Domino Multicomponent Michael–Michael–Aldol Reactions under Phase-Transfer Catalysis: Diastereoselective Synthesis of Pentasubstituted Cyclohexanes

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Received 8 October 2009

Abstract: A simple, efficient, and environmental friendly domino multicomponent reaction to construct new cyclohexane derivatives with five new stereocenters, one of them quaternary, under phase-transfer catalysis is reported. This novel one-pot reaction allows the transformation of very simple starting materials into pentasubstituted cyclohexane derivatives bearing hydroxy, nitro, and ketone moieties and involving the formation of three new C–C bonds. All compounds have been formed in a completely diastereoselective way and have been isolated in high yields.

Key words: domino reaction, multicomponent reaction, phase-transfer catalysis, diastereoselectivity

Discovery of rapid, efficient, and low-cost methods to construct cyclohexanes with multiple stereogenic centers has been an important goal in organic chemistry[1] because these ring systems are common structures in natural products[2] and biologically significant molecules.[3] Domino multicomponent reactions[4] have emerged as a powerful tool in organic synthesis and have received considerable attention due to their advantages over conventional synthesis. Most important features are the generation of multiple C–C bonds in a multistep reaction concomitant with the creation of many stereocenters from simple precursors. These allow a rapid construction of structurally complex molecules from cheap and easily available starting materials in a simple operation, thereby minimizing the cost, waste, and manual efforts and avoiding the need to protect groups and isolate intermediates.

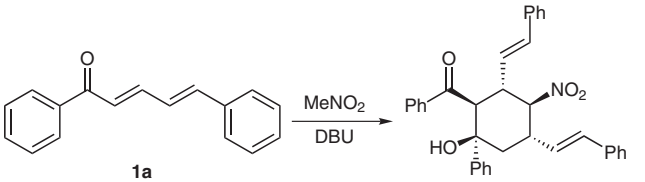
Phase-transfer catalysis (PTC) has long been recognized as a versatile methodology for synthesis,[5] featuring simple experimental operations, mild reaction conditions, inexpensive and environmentally benign reagents and solvents, and the possibility to conduct large-scale preparations. Combining the advantages of domino multicomponent reactions with those from PTC is an important target in green chemistry.[6]

The synthesis of cyclohexanes with two,[7] three,[8] or four[1,3a,9] stereogenic centers from a domino multicomponent reaction is known, although pentasubstituted cyclohexanes have only been generated by two routes.[10] On the other hand, the development of structures including a stereogenic quaternary carbon is an important task in organic synthesis since the number of natural products and pharmaceutical agents possessing quaternary centers is growing.[11]

Herein we report the development of new methodology involving domino multicomponent Michael–Michael–aldol reactions from (*E*,*E*)-1,5-diarylpenta-2,4-dien-1-one (cinnamylideneacetophenones) and nitromethane under PTC.

In our initial studies, we initiated the reaction between cinnamylideneacetophenone **1a** and nitromethane (Table 1) with DBU as base at room temperature. The synthesis of (*E*,*E*,1*R**,2*S**,3*S**,4*S**,5*S**)-2-benzoyl-1-hydroxy-4-nitro-1-phenyl-3,5-distyrylcyclohexane (**2a**) took place with total diastereoselectivity in all solvents (entries 1–7), with acetonitrile (entry 1) attending the highest yield.

Table 1 Domino Multicomponent Reaction of **1a** with Nitromethane Using DBU as Base[a]



1a (*E*,*E*,1*R**,2*S**,3*S**,4*S**,5*S**)-**2a**

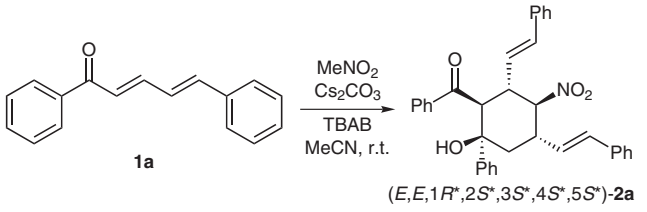
Entry	Solvent	Yield (%)[b]	dr (%)[c]
1	MeCN	63	>99
2	EtOH	52	>99
3	MeOH	33	>99
4	$CHCl_3$	23	>99
5	toluene	26	>99
6	CH_2Cl_2	36	>99
7	THF	24	>99

[a] Reactions were carried out at 0.2 M solution of **1a** (20.0 mg, 0.085 mmol) in solvent (0.43 mL), and it was added DBU (14 mL, 0.094 mmol) and $MeNO_2$ (2.8 mL, 0.051 mmol) at r.t. for 7 d. DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene.
[b] Isolated yield after chromatography.
[c] Diastereomeric ratio based on ^1H NMR analyses.

SYNLETT 2010, No. 1, pp 0115–0118
Advanced online publication: 20.11.2009
DOI: 10.1055/s-0029-1218523; Art ID: D28809ST

After selecting acetonitrile as the most efficient solvent, we proceeded to explore the reaction under PTC conditions (Table 2). We began with 0.5 mol equivalents of Cs_2CO_3 and nitromethane (entry 1), with **2a** being obtained in a moderate yield. Next we increased the mol equivalents of base to 0.85 and of TBAB to 0.2 (entries 2–4) and varied the reaction time. We found that the best yield was obtained when the reaction took place over 20 hours (entry 3). Yields stayed good when the mol equivalents of catalyst was increased to 0.3 (entry 5) for 20 hours of reaction time, but longer reaction times resulted in lower yields (entry 6). With 1 mol equivalent of Cs_2CO_3 (entries 7–9), we found that the best conditions were 0.5 mol equivalents of nitromethane, 0.3 mol equivalents of TBAB and 20 hours reaction time (entry 8) which led to a 79% yield. The increase to 0.7 mol equivalents of nitromethane did not improve the yield (entry 9). Notably, complete diastereoselectivity was obtained in all reactions.

Table 2 Domino Multicomponent Reaction of **1a** with Nitromethane under PTC[a]



Entry	Cs_2CO_3 (mol equiv)	TBAB (mol equiv)	Time (h)	Yield (%)[b]	dr (%)[c]
1	0.50	0.1	20	59	>99
2	0.85	0.2	3	21	>99
3	0.85	0.2	20	62	>99
4	0.85	0.2	74	54	>99
5	0.85	0.3	20	60	>99
6	0.85	0.3	48	48	>99
7	1.0	0.2	20	58	>99
8	1.0	0.3	20	79	>99
9[d]	1.0	0.3	20	53	>99

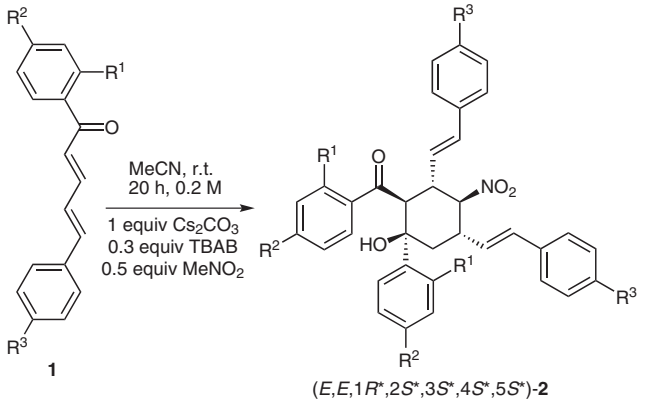
[a] Reactions were carried out at 0.2 M solution of **1a** (20.0 mg, 0.085 mmol) in MeCN (0.43 mL), and it was added TBAB, Cs_2CO_3, and 0.5 mol equiv of $MeNO_2$ (2.3 mL, 0.043 mmol) at r.t. TBAB: tetrabutylammonium bromide.
[b] Isolated yield after chromatography.
[c] Diastereomeric ratio based on ^1H NMR analyses.
[d] Reaction was carried out with 0.7 mol equiv of $MeNO_2$ (3.2 mL, 0.060 mmol).

After establishing optimal reaction conditions, the scope of the reaction for different cinnamylideneacetophenones **1b–h**[12,13] was investigated (Table 3). The synthesis of new cyclohexane derivatives **2b–h**[14] took place with total diastereoselectivity, independently of the nature and position of the substituents in good isolated yield (45–97%). When the ketone aryl group possessed *ortho* substitution (Table 3, entry 1) the yield decreased significantly probably because the OH most likely forms an intramolecular hydrogen bond with the carbonyl group and the α,β,δ,γ-system of **1b** is less reactive. Derivatives with either electron-donating or electron-withdrawing groups at the *para* position on the α-aryl group of cinnamylideneacetophenones afforded the corresponding cyclohexanes in good to high yields (entries 2–6). In addition, we explored the reaction with a methoxy substitution in the δ-aryl group of the system which also led to high isolated yields (entry 7).

The relative stereochemistry of compounds **2a–h** was assigned by analysis of ^1H–^1H coupling constants of the cyclohexane ring and of the NOESY spectrum of derivative **2a**, which confirmed the relative configuration of all neighboring substitution (Figure 1). This was also confirmed by the single-crystal X-ray diffraction studies of **2a** (Figure 2)[15] which clearly show that the 1-OH group is engaged in an intramolecular hydrogen bond with the C=O of the benzoyl group.

The mechanism proposed for the formation of compounds **2** is depicted in Scheme 1. It starts with the formation of

Table 3 Scope of the Domino Multicomponent Reaction[a]



Entry	**1**	R^1	R^2	R^3	Time (h)	**2** (%)[b]	dr (%)[c]
1	**1b**	OH	H	H	60	**2b** (45)	>99
2	**1c**	H	Me	H	60	**2c** (70)	>99
3	**1d**	H	OMe	H	40	**2d** (58)	>99
4	**1e**	H	Br	H	40	**2e** (91)	>99
5	**1f**	H	CN	H	20	**2f** (90)	>99
6	**1g**	H	Cl	H	60	**2g** (97)	>99
7	**1h**	H	H	OCH_3	20	**2h** (81)	>99

[a] Reactions were carried out at 0.2 M solution of **1b–h** (0.085 mmol) in MeCN (0.43 mL), and it was added TBAB (9.2 mg, 0.028 mmol), Cs_2CO_3 (27.7 mg, 0.085 mmol), and $MeNO_2$ (2.3 mL, 0.043 mmol) for 20 h at r.t. TBAB: tetrabutylammonium bromide.
[b] Isolated yield after chromatography.
[c] Diastereomeric ratio based on ^1H NMR analyses.

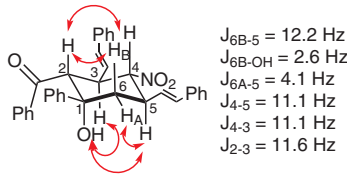


Figure 1 Main NOE effects and *J* values of **2a**

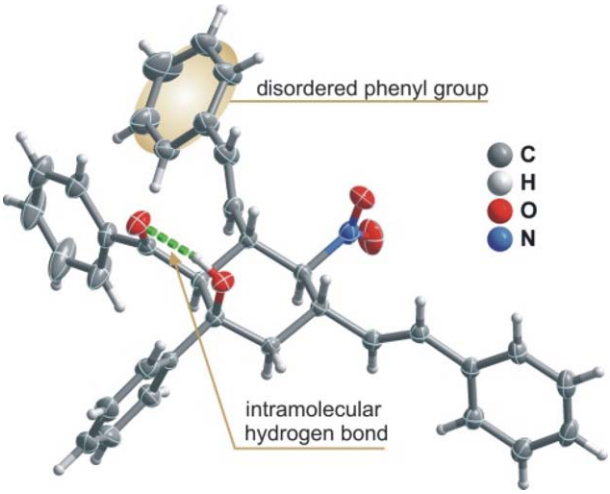
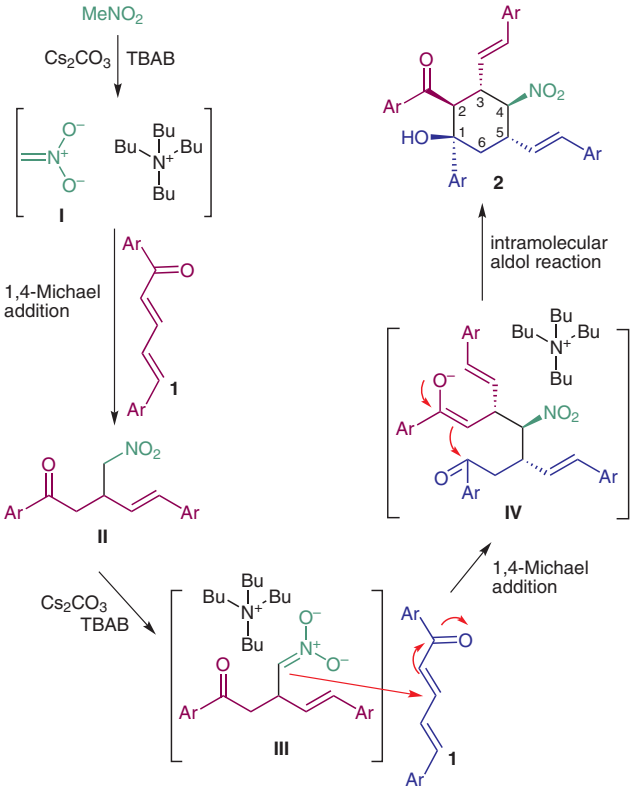


Figure 2 Schematic representation of the (*E*,*E*,1*R*,2*S*,3*S*,4*S*,5*S*)-**2a** molecular unit present in the crystal structure[16]



Scheme 1 Mechanism proposed for the Michael–Michael–aldol reaction

nitromethane anion **I** following by a 1,4-Michael addition to **1** providing the intermediate **II**, which can be isolated and identified. Next, anion **III**[17] is involved in a 1,4-Michael addition to **1** leading to the intermediate **IV**. Finally, an intramolecular aldol reaction takes place to afford the cyclohexane derivatives **2**. According to the proposed mechanism for the formation of **2**, it is easy to understand that the relative configuration of C3 and C5 dictate those of the remaining stereocenters. Furthermore, the relative C1/C2 stereochemistry is ruled by the steric hindrance originating from the two aryl groups.

In conclusion, we have described a very simple, efficient, and environmentally friendly domino multicomponent reaction for the synthesis of pentasubstituted cyclohexane derivatives in high yield and in a completely regio- and diastereoselective manner under PTC. This novel transformation allows the generation of three new C–C bonds and five new stereocenters, which contain hydroxy, nitro, and ketone functional groups and also include a stereogenic quaternary carbon.

Acknowledgment

Thanks are due to the University of Aveiro, to 'Fundação para a Ciência e a Tecnologia' and FEDER for funding the Organic Chemistry Research Unit and for the financial support towards the purchase of the single-crystal diffractometer.

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(13) **General Procedure for the Syntheses of 1e–g**
An aqueous solution of NaOH (60%, 25 mL) was slowly added to a methanolic solution (30 mL) of appropiate acetophenone (5.0 mmol). After cooling the solution to r.t., cinnamaldehyde (792 mg, 6.0 mmol) was added. The mixture was stirred at r.t. for 20 h, and then it was poured into H_2O (100 mL), ice (100 g), and HCl (pH adjusted to ca. 2). The solid obtained was removed by filtration, dissolved in $CHCl_3$ (50 mL), and washed with an aq solution of $NaHCO_3$ (5%, 30 mL). The organic layer was collected, dried over anhyd Na_2SO_4, and the solution evaporated to dryness. The residue was purified by silica gel column chromatography using CH_2Cl_2 as eluent. Finally, the isolated compounds were recrystallized from EtOH.
Selected Data for 1g
Yellow solid (1.13 g, 84% yield); 143–144 °C. ^{1}H NMR (300.13 MHz, $CDCl_3$, 20 °C): δ = 7.04–7.01 (m, 2 H, H-4, H-5), 7.05 (d, $^3J_{trans}$ = 15.0 Hz, 1 H, H-2), 7.41–7.30 (m, 3 H, H-3″,5″, H-4″), 7.52–7.44 (m, 4 H, H-2″,6″, H-3′,5′), 7.65–7.57 (m, 1 H, H-3), 7.92 (AA′BB′, $^3J_{AB}$ = 8.6 Hz, $^4J_{AA'}$ = 2.2 Hz, $^5J_{AB'}$ = 1.9 Hz, 2 H, H-2′,6′) ppm. ^{13}C NMR (125.77 MHz, $CDCl_3$, 20 °C): δ = 124.8 (C-2), 126.7 (C-5), 127.4 (C-2″,6″), 128.9 (C-3′,5′, C-3″,5″), 129.4 (C-4″), 129.8 (C-2′,6′), 136.0 (C-1″), 136.5 (C-1′), 139.1 (C-4′), 142.4 (C-4), 145.4 (C-3), 189.1 (C-1) ppm. Anal. Calcd: C, 75.98; H, 4.88. Found: C, 75.92; H, 4.86.
(14) **General Procedure for the Synthesis of 2a–g**
To a stirred 0.2 M solution of the appropriate 1,5-diaryl-penta-2,4-dien-1-ones **1** (0.085 mmol) in MeCN (0.43 mL) was added TBAB (9.2 mg, 0.028 mmol), Cs_2CO_3 (27.7 mg, 0.085), and $MeNO_2$ (2.3 μL, 0.043 mmol). The mixture was stirred at r.t. for 20 h, quenched with H_2O (5 mL), and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were dried over $MgSO_4$. Evaporation of the solvent under reduced pressure afforded an oil, which was purified by column chromatography (hexane–EtOAc = 9:1 as eluent) and crystallized (hexane–EtOAc) to afford the desired products **2a–g** as single diastereomers.
Selected Data for (*E*,*E*,1*R,2*S**,3*S**,4*S**,5*S**)-2-Benzoyl-1-hydroxy-4-nitro-1-phenyl-3,5-distyrylcyclohexane (2a)**
White solid (17.7 mg, 79% yield; Figure 3); 227–229 °C. ^{1}H NMR (500.13 MHz, $CDCl_3$, 20 °C): δ = 2.00 (ddd, *J* = 14.4, 12.2, 2.6 Hz, 1 H, H-6B), 2.20 (dd, *J* = 14.4, 4.1 Hz, 1 H, H-6A), 3.72–3.84 (m, 2 H, H-3, H-5), 4.14 (d, *J* = 11.6 Hz, 1 H, H-2), 4.64 (t, *J* = 11.1 Hz, 1 H, H-4), 5.34 (d, *J* = 2.6 Hz, 1 H, OH), 5.71 (dd, *J* = 15.7, 9.8 Hz, 1 H, H-α′), 6.03 (dd, *J* = 15.7, 8.8 Hz, 1 H, H-α″), 6.36 (d, *J* = 15.7 Hz, 1 H, H-β′), 6.56 (d, *J* = 15.7 Hz, 1 H, H-β″), 6.85–6.87 (m, 2 H, H-2‴,6‴), 7.10–7.11 (m, 4 H, H-3′,5′, H-3‴,5‴), 7.20–7.31 (m, 9 H, H-2⁗,6⁗, H-3″,5″, H-3⁗,5⁗, H-4′, H-4‴, H-4⁗), 7.42 (t, *J* = 8.3 Hz, 1 H, H-4″), 7.45 (dd, *J* = 8.3, 1.0 Hz, 2 H, H-2′,6′), 7.56 (dd, *J* = 8.3, 1.2 Hz, 2 H, H-2″,6″) ppm. ^{13}C NMR (125.77 MHz, $CDCl_3$, 20 °C): δ = 40.9 (C-5), 44.0 (C-6), 45.6 (C-3), 53.2 (C-2), 74.3 (C-1), 94.1 (C-4), 123.9 (C-α″), 124.5 (C-2′,6′), 126.4 (C_{Ar}), 126.5 (C-2‴,6‴), 126.6 (C-α′), 127.4 (C_{Ar}), 127.8 (C_{Ar}), 127.9 (C_{Ar}), 128.1 (C-2″,6″), 128.2 (C_{Ar}), 128.4 (C_{Ar}), 128.5 (C_{Ar}), 128.6 (C_{Ar}), 133.5 (C-β″), 133.6 (C-4″), 135.5 (C-β′), 135.8 (C-1‴), 136.4 (C-1⁗), 137.8 (C-1″), 144.7 (C-1′), 205.0 (C=O) ppm. HRMS (ESI$^+$): *m/z* calcd for $[C_{35}H_{31}NO_4 + Na]^+$: 552.2145; found: 552.2147. Anal. Calcd: C, 79.37; H, 5.90; N, 2.64. Found: C, 78.97; H, 5.91; N, 2.73.

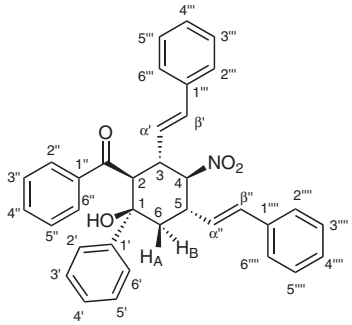

Figure 3

(15) **Crystal Data**
$C_{35}H_{31}NO_4$, *M* = 529.61, monoclinic, space group $P2_1/n$, *Z* = 4, *a* = 5.6904 (2) Å, *b* = 15.8717 (5) Å, *c* = 31.4292 (9) Å, β = 91.793 (2)°, *V* = 2837.18 (16) Å^3, colorless needles with crystal size of 0.20 × 0.08 × 0.06 mm^3. Of a total of 34281 reflections collected, 7584 were independent (R_{int} = 0.0843). Final *R*1 = 0.0588 [$I > 2\sigma(I)$] and *wR*2 = 0.1497 (all data). CCDC-743412 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data request/cif.
(16) Nonhydrogen atoms are represented as thermal ellipsoids drawn at the 50% probability level and hydrogen atoms as small spheres with arbitrary radii. For simplicity only one position of the disordered phenyl group is represented. Hydrogen-bonding geometry details of the intramolecular O–H···O interaction (dashed green line): $d_{O\cdots O}$ = 2.6726 (19) Å and <(DHA) = 141.3°.
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