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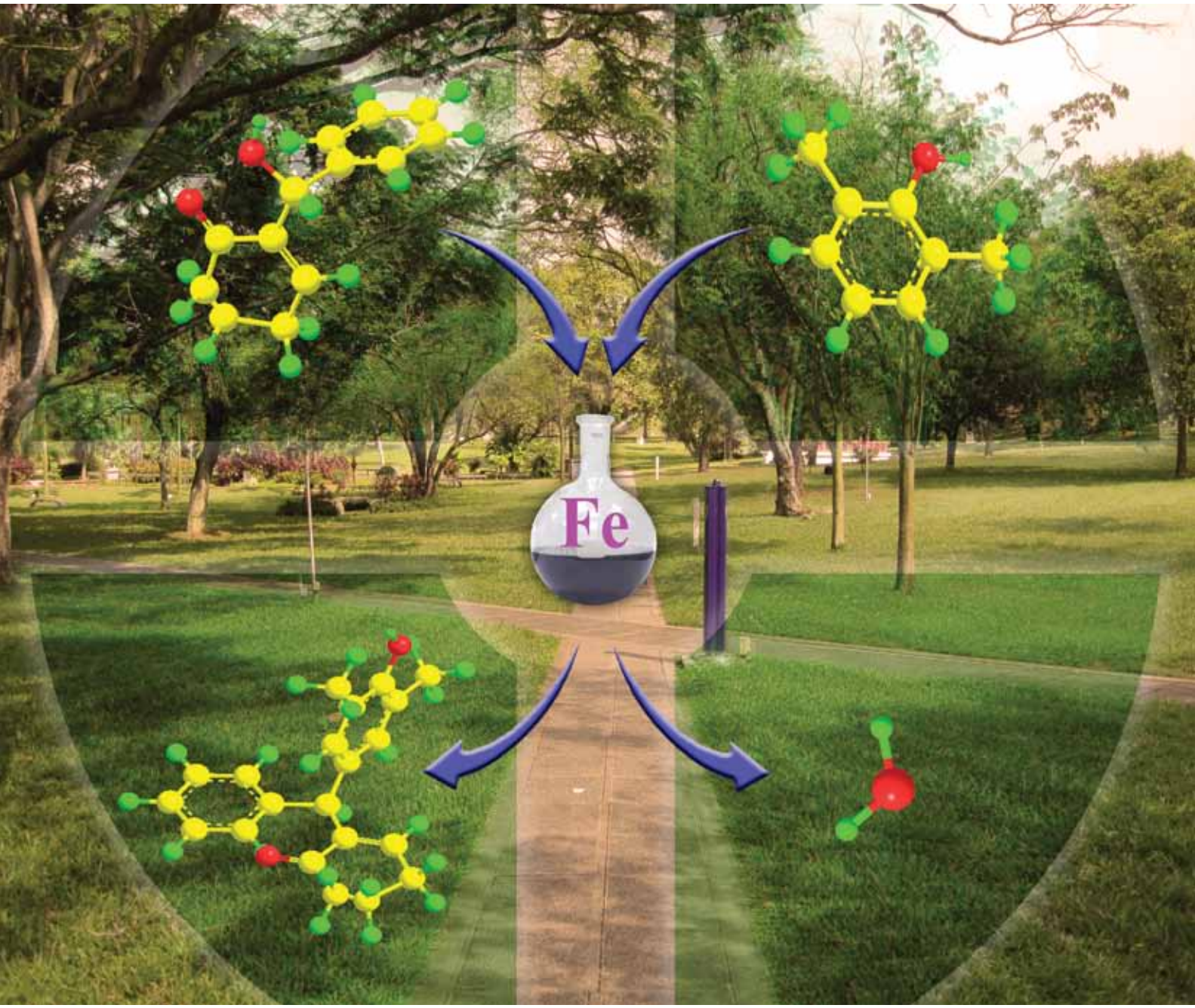

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Iron(III) chloride-catalysed direct nucleophilic α-substitution of Morita-Baylis-Hillman alcohols with alcohols, arenes, 1,3-dicarbonyl compounds, and thiols†

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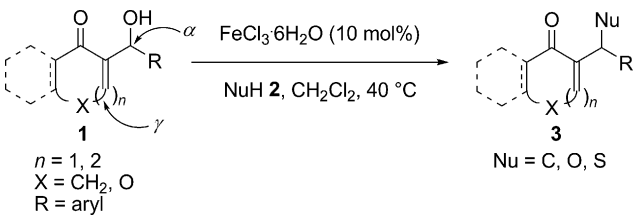
A general and efficient direct method for the α-substitution of Morita-Baylis-Hillman alcohols with carbon- and heteroatom-centred nucleophiles such as alcohols, arenes, 1,3-dicarbonyl compounds, and thiols in the presence of $FeCl_3 \cdot 6H_2O$ as catalyst has been developed. The reaction is operationally straightforward, accomplished in good to excellent product yields (40–99%) and with exclusive α-regioselectivity under mild conditions that did not need an inert and moisture-free environment.

Introduction

Nucleophilic substitution of Morita-Baylis-Hillman (MBH) adducts has received an increasing amount of attention in recent years due to their versatility as building blocks in organic synthesis.[1–3] Generally, the MBH acetate is used as the substrate in this type of reaction presumably due to the perceived poor leaving group ability and low reactivity of the hydroxyl group in the alcohol precursor.[1,2] Although shown to be highly efficient, a drawback of this approach is the need to perform the acylation step. Added to this is the possibility of competitive side reactions mediated by the acetic acid byproduct formed during the course of the reaction. For this reason, the establishing of strategies for the direct nucleophilic substitution of MBH alcohols has been actively pursued since the only potential byproduct produced in such reactions would be H_2O.[3–11] As part of an ongoing program examining the utility of alcohols as pro-electrophiles,[8] we recently reported that the direct α-arylation of a cyclic MBH alcohol with 2,6-dimethylphenol could be accomplished in near quantitative yield using gold catalysis.[8d] The efficiency of the catalysis led us to explore the scope of these substitutions due to their frequent use as intermediates in numerous synthetic routes to heterocycles and compounds of biological interest.[1–3] We envisioned the method would also greatly benefit from the use of cheaper and commercially available catalysts, such as iron complexes. Recently, iron-mediated substitutions of alcohol pro-electrophiles with a variety of nucleophiles as the basis for efficient and selective C–X (X = C, N, O, S, halide) have been reported.[5,12] While the majority of these works have focused on the reactions of allylic, benzylic and propargylic alcohols, this has also hitherto included three reports on regioselective substitutions of acyclic and cyclic MBH alcohols. Das and co-workers described an efficient iron-catalyzed γ-chlorination of acyclic MBH alcohols that gave the corresponding γ-allylic chlorides in good yields.[9] Following this work, Jia and co-workers reported a similar iron-mediated approach for the γ-alkoxylation of acyclic MBH alcohols.[10] At about the same time, Kim and co-workers also showed nucleophilic substitution of cyclic MBH alcohols with sulfonamides that proceeded with complete α-regioselectivity in excellent yields.[11] To our knowledge, however, the analogous iron-catalysed α-substitution reactions of cyclic MBH alcohols with C-, O- and S-centered nucleophiles are not known. Herein, we report the use of $FeCl_3 \cdot 6H_2O$ for the α-substitution of cyclic MBH alcohols with a wide variety of carbon- and heteroatom-centered nucleophiles that include alcohols, arenes, 1,3-dicarbonyl compounds, and thiols (Scheme 1). The substituted cyclic MBH products were afforded in good to excellent yields with exclusive α-regioselectivity and without the need for inert and moisture-free conditions.



Scheme 1 $FeCl_3 \cdot 6H_2O$-catalysed direct nucleophilic α-substitution of MBH alcohols.

Results and discussion

At the outset of this study, we chose 2-(hydroxy(phenyl)-methyl)cyclohex-2-enone **1a** and 1,3-diphenylpropane-1,3-dione **2a** as the model substrates to establish the reaction conditions (Table 1). This revealed that treating an open round flask containing **1a** and **2a** in CH_2Cl_2 with 10 mol% of $FeCl_3 \cdot 6H_2O$ at 40 °C for 4 h gave the best result (entry 1). Under these conditions, 2-((6-oxocyclohex-1-enyl)(phenyl)methyl)-1,3-diphenylpropane-1,3-dione **3a** was afforded as the sole product in 90% yield. No side-products that could be attributed to competitive substitution at the γ-carbon or elimination of the hydroxyl group of **1a** could be

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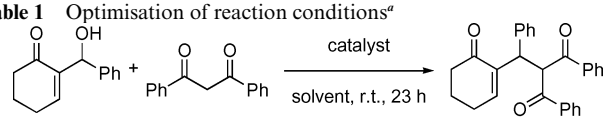
† Electronic supplementary information (ESI) available: ^1H and ^{13}C NMR spectra for all compounds and HPLC measurements for the reaction of **1a**. CCDC reference numbers 711037 and 729201. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b908447a

Table 1 Optimisation of reaction conditions[a]



1a **2a** **3a**

Entry	Catalyst	Solvent	Yield (%)
1[b]	$FeCl_3·6H_2O$	CH_2Cl_2	90
2	$FeCl_3·6H_2O$	CH_2Cl_2	92
3	$FeCl_3·6H_2O$	CH_2ClCH_2Cl	89
4[c]	$FeCl_3·6H_2O$	CH_2ClCH_2Cl	77
5	$FeCl_3·6H_2O$	PhMe	37
6	$FeCl_3·6H_2O$	MeCN	26
7	$FeCl_3·6H_2O$	$MeNO_2$	40
8	$FeCl_3·6H_2O$	THF	—[d]
9	$Yb(OTf)_3$	CH_2Cl_2	—[d]
10	AgOTf	CH_2Cl_2	—[d]
11	CuOTf	CH_2Cl_2	29
12	$InCl_3$	CH_2Cl_2	25

[a] All reactions were performed at room temperature for 23 h with a catalyst:**1a**:**2a** ratio of 1:10:20. [b] Reaction conducted at 40 °C for 4 h. [c] Reaction conducted with a catalyst loading of 5 mol%. [d] No reaction detected based on TLC and ^{1}H NMR analysis.

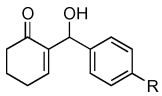
detected by ^{1}H NMR analysis of the crude reaction mixture.[13] The α-substituted MBH product was confirmed by ^{1}H NMR analysis and X-ray crystal structure determination of two closely related products (see later). At room temperature, a longer reaction time of 23 h was required to obtain a comparable product yield (entry 2). Under these latter conditions at room temperature, repeating the reaction with a catalyst loading of 5 or 10 mol% and 1,2-dichloroethane as the solvent was also found to give **3a** in similar yields of 89 and 77%, respectively (entries 3–4). In contrast, performing the reaction in other solvents at room temperature was found to be markedly less effective (entries 5–8). When either toluene, MeCN or $MeNO_2$ were employed as the solvent, low product yields of 26–40% were obtained (entries 5–7). On the other hand, TLC and ^{1}H NMR analysis of the crude mixture of the reaction conducted in THF detected only the starting alcohol and 1,3-dicarbonyl compound (entry 8). Inspection of entries 9–12 in Table 1 also revealed the reaction proceeded less well with other common and commercially available Lewis acid catalysts. In these latter reactions, the use of either CuOTf or $InCl_3$ resulted in the formation of **3a** in markedly lower yields of 29 and 25%, respectively (entries 11–12). However, switching the catalyst to $Yb(OTf)_3$ or AgOTf was found to lead to no reaction on the basis of TLC and ^{1}H NMR analysis (entries 9–10).

Applying the conditions shown in entry 1 of Table 1, a variety of substituted cyclic MBH alcohols and 1,3-dicarbonyl compounds were examined to determine the substrate scope of the present procedure (Table 2). As shown in entries 1–3, substitution of **1a** with a variety of substituted 1,3-dicarbonyl compounds gave the corresponding α-substituted cyclic MBH products **3b–d** in excellent yields. Notably, this included α-substitution of **1a** with the less acidic β-ketoester **2d**, which gave **3d** as a separable 5:1 mixture of diastereomers in near quantitative yield (entry 3). The present procedure was also shown to work well for reactions of **2a** with cyclic MBH alcohols with a pendant electron-withdrawing aryl group on the carbinol carbon centre, affording **3e–h** in excellent yields (entries 4–7). In our hands, reaction of **1b** with **2a** was the only example where a low product yield of 27% was obtained under the standard conditions but could be increased to 80% yield on repeating with a catalyst loading of 50 mol% (entry 4). On the other hand, moderate to good product yields were afforded for reactions of **1f** and **1g** bearing an electron-donating aryl group on the carbinol carbon centre (entries 8–9). Mixtures of side-products were also afforded in both reactions that could not be identified by ^{1}H NMR analysis. Stereoelectronic effects of the cyclic MBH alcohol may also play a role since a substrate containing the strongly coordinating *o*-nitrophenyl group on the carbinol carbon resulted in no reaction (entry 10). A similar outcome was found on repeating this reaction with a stoichiometric amount of catalyst. In contrast, α-substitution of **1i**, which contains a bulky *o*-chlorophenyl group on the carbinol carbon, with **2a** was found to give **3l** in 88% yield (entry 11). Reactions of starting alcohols containing an α,β-unsaturated cyclopentanone or 2,3-dihydropyran-4-one ring moiety with **2a** were also shown to provide **3m** and **3n** in good to excellent yields (entries 12–13).

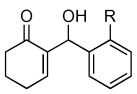
In this work, the $FeCl_3·6H_2O$-catalysed direct α-substitution of **1a** with a variety of different carbon, oxygen and sulfur-centered nucleophiles was also examined (Table 3). Under the standard conditions, Friedel-Crafts arylation of **1a** with arenes **2e** and **2f** afforded the α-substituted MBH products **3o** and **3p** in 62 and 88% yield (entries 1–2). Inspection of entries 3–8 revealed that the present procedure also proceeds well on switching C-centered nucleophiles to O- and S-centered nucleophiles. When EtOH **2g** was employed as the nucleophile, the reaction was found to give **3q** in 94% yield (entry 3). We were also pleased to find comparable high product yields of 95 and 85% could be furnished for the analogous $FeCl_3·6H_2O$-catalysed α-substitutions of **1a** with **2h** and **2i**, respectively (entries 4–5). Similarly, when **1a** was treated with ethanethiol **2j** under the standard conditions, the corresponding MBH thioether adduct **3t** was afforded in 96% yield (entry 6). In our hands, the arylthiols **2k** and **2l**, which contain either a *para*-substituted electron-withdrawing or electron-donating aryl group, respectively, were also found to be good sulfur sources (entries 7–8). In these reactions, the corresponding α-substituted cyclic MBH thioethers **3u** and **3v** were furnished in yields of 83–87%. Consistent with our earlier findings for the substitution of **1a** with **2a**, in all the above reactions no side-products resulting from competitive γ-substitution or elimination of the hydroxyl group of the MBH alcohol could be detected by ^{1}H NMR and TLC analysis. Without exception, the α-substituted MBH adduct was obtained as the sole product in every case. This was further confirmed by X-ray crystal structure determination of **3m** and **3p**, as shown in Fig. 1.[14]

Although a mechanistic discussion would be highly speculative at this juncture, we tentatively propose one possible pathway in Scheme 2 for the present $FeCl_3·6H_2O$-catalysed α-substitution reaction. This could involve activation of the alcohol substrate through coordination of the iron catalyst with the hydroxyl and carbonyl groups. This delivers an iron(III)-coordinated intermediate **6** which can undergo elimination to give a putative carbocation species **7**. It is possible that the newly formed cationic species subsequently undergoes nucleophilic attack by **2** and protodemetallation of [Fe]-OH to deliver the α-substituted cyclic MBH product **3** and metal catalyst. The role of the iron catalyst in facilitating dehydroxylation of the cyclic MBH

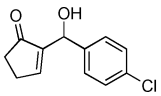
Table 2 $FeCl_3 \cdot 6H_2O$-catalysed α-substitution of **1a-k** with **2a-d**[a]



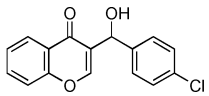
1b, R = NO_2
1c, R = F
1d, R = Cl
1e R = Br
1f, R = Me
1g, R = OEt



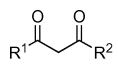
1h, R = NO_2
1i, R = Cl



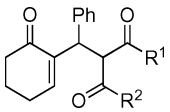
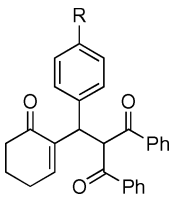
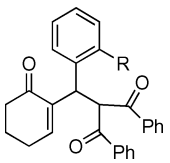
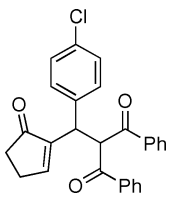
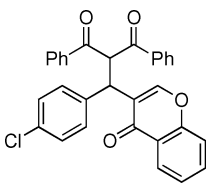
1j



1k

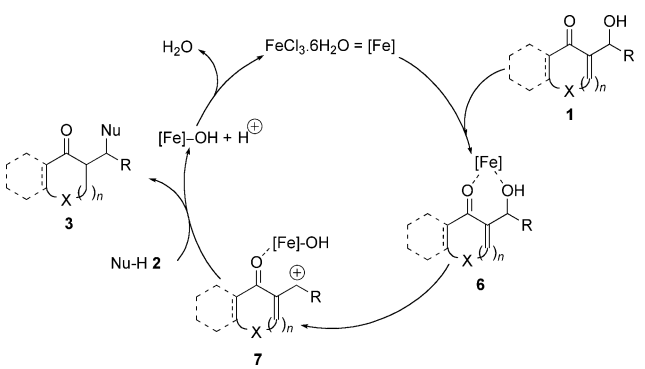


2b, $R^1 = R^2$ = Me
2c, R^1 = Ph, R^2 = Me
2d, R^1 = Ph, R^2 = OEt

Entry	Substrates	Time (h)	Product		Yield (%)
1	**1a** + **2b**	4		**3b**, $R^1 = R^2$ = Me	90
2	**1a** + **2c**	4		**3c**, R^1 = Ph, R^2 = Me	92
3	**1a** + **2d**	1.5		**3d**, R^1 = Ph, R^2 = OEt	97[b]
4[c]	**1b** + **2a**	1		**3e**, R = NO_2	80
5	**1c** + **2a**	1		**3f**, R = F	99
6	**1d** + **2a**	1.5		**3g**, R = Cl	95
7	**1e** + **2a**	2		**3h**, R = Br	91
8	**1f** + **2a**	4		**3i**, R = Me	66
9	**1g** + **2a**	3.5		**3j**, R = OEt	40
10	**1h** + **2a**	3		**3k**, R = NO_2	—[d]
11	**1i** + **2a**	48		**3l**, R = Cl	88
12	**1j** + **2a**	1		**3m**	84
13	**1k** + **2a**	72		**3n**	61

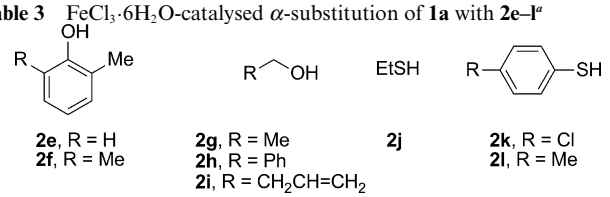
[a] All reactions were performed at 40 °C with a catalyst:**1**:**2** ratio of 1:10:20. [b] Obtained as a 5:1 mixture of diastereomers separable by flash column chromatography. [c] Reaction conducted with 50 mol% of $FeCl_3 \cdot 6H_2O$. [d] No reaction based on TLC and ^1H NMR analysis.

alcohol would account for our earlier findings showing the need for a catalyst loading of 50 mol% and no product formation for the respective reactions of **1b** and **1h** with **2a** (entries 4 and 10 in Table 2). It would not be inconceivable that such interactions are weakened due to the introduction of a strongly coordinating nitro moiety on the alcohol substrate. It is possible that the α-regioselectivities obtained could also be attributed to such interactions since coordination of the metal catalyst to the carbonyl oxygen would give a stable six-membered ring coordinate in **6**, as shown in Scheme 2. The gradual decrease in product yields with increasing electron-donating ability of the substituent on the carbinol on going from **1a** → **1f** → **1g** shown in entry 1 in Table 1 and entries 8–9 in Table 2 would be consistent with the formation of the resultant carbocation



Scheme 2 Tentative mechanism for $FeCl_3 \cdot 6H_2O$-catalysed direct nucleophilic α-substitution of MBH alcohols.

Table 3 $FeCl_3 \cdot 6H_2O$-catalysed α-substitution of **1a** with **2e–l**[a]

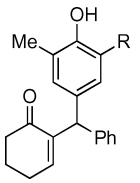
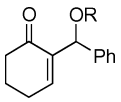
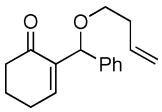
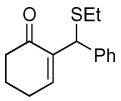
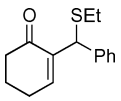


2e, R = H
2f, R = Me

2g, R = Me
2h, R = Ph
2i, R = $CH_2CH{=}CH_2$

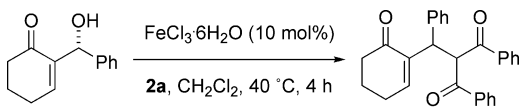
2j

2k, R = Cl
2l, R = Me

Entry	Nuc	Product		Yield (%)
1[b]	**2e**		**3o**, R = H	62
2[b]	**2f**		**3p**, R = Me	88
3[c]	**2g**		**3q**, R = Et	94
4[c]	**2h**		**3r**, R = Bn	95
5[b]	**2i**		**3s**	85
6[d]	**2j**		**3t**	96
7[d]	**2k**		**3u**, R = Cl	87
8[d]	**2l**		**3v**, R = Me	83

[a] All reactions were performed at 40 °C with a catalyst:**1**:**2** ratio of 1:10:20. [b] Reaction time = 2 h. [c] Reaction time = 3 h. [d] Reaction time = 4 h.

species. It might be expected that this is a result of decreasing reactivity as inductive and resonance stabilization of the cation species increases with increasing electron-donating ability of the substituent. The involvement of a carbocation intermediate would also account for our results on the reaction of enantioenriched **1a** with **2a**. Under our experimental conditions, the α-substituted cyclic MBH product **3a** was obtained as a racemic mixture in 80% yield, as shown in Scheme 3.



1a
54% ee

3a
80% yield, 0% ee

Scheme 3 $FeCl_3 \cdot 6H_2O$-catalysed direct nucleophilic α-substitution of enantioriched **1a** with **2a**.

Conclusions

In summary, a general and efficient iron-catalysed method for the direct nucleophilic α-substitution of MBH alcohols with a structurally diverse set of nucleophiles that include alcohols, 1,3-dicarbonyl compounds, sulfamates and thiols, has been reported. These results show the reaction to proceed with complete

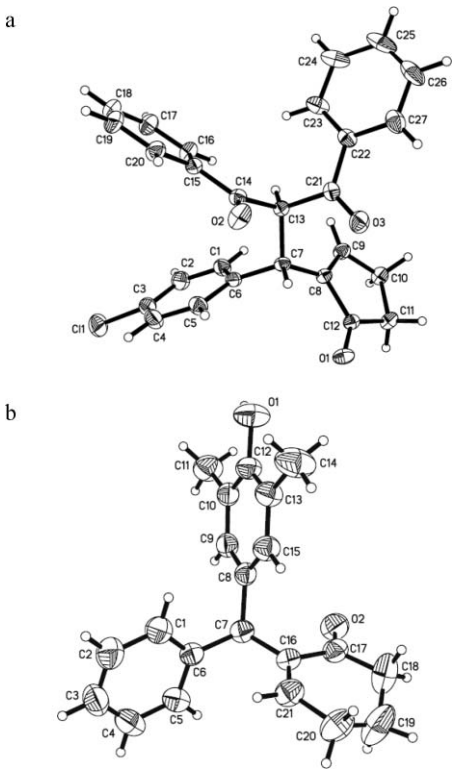


Fig. 1 ORTEP drawings of (a) **3m** and (b) **3p** with thermal ellipsoids at 50% probability levels.[14]

α-regioselectivity and provide the corresponding α-substituted MBH products in good to excellent yields. The reaction was also demonstrated to be practical and operationally straightforward since inert and moisture-free conditions were not required. Moreover, the present method offers a highly atom economical synthetic route to important building blocks from simple alcohol substrates that can be accessed in one step from low cost starting materials and an iron catalyst that is also inexpensive. Efforts to apply the method to the preparation of heterocycles and natural products synthesis are currently underway and will be reported in due course.

Experimental section

General details

All reactions were performed open to the atmosphere. Unless specified, all reagents and starting materials were purchased from commercial sources and used as received. All cyclic MBH alcohol substrates reported in this work were prepared following literature procedures.[15] Solvents were purified following standard literature procedures; CH_2Cl_2 was purified prior to use by passing through a PURESOLV(tm) Solvent Purification System. Analytical thin layer chromatography (TLC) was performed using Merck 60 F254 pre-coated silica gel plate. Visualization was achieved by UV light (254 nm). Flash chromatography was performed using Merck silica gel 60 with freshly distilled solvents. Unless otherwise stated, ^1H and ^{13}C NMR spectra were measured on Bruker Avance 400 MHz spectrometer. Unless otherwise stated, chemical shifts (ppm) were recorded with respect to TMS in $CDCl_3$. Multiplicities were given as: s (singlet), bs (broad singlet), d (doublet), t (triplet),

dd (doublet, doublet) or m (multiplet). The number of protons (n) for a given resonance is indicated by nH. Coupling constants are reported as a J value in Hz. Infrared spectra were recorded on Shimadzu IR Prestige-21 FTIR Spectrometer. High Resolution Mass (HRMS) spectra were obtained using Finnigan MAT95XP LC/HRMS. Mass spectral data were reported in units of mass to charge (m/z). Enantioselectivities were determined by high performance liquid chromatography (HPLC) analysis employing a Daicel Chirapak AD-H or OJ-H column.

General procedure for optimising the Lewis acid-catalysed α-substitution of 1a with 2a

To a solution of CH_2Cl_2 (3 mL) contained in a round bottom flask open to air at room temperature was successively added **1a** (0.25 mmol), **2a** (0.5 mmol) and 10 mol% of the Lewis acid. The reaction mixture was stirred at room temperature or 40 °C and monitored by TLC analysis. On completion, the solvent was removed under reduced pressure and the resultant residue obtained was directly purified by flash column chromatography (EtOAc/*n*-hexane) to afford the product **3a**.

General procedure for iron(III) chloride-catalysed α-substitution of cyclic MBH alcohols 1a–k with 2a–l

To a solution of CH_2Cl_2 (3 mL) contained in a round bottom flask open to air at room temperature was successively added **1** (0.25 mmol), **2** (0.5 mmol) and $FeCl_3{\cdot}6H_2O$ (0.025 mmol). The reaction mixture was stirred at 40 °C and monitored by TLC analysis. On cooling to room temperature, the solvent was removed under reduced pressure and the resultant residue obtained was directly purified by flash column chromatography (EtOAc/*n*-hexane) to afford the product **3**.

2-((6-Oxocyclohex-1-enyl)(phenyl)methyl)-1,3-diphenylpropane-1,3-dione (3a). White solid; yield: 92%; m.p. 177–178 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.56–1.65 (m, 1H), 1.72–1.79 (m, 1H), 2.05–2.25 (m, 4H), 4.87 (d, J = 11.4 Hz, 1H), 6.73 (d, J = 11.4 Hz, 1H), 6.95 (t, J = 4.1 Hz, 1H), 7.03–7.54 (m, 11H), 7.86 (d, J = 7.4 Hz, 2H), 8.00 (d, J = 7.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 22.3, 26.2, 39.0, 50.0, 59.2, 126.6, 128.2, 128.5, 128.6, 128.7, 128.8, 129.0, 133.2, 133.5, 136.8, 137.0, 139.4, 140.4, 148.7, 194.4, 195.1, 199.2; IR (neat): 3019, 1697, 1670, 1215, 756, 667, 513 cm^{-1}; MS (ESI) m/z 409 [M + H]$^+$; HRMS (ESI) calcd for $C_{28}H_{25}O_3$: 409.1804, found: 409.1811.

3-((6-Oxocyclohex-1-enyl)(phenyl)methyl)pentane-2,4-dione (3b). White solid; yield: 90%; m.p. 110–111 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.89–1.90 (m, 5H), 2.14 (s, 3H), 2.33–2.38 (m, 4H), 4.68 (d, J = 12.5 Hz, 1H), 4.78 (d, J = 12.5 Hz, 1H), 6.90 (t, J = 3.8 Hz, 1H), 7.17–7.27 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 22.5, 26.2, 28.5, 30.7, 38.6, 44.5, 72.8, 127.0, 128.1, 128.6, 139.5, 140.0, 146.3, 197.9, 202.9, 203.1; IR (neat): 3019, 1730, 1697, 1674, 1215, 756, 667 cm^{-1}; MS (ESI) m/z 285 [M + H]$^+$; HRMS (ESI) calcd for $C_{18}H_{21}O_3$: 285.1491, found: 285.1490.

2-((6-Oxocyclohex-1-enyl)(phenyl)methyl)-1-phenylbutane-1,3-dione (3c). Pale yellow solid; yield: 92%; m.p. 120–121 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.68–1.77 (m, 2H), 1.91–1.94 (m, 2H), 1.99 (s, 3H), 2.12 (s, 3H), 2.21–2.22 (m, 4H), 2.38–2.41 (m, 4H), 4.86 (d, J = 12.0 Hz, 1H), 5.05 (d, J = 12.1 Hz, 1H), 5.58 (d, J = 12.1 Hz, 1H), 5.78 (d, J = 12.0 Hz, 1H), 6.84 (t, J = 4.0 Hz, 1H), 7.02–7.89 (m, 17H), 7.88 (d, J = 7.6, 2H), 8.05 (d, J = 7.6, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 22.3, 22.5, 26.1, 26.3, 27.5, 28.6, 38.7, 38.8, 45.1, 46.9, 66.3, 67.2, 126.7, 127.0, 128.1, 128.4, 128.4, 128.6, 128.7, 128.7, 128.9, 128.9, 133.6, 133.7, 136.9, 137.0, 139.5, 139.7, 140.1, 140.4, 146.6, 147.8, 194.5, 194.7, 198.2, 198.4, 202.9, 203.5; IR (neat): 3024, 2926, 1722, 1676, 1595, 1236, 756, 665 cm^{-1}; MS (ESI) m/z 347 [M + H]$^+$; HRMS (ESI) calcd for $C_{23}H_{23}O_3$: 347.1647, found: 347.1648.

Ethyl 2-benzoyl-3-(6-oxocyclohex-1-enyl)-3-phenylpropanoate (3d). Yield: 97%; Major isomer: white solid; m.p. 166–167 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.91 (t, J = 7.1 Hz, 3H), 1.72–1.79 (m, 2H), 2.15–2.28 (m, 4H), 3.86–3.89 (m, 2H), 4.76 (d, J = 11.8 Hz, 1H), 5.57 (d, J = 11.8 Hz, 1H), 6.84 (t, J = 4.0 Hz, 1H), 7.18–7.58 (m, 8H), 8.07 (d, J = 7.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 13.7, 22.3, 26.1, 38.8, 47.1, 57.4, 61.4, 126.8, 128.3, 128.5, 128.7, 128.9, 133.6, 136.6, 139.6, 140.4, 146.5, 168.0, 193.7, 198.3; IR (neat): 3019, 1733, 1682, 1215, 756, 667 cm^{-1}; MS (ESI) m/z 377 [M + H]$^+$; HRMS (ESI) calcd for $C_{24}H_{25}O_4$: 377.1753, found: 377.1735. Minor isomer: white solid; m.p. 120–121 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.14 (t, J = 7.0 Hz, 3H), 1.90–1.94 (m, 2H), 2.36–2.40 (m, 4H), 4.02–4.13 (m, 2H), 4.82 (d, J = 11.8 Hz, 1H), 5.58 (d, J = 11.8 Hz, 1H), 7.02–7.54 (m, 9H), 7.95 (d, J = 7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.1, 22.6, 26.3, 38.9, 46.7, 56.8, 61.5, 126.5, 128.2, 128.2, 128.6, 128.7, 133.4, 136.7, 140.0, 140.3, 147.0, 168.3, 193.2, 198.1; IR (neat): 3019, 1734, 1682, 1215, 754, 665 cm^{-1}; MS (ESI) m/z 377 [M + H]$^+$; HRMS (ESI) calcd for $C_{24}H_{25}O_4$: 377.1753, found: 377.1744.

2-((4-Nitrophenyl)(6-oxocyclohex-1-enyl)methyl)-1,3-diphenylpropane-1,3-dione (3e). Pale yellow solid; yield: 80% m.p. 174–175 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.53–1.56 (m, 1H), 1.73–1.76 (m, 1H), 2.00–2.27 (m, 4 H), 4.89 (d, J = 11.3 Hz, 1H), 6.77 (d, J = 11.3 Hz, 1 H), 7.00 (t, J = 4.1 Hz, 1 H), 7.34–7.60 (m, 8 H), 7.89 (d, J = 7.2 Hz, 2H), 8.00–8.03 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 22.1, 26.2, 38.8, 50.3, 58.0, 123.4, 128.6, 128.8, 129.0, 129.0, 129.3, 133.7, 133.9, 136.5, 138.1, 146.5, 148.2, 150.3, 193.5, 194.7, 199.2; IR (neat): 3019, 1694, 1668, 1215, 756, 667 cm^{-1}; MS (ESI) m/z 454 [M + H]$^+$; HRMS (ESI) calcd for $C_{28}H_{24}NO_5$: 454.1654, found: 454.1646.

2-((4-Fluorophenyl)(6-oxocyclohex-1-enyl)methyl)-1,3-diphenylpropane-1,3-dione (3f). White solid; yield: 99%; m.p. 160–162 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.61–1.77 (m, 2H), 2.05–2.12 (m, 1H), 2.19–2.26 (m, 3H), 4.85 (d, J = 11.4 Hz, 1H), 6.69 (d, J = 11.4 Hz, 1H), 6.79–6.83 (m, 2H), 6.94 (t, J = 8.3 Hz 1H), 7.27–7.54 (m, 8H), 7.86 (d, J = 7.6 Hz, 2H), 8.00 (d, J = 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 22.3, 26.2, 39.0, 49.4, 59.2, 114.9, 115.1, 128.6, 128.8, 128.9, 130.0, 130.1, 133.3, 133.5, 136.1, 136.8, 136.9, 139.2, 148.8, 160.2, 162.7, 194.2, 194.9, 199.3; IR (neat): 3017, 2928, 1694, 1670, 1595, 1223, 754, 687 cm^{-1}; MS (ESI) m/z 427 [M + H]$^+$; HRMS (ESI) calcd for $C_{28}H_{24}FO_4$: 427.1709, found: 427.1703.

2-((4-Chlorophenyl)(6-oxocyclohex-1-enyl)methyl)-1,3-diphenylpropane-1,3-dione (3g). White solid; yield: 95%; m.p. 178–179 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.62–1.63 (m, 1H), 1.74–1.79 (m, 1H), 2.03–2.10 (m, 1H), 2.17–2.27 (m, 3H), 4.82 (d, J = 11.4 Hz, 1H), 6.70 (d, J = 11.4 Hz, 1H), 6.94 (t, J = 8.1 Hz 1H), 7.09–7.56

(m, 10H), 7.87 (d, $J = 7.6$ Hz, 2H), 7.99 (d, $J = 8.0$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 22.2, 26.2, 39.0, 49.7, 58.9, 128.3, 128.3, 128.6, 128.7, 128.8, 129.0, 129.9, 132.3, 133.4, 133.6, 136.7, 136.9, 139.0, 149.1, 194.0, 194.9, 199.2; IR (neat): 3019, 1695, 1653, 1215, 756, 667 cm^{-1}; MS (ESI) m/z 443 $[M + H]^+$; HRMS (ESI) calcd for $C_{28}H_{24}ClO_3$: 443.1414, found: 443.1416.

2-((4-Bromophenyl)(6-oxocyclohex-1-enyl)methyl)-1,3-diphenylpropane-1,3-dione (3h). White solid; yield: 91%; m.p. 190–191 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.57–1.60 (m, 1H), 1.62–1.78 (m, 1H), 2.05–2.09 (m, 1H), 2.16–2.26 (m, 3H), 4.81 (d, $J = 11.4$ Hz, 1H), 6.70 (d, $J = 11.4$ Hz, 1H), 6.94 (t, $J = 4.2$ Hz 1H), 7.20–8.00 (m, 14H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 22.2, 26.2, 38.9, 49.7, 58.8, 120.5, 128.6, 128.7, 128.8, 129.0, 130.2, 131.3, 133.4, 133.6, 136.7, 136.8, 138.9, 139.5, 149.2, 194.0, 194.9, 199.2; IR (neat): 3019, 1695, 1653, 1215, 756, 667 cm^{-1}; MS (ESI) m/z 487 $[M + H]^+$; HRMS (ESI) calcd for $C_{28}H_{24}BrO_3$: 487.0909, found: 487.0912.

2-((6-Oxocyclohex-1-enyl)(*p*-tolyl)methyl)-1,3-diphenylpropane-1,3-dione (3i). Pale brown solid; yield: 66%; m.p. 204–205 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.58–1.61 (m, 1H), 1.70–1.75 (m, 1H), 2.04–2.09 (m, 2H), 2.18 (s, 3H), 2.21–2.22 (m, 2H), 4.86 (d, $J = 11.4$ Hz, 1H), 6.72 (d, $J = 11.4$ Hz, 1H), 7.20–7.22 (m, 3H), 7.26–7.52 (m, 8H), 7.87 (d, $J = 7.6$ Hz, 2H), 8.01 (d, $J = 7.6$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.9, 22.3, 26.2, 39.0, 49.6, 59.4, 128.3, 128.5, 128.7, 128.7, 129.0, 129.0, 133.1, 133.4, 136.0, 136.9, 137.1, 137.4, 139.5, 148.5, 194.3, 195.2, 199.2; IR (neat): 3019, 1690, 1667, 1215, 756, 667 cm^{-1}; MS (ESI) m/z 445 $[M + Na]^+$; HRMS (ESI) calcd for $C_{29}H_{26}O_3Na$: 445.1780, found: 445.1768.

2-((4-Ethoxyphenyl)(6-oxocyclohex-1-enyl)methyl)-1,3-diphenylpropane-1,3-dione (3j). White solid; yield: 40%; m.p. 215–216 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.31 (t, $J = 7.0$ Hz, 3H), 1.63–1.79 (m, 2H), 2.04–2.26 (m, 4H), 3.88 (q, $J = 7.2$ Hz, 2H), 4.83 (d, $J = 11.4$ Hz, 1H), 6.64–6.69 (m, 3H), 6.92 (t, $J = 3.9$ Hz, 1H), 7.21–7.53 (m, 8H), 7.86 (d, $J = 8.0$ Hz, 2H), 7.99 (d, $J = 8.0$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.8, 22.3, 26.2, 39.0, 49.2, 59.7, 63.2, 114.2, 128.5, 128.7, 128.7, 129.0, 129.5, 132.3, 133.1, 133.4, 136.9, 137.1, 139.6, 148.3, 157.5, 194.5, 195.1, 199.3; IR (neat): 3019, 1692, 1674, 1661, 1215, 756, 667 cm^{-1}; MS (ESI) m/z 475 $[M + Na]^+$; HRMS (ESI) calcd for $C_{30}H_{28}O_4Na$: 475.1885, found: 475.1881.

2-((2-Chlorophenyl)(6-oxocyclohex-1-enyl)methyl)-1,3-diphenylpropane-1,3-dione (3l). White solid; yield: 88%; m.p. 169–170 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.43–1.48 (m, 1H), 1.68–1.70 (m, 1H), 1.96–2.24 (m, 4H), 5.20 (d, $J = 11.2$ Hz, 1H), 6.92 (d, $J = 11.2$ Hz, 1H), 6.99–7.08 (m, 3H), 7.22–7.68 (m, 8H), 7.89 (d, $J = 7.2$ Hz, 2H), 8.04 (d, $J = 7.6$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 22.1, 26.2, 39.1, 47.2, 57.7, 126.3, 127.7, 128.5, 128.6, 128.8, 129.0, 129.9, 133.3, 133.6, 133.6, 134.5, 136.3, 136.9, 136.9, 137.2, 152.1, 193.5, 195.5, 199.7; IR (neat): 3019, 1697, 1670, 1215, 756, 667 cm^{-1}; MS (ESI) m/z 443 $[M + H]^+$; HRMS (ESI) calcd for $C_{28}H_{24}ClO_3$: 443.1414, found: 443.1408.

2-((4-Chlorophenyl)(5-oxocyclopent-1-enyl)methyl)-1,3-diphenylpropane-1,3-dione (3m). White solid; yield: 84%; m.p. 195–196 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.17–2.33 (m, 2H), 2.46–2.47 (m, 2H), 4.97 (d, $J = 11.2$, 1H), 6.75 (d, $J = 11.2$ Hz, 1H), 7.08–7.10 (m, 2 H), 7.31–7.52 (m, 9H), 7.81 (d, $J = 7.6$ Hz, 2H), 7.97 (d, $J = 7.2$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 26.7, 35.3, 45.1, 58.9, 128.6, 128.6, 128.7, 128.8, 128.9, 130.1, 132.8, 133.4, 133.6, 136.6, 136.7, 138.3, 145.3, 161.7, 194.2, 194.3, 209.4; IR (neat): 3393, 1686, 1659, 756 cm^{-1}; MS (ESI) m/z 429 $[M + H]^+$; HRMS (ESI) calcd for $C_{27}H_{22}ClO_3$: 429.1257, found: 429.1260.

2-((4-Chlorophenyl)(4-oxo-4H-chromen-3-yl)methyl)-1,3-diphenylpropane-1,3-dione (3n). Pale yellow solid; yield: 61%; m.p. 213–214 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.93 (d, $J = 10.9$ Hz, 1H), 7.09–7.12 (m, 2H), 7.31–7.60 (m, 12H), 7.93–8.12 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 47.4, 57.4, 118.1, 123.6, 124.3, 125.2, 125.7, 128.5, 128.7, 128.7, 128.9, 128.9, 130.2, 132.8, 133.5, 133.7, 136.7, 136.7, 138.5, 155.1, 155.9, 178.0, 194.2, 194.7; IR (neat): 3019, 1690, 1634, 1466, 1263, 1215, 756, 667 cm^{-1}; MS (ESI) m/z 493 $[M + H]^+$; HRMS (ESI) calcd for $C_{31}H_{22}ClO_4$: 493.1207, found: 493.1214.

2-((4-Hydroxy-3-methylphenyl)(phenyl)methyl)cyclohex-2-enone (3o). Colourless oil; yield: 62%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.99–2.02 (m, 2H), 2.15 (s, 1H), 2.37–2.38 (m, 2H), 2.44–2.47 (m, 2 H), 5.36 (s, 1 H), 5.39 (s, 1 H), 6.42 (s, 1 H), 6.58–6.60 (m, 2H), 6.71–6.74 (m, 1H), 6.83 (s, 1H), 7.06–7.08 (m, 2H), 7.15–7.18 (m, 1H), 7.23–7.27 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 16.0, 22.9, 26.2, 38.7, 48.6, 114.7, 123.8, 126.2, 127.4, 128.3, 129.0, 131.6, 134.1, 142.8, 143.0, 148.2, 152.5, 198.7; IR (neat) 1662, 1505, 1269, 910, 730 cm^{-1}; MS (ESI) m/z 293 $[M + H]^+$; HRMS (ESI) calcd. for $C_{20}H_{21}O_2$: 293.1542, found: 293.1542.

2-({4-Hydroxy-3,5-dimethylphenyl}(phenyl)methyl)cyclohex-2-enone (3p). White solid; yield: 88%; m.p. 174–176 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.98–2.04 (m, 2H), 2.17 (s, 6H), 2.37–2.47 (m, 4H), 4.60 (s, 1H), 5.36 (s, 1H), 6.41 (t, 1H, $J = 4.0$ Hz), 6.68 (s, 2H), 7.07–7.27 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.1, 22.9, 26.2, 38.7, 48.6, 122.8, 126.1, 128.2, 129.0, 129.1, 133.8, 142.8, 143.1, 147.8, 150.7, 198.2; IR (neat) 1670, 1489, 1263, 908, 738 cm^{-1}; HRMS (ESI) calcd. for $C_{21}H_{22}O_2Na$: 329.1517, found: 329.1977.

2-(Ethoxy(phenyl)methyl)cyclohex-2-enone (3q). Colourless oil; yield: 94%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.20 (t, $J = 7.0$ Hz, 3H), 1.92–2.00 (m, 2H), 2.32–2.45 (m, 4H), 3.44 (q, $J = 7.2$ Hz, 2H), 5.38 (s, 1H), 7.02 (t, $J = 4.8$ Hz, 1H), 7.20–7.36 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 15.3, 22.6, 25.8, 38.4, 64.6, 76.3, 127.1, 127.3, 128.2, 140.9, 142.2, 145.7, 197.9; IR (neat): 2926, 1672, 1454, 1377, 1169, 1086, 698 cm^{-1}; MS (ESI) m/z 185 $[M - OC_2H_5]^+$; HRMS (ESI) calcd for $C_{13}H_{13}O$: 185.0966, found: 185.0958.

2-(Benzyloxy(phenyl)methyl)cyclohex-2-enone (3r). Pale yellow oil; yield: 95%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.90–2.00 (m, 2H), 2.34–2.43 (m, 4H), 4.42–4.48 (m, 2H), 5.48 (s, 1H), 7.10 (t, $J = 4.0$ Hz 1H), 7.23–7.40 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 22.6, 25.8, 38.5, 71.0, 76.4, 127.3, 127.5, 127.6, 127.8, 128.3, 128.3, 138.4, 140.7, 140.8, 145.9, 197.8; IR (neat): 3391, 2922, 1663, 1452, 1375, 1169, 734, 696 cm^{-1}; MS (ESI) m/z 293 $[M + H]^+$; HRMS (ESI) calcd for $C_{20}H_{21}O_2$: 293.1542, found: 293.1536.

2-((But-3-enyloxy)(phenyl)methyl)cyclohex-2-enone (3s). Pale yellow oil; yield: 85%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.90–2.00 (m, 2H), 2.31–2.43 (m, 6H), 3.41–3.46 (m, 2H), 4.99–5.07 (m, 2H),

5.36 (s, 1H), 5.74–5.85 (m, 1H), 7.23 (t, $J = 7.2$ Hz, 1H), 7.25–7.35 (m, 5 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 22.6, 25.8, 34.3, 38.4, 68.5, 76.5, 116.3, 127.1, 127.4, 128.2, 135.3, 140.8, 141.1, 145.8, 197.9; IR (neat): 2926, 1674, 1641, 1454, 1375, 1086, 1074, 914, 700, 525 cm^{-1}; MS (ESI) m/z 185 [M – OC_4H_6]$^+$; HRMS (ESI) calcd for $C_{13}H_{13}O$: 185.0966, found: 185.0961.

2-((Ethylthio)(phenyl)methyl)cyclohex-2-enone (3t). White solid; yield: 96%; m.p. 41–42 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.17–1.21 (m, 3H), 1.92–2.00 (m, 2H), 2.35–2.5 (m, 6H), 5.25 (s, 1H), 7.12 (t, $J = 3.8$, 1H), 7.18–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.2, 22.7, 26.2, 26.4, 38.4, 45.2, 127.0, 128.3, 128.4, 140.0, 141.0, 147.3, 197.2; IR (neat): 3017, 1670, 1454, 1373, 1215, 756, 667 cm^{-1}; MS (ESI) m/z 185 [M – SC_2H_5]$^+$; HRMS (ESI) calcd for $C_{13}H_{13}O$: 185.0966, found: 185.0959.

2-((4-Chlorophenylthio)(phenyl)methyl)cyclohex-2-enone (3u). Colourless oil; yield: 87%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.94–1.97 (m, 2H), 2.39–2.46 (m, 4H), 5.63 (s, 1H), 7.12–7.35 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 22.6, 26.2, 38.3, 49.0, 127.4, 128.3, 128.5, 128.9, 131.5, 132.6, 134.5, 139.0, 139.7, 148.2, 197.1; IR (neat): 2947, 2926, 1672, 1476, 1452, 1371, 1246, 1167, 1094, 1011, 812, 723, 696, 507 cm^{-1}; MS (ESI) m/z 185 [M – $SClC_6H_4$]$^+$; HRMS (ESI) calcd for $C_{13}H_{13}O$: 185.0966, found: 185.0961.

2-(Phenyl(*p*-tolylthio)methyl)cyclohex-2-enone (3v). Colourless oil; yield: 83%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.92–1.97 (m, 2H), 2.26 (s, 3H), 2.38–2.47 (m, 4H), 5.60 (s, 1H), 6.98–7.00 (m, 2H), 7.13–7.27 (m, 4H), 7.35–7.37 (m, 2H), 7.97 (d, $J = 7.2$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.1, 22.6, 26.2, 38.4, 49.4, 127.1, 128.3, 128.4, 129.6, 130.9, 132.2, 136.7, 139.3, 140.3, 148.0, 197.2; IR (neat): 3026, 2945, 2866, 1672, 1634, 1597, 1492, 1452, 1371, 1246, 1167, 1130, 1090, 979, 802, 721, 698, 525 cm^{-1}; MS (ESI) m/z 185 [M – SC_7H_7]$^+$; HRMS (ESI) calcd for $C_{13}H_{13}O$: 185.0966, found: 185.0960.

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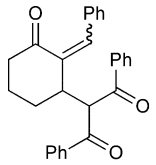

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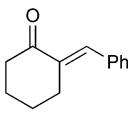

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14 CCDC 711037 and 729201 contains the supplementary crystallographic data for this paper†.

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