1 H), 2.29–2-132 (m, 3 H), 1.72–1.47 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 150.8, 148.7, 137.4, 134.0, 124.6, 89.2, 68.3, 42.9, 40.3, 32.8, 29.8 ppm. IR (KBr): $\tilde{\nu}$ = 2945, 1546, 1471, 1364, 1064, 762 cm^{-1}. MS (ESI): m/z = 255 [M + H]$^+$. HRMS (ESI): calcd. for $C_{11}H_{13}ClN_2NaO_3$ [M + Na]$^+$ 279.0507; found 279.0532.

3-(6-Chloropyridin-3-yl)-4-nitrocyclohexyl Methanesulfonate (8): To a stirred solution of alcohol **7** (1 mmol) in dry dichloromethane (DCM, 5 mL) were added triethylamine (3 mmol) and DMAP (cat.), followed by methanesulfonyl chloride (2 mmol) at 0 °C. The reaction mixture was stirred at the same temperature for 10 min. The mixture was then diluted by the addition of ice-cold water (20 mL), and the aqueous phase was extracted with DCM (2 × 10 mL). The combined organic layers were washed with brine (25 mL), dried with Na_2SO_4, and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexanes/EtOAc = 90:10) to yield the pure product. Brown solid; m.p. 120–121 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.29 (d, J = 2.7 Hz, 1 H), 7.54 (dd, J = 8.3, 2.7 Hz, 1 H), 7.32 (d, J = 8.3 Hz, 1 H), 4.83 (ddd, J = 11.5, 4.5, 3.8 Hz, 1 H), 4.66 (td, J = 11.3, 3.8 Hz, 1 H), 3.38 (td, J = 11.3, 3.8 Hz, 1 H), 3.06 (s, 3 H), 2.55–2.40 (m, 3 H), 2.22–2.09 (m, 1 H), 1.98–1.77 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 151.2, 148.6, 137.4, 132.9, 124.6, 87.9, 76.4, 42.7, 38.7, 37.7, 30.3, 29.2 ppm. IR (KBr): $\tilde{\nu}$ = 2926, 1550, 1460, 1351, 1174, 949, 853, 758, 530 cm^{-1}. MS (ESI): m/z = 335 [M + H]$^+$. HRMS (ESI): calcd. for $C_{12}H_{16}ClN_2O_5S$[M + H]$^+$ 335.0463; found 335.0421.

2-(6-Chloropyridin-3-yl)-7-azabicyclo[2.2.1]heptane (*endo*-3): To a stirred solution of mesylated compound **8** (0.1 mmol) in THF (1 mL) were added AcOH (1 mL) and Zn (1 mmol) at room temperature. After 2 h, the mixture was filtered through a pad of Celite (AcOEt as eluent). The organic layer was washed with a saturated aqueous Na_2CO_3 solution and brine, and dried with K_2CO_3; evaporation of the solvent afforded the amine product. A solution of the amine product in $CHCl_3$ (4 mL) was heated at 60 °C. After 3 d, the reaction mixture was diluted with additional $CHCl_3$ (10 mL), and then 10% aqueous K_2CO_3 was added (15 mL). The mixture was extracted with $CHCl_3$ (3 × 10 mL). The combined extracts were dried with K_2CO_3, filtered, and the solvents were evaporated. The residue was purified by flash column chromatography ($CHCl_3$/MeOH/30% aqueous NH_3, 20:1:0.1 as eluent) to afford the pure product as a viscous liquid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.24 (d, J = 2.5 Hz, 1 H), 7.50 (dd, J = 8.3, 2.5 Hz, 1 H), 7.35 (d, J = 8.3 Hz, 1 H), 3.81 (q, J = 5.4 Hz, 2 H), 3.35 (m, 1 H), 2.15 (br., 1 H), 1.73–1.65 (m, 1 H); 1.52 (dd, J = 8.3, 5.7 Hz, 1 H), 1.48–1.36 (m, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 149.5, 149.2, 138.3, 135.5, 123.7, 61.1, 57.6, 44.6, 34.6, 30.8, 23.9 ppm. IR (KBr): $\tilde{\nu}$ = 2959, 1460, 1367, 1104, 1023, 832, 737 cm^{-1}. MS (ESI): m/z = 209 [M + H]$^+$. HRMS (ESI): calcd. for $C_{11}H_{14}ClN_2$ [M + H]$^+$ 209.0840; found 209.0855.

4-Nitro-3-phenylcyclohexanol (9): The procedure followed that described for **7**. White amorphous solid; m.p. 129–130 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35–7.17 (m, 5 H), 4.65 (td, J = 11.3, 4.5 Hz, 1 H), 3.96–3.85 (m, 1 H), 3.26 (td, J = 11.3, 3.8 Hz, 1 H), 2.45–2.36 (m, 1 H), 2.27–2-07 (m, 3 H), 1.73–1.45 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 139.2, 128.9, 127.7, 127.0, 89.8, 68.7, 46.1, 41.1, 32.9, 29.8 ppm. IR (KBr): $\tilde{\nu}$ = 3574, 3453, 2938, 2866, 1550, 1374, 1062, 700, 560 cm^{-1}. MS (ESI): m/z = 221 [M + H]$^+$. $C_{12}H_{15}NO_3$ (221.25): calcd. C 65.14, H 6.83, N 6.33; found C 64.77, H 6.68, N 5.92.

4-Nitro-3-phenylcyclohexyl Methanesulfonate (10): The procedure followed that described for **8**. White amorphous solid; m.p. 165–166 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.16 (m, 5 H), 4.91–4.78 (m, 1 H), 4.67 (td, J = 11.5, 3.9 Hz, 1 H), 3.32 (td, J = 11.3, 3.6 Hz, 1 H), 3.03 (s, 3 H), 2.54–2.39 (m, 3 H), 2.23–2.12 (m, 1 H), 1.99–1.76 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 137.9, 128.8, 127.9, 126.8, 88.4, 76.3, 45.6, 38.5, 38.0, 30.3, 29.1 ppm. IR (KBr): $\tilde{\nu}$ = 2925, 1545, 1339, 1169, 849, 763, 696, 524 cm^{-1}. MS (ESI): m/z = 300 [M + H]$^+$. $C_{13}H_{17}NO_5S$ (299.34): calcd. C 52.16, H 5.72, N 4.68; found C 52.4, H 5.61, N 4.92.

2-Phenyl-7-azabicyclo[2.2.1]heptane (11): The procedure followed that described for *endo*-**3**. Viscous liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.38–7.32 (m, 3 H), 7.27–7.22 (m, 2 H), 3.82 (q, J = 4.6 Hz, 2 H), 3.46–3.40 (m, 1 H), 2.13 (m, 1 H), 1.74–1.61 (m, 2 H) 1.55–1.39 (m, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 141.2, 128.3, 128.1, 126.0, 61.6, 57.8, 47.8, 34.6, 30.9, 24.0 ppm. IR (KBr): $\tilde{\nu}$ = 2958, 2923, 1551, 1460, 1355, 1175, 943, 700, 530 cm^{-1}. MS (ESI): m/z = 196 [M + Na]$^+$. $C_{12}H_{15}N$ (173.25): calcd. C 83.19, H 8.73, N 8.08; found C 82.9, H 8.40, N 8.52.

Supporting Information (see footnote on the first page of this article): Copies of ^{1}H and ^{13}C NMR spectra.

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[1] a) K. Morita, Z. Suzuki, H. Hirose, *Bull. Chem. Soc. Jpn.* **1968**, *41*, 2815–2819; b) A. B. Baylis, M. E. D. Hillman, German patent 2155113, **1972**; *Chem. Abstr.* **1972**, *77*, 34174q.

[2] For reviews, see: a) D. Basavaiah, G. Veeraraghavaiah, *Chem. Soc. Rev.* **2012**, *41*, 68–78; b) D. Basavaiah, D. V. Lenin, *Eur. J. Org. Chem.* **2010**, 5650–5658; c) D. Basavaiah, B. S. Reddy,

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S. S. Badsara, *Chem. Rev.* **2010**, *110*, 5447–5674; d) V. Declerck, J. Martinez, F. Lamaty, *Chem. Rev.* **2009**, *109*, 1–48; e) V. Singh, S. Batra, *Tetrahedron* **2008**, *64*, 4511–4574; f) Y. L. Shi, M. Shi, *Eur. J. Org. Chem.* **2007**, 2905–2916; g) K. Y. Lee, S. Gowrisankar, J. N. Kim, *Bull. Korean Chem. Soc.* **2005**, *26*, 1481–1490; h) D. Basavaiah, A. J. Rao, T. Satyanarayana, *Chem. Rev.* **2003**, *103*, 811–891.

[3] a) C. G. Lima Junior, M. L. L. A. Vasconcellos, *Bioorg. Med. Chem.* **2012**, *20*, 3954–3971.

[4] M. Dadwal, R. Mohan, D. Panda, S. M. Mobinc, I. N. N. Namboothiri, *Chem. Commun.* **2006**, *42*, 338–340.

[5] a) Ch. R. Reddy, M. D. Reddy, B. Srikanth, *Org. Biomol. Chem.* **2012**, *10*, 4280–4288; b) Ch. R. Reddy, M. D. Reddy, B. Srikanth, K. R. Prasad, *Org. Biomol. Chem.* **2011**, *9*, 6027–6033; c) Ch. R. Reddy, N. Kiranmai, G. S. K. Babu, G. D. Sarma, B. Jagadeesh, S. Chandrasekhar, *Tetrahedron Lett.* **2007**, *48*, 215–218; d) Ch. R. Reddy, N. Kiranmai, K. Johny, M. Pendke, P. Naresh, *Synthesis* **2009**, 399–402.

[6] P. Shanbhag, P. R. Nareddy, M. Dadwal, S. M. Mobin, I. N. N. Namboothiri, *Org. Biomol. Chem.* **2010**, *8*, 4867–4873.

[7] a) Z. Pei, X. Li, T. W. von Geldern, D. J. Madar, K. Longenecker, H. Yong, T. H. Lubben, K. D. Stewart, B. A. Zinker, B. J. Backes, A. S. Judd, M. Mulhern, S. J. Ballaron, M. A. Stashko, A. K. Mika, D. W. A. Beno, G. A. Reinhart, R. M. Fryer, L. C. Preusser, A. J. Kempf-Grote, H. L. Sham, J. M. Trevillyan, *J. Med. Chem.* **2006**, *49*, 6439–6442; b) G. Szanto, L. Hegedus, L. Mattyasovszky, A. Simon, A. Simon, I. Kadas, *Tetrahedron Lett.* **2009**, *50*, 2857–2859; c) G. Szanto, L. Hegedus, L. Mattyasovszky, A. Simon, A. Simon, I. Bitter, G. Toth, L. Toke, I. Kadas, *Tetrahedron* **2009**, *65*, 8412–8417; d) N. Ayyagari, D. Jose, S. M. Mobin, I. N. N. Namboothiri, *Tetrahedron Lett.* **2011**, *52*, 258–262; e) I. N. N. Namboothiri, N. Ayyagari, D. Jose, Int. Pat. Appl. PCT/IB2010/001337; US Pat. Appl. IN-700642–02-US-REG; Ind. Pat. Appl. 3024/MUM/2009.

[8] a) T. F. Spande, H. M. Garraffo, M. W. Edwards, H. J. C. Yeh, L. Pannell, J. W. Daly, *J. Am. Chem. Soc.* **1992**, *114*, 3475–3478; b) H. M. Garraffo, T. F. Spande, M. Williams, *Heterocycles* **2009**, *79*, 207–217.

[9] a) M. Node, K. Nishide, H. Imazato, R. Kurosaki, T. Inoue, T. Ikariya, *Chem. Commun.* **1996**, *32*, 2559–2560; b) J. Barluenga, F. F. Aznar, C. Ribas, C. Valdes, *J. Org. Chem.* **1997**, *62*, 6746–6753.

[10] a) B. Wu, G. Lui, M. li, Y. Zhang, S. Zhang, J. Qiu, X. Xu, S. Ji, X. Wang, *Chem. Commun.* **2011**, *47*, 3992–3994; b) Y. Hoashi, T. Yabuta, P. Yuan, H. Miyabe, Y. Takemoto, *Tetrahedron* **2006**, *62*, 365–374; c) Y. Hoashi, T. Yabuta, Y. Takemoto, *Tetrahedron Lett.* **2004**, *45*, 9185–9188.

[11] a) D. R. Boyd, N. D. Sharma, M. Kaik, P. B. A. McIntyre, P. J. Stevenson, C. C. R. Allen, *Org. Biomol. Chem.* **2012**, *10*, 2774–2779; b) I. Kulu, N. Ocal, *Helv. Chim. Acta* **2011**, *94*, 2054–2060; c) J. Bexrud, M. Lautens, *Org. Lett.* **2010**, *12*, 3160–3163; d) H. F. Olivo, M. S. Hemenway, *Org. Prep. Proced. Int.* **2002**, *34*, 1–25; e) A. Barco, S. Benetti, C. D. Risi, P. Marchetti, G. P. Pollini, V. Zanirato, *Eur. J. Org. Chem.* **2001**, 975–986; f) A. Barco, S. Benetti, C. D. Risi, P. Marchetti, G. P. Pollini, V. Zanirato, *Tetrahedron Lett.* **1998**, *39*, 1973–1976; g) N. S. Sirisoma, C. R. Johnson, *Tetrahedron Lett.* **1998**, *39*, 2059–2062; h) C. Szhntaya, Z. Kardos-Balogh, I. Moldvai, C. Szantay Jr., E. Temesvari-Major, G. Blasko, *Tetrahedron* **1996**, *52*, 11053–11062; i) C. Zhang, M. L. Trudell, *J. Org. Chem.* **1996**, *61*, 7189–7191; j) E. Albertini, A. Barco, S. Benetti, C. Derisi, G. P. Pollini, R. Romagnoli, V. Zanirato, *Tetrahedron Lett.* **1994**, *35*, 9297–9300; k) G. Pandey, T. D. Bagul, G. Lakshmaiah, *Tetrahedron Lett.* **1994**, *35*, 7439–7442; l) K. Sestanj, E. Melenski, I. Jirkovsky, *Tetrahedron Lett.* **1994**, *35*, 5417–5420; m) K. Okabe, M. Natsume, *Chem. Pharm. Bull.* **1994**, *42*, 1432–1436; n) S. R. Fletcher, R. Baker, M. S. Chambers, R. H. Herbert, S. C. Hobbs, S. R. Thomas, H. M. Verrier, A. P. Watt, R. G. Ball, *J. Org. Chem.* **1994**, *59*, 1771–1778; o) C. Szantay, Z. Kardos-Balogh, I. Moldvai, C. Szantay Jr., E. Temesvari-Major, G. Blasko, *Tetrahedron Lett.* **1994**, *35*, 3171–3174; p) S. Fletcher, R. Baker, M. S. Chambers, S. C. Hobbs, P. J. Mitchell, *J. Chem. Soc., Chem. Commun.* **1993**, 1216–1218; q) J. Habermann, S. V. Ley, J. S. Scoot, *J. Chem. Soc. Perkin Trans. 1* **1999**, 1253–1255; r) D. F. Huang, T. Y. Shen, *Tetrahedron Lett.* **1993**, *34*, 4477–4480.

[12] A. Palmgren, A. L. E. Larsson, J. E. Backvall, *J. Org. Chem.* **1999**, *64*, 836–842.

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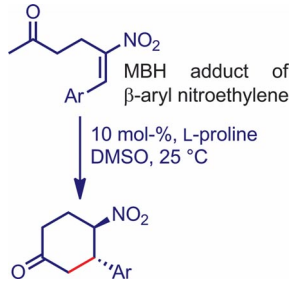
Organocatalysis

Morita–Baylis–Hillman (MBH) adducts of β-arylnitroethylenes have been successfully converted into 3-aryl-4-nitrocyclohexanones through an organocatalyzed diastereoselective intramolecular Michael addition. The application of the method towards (±)-epibatidine and its analogues has also been achieved.



Keywords: Organocatalysis / Michael addition / Morita–Baylis–Hillman reaction / Nitroalkenes / Cyclohexanone / Epibatidine

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