On the preparation of cyclopentadienes by a novel homolytic annulation of but-3-en-1-ones with alkynes mediated by samarium diiodide

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Dedicated to Douglas Lloyd on the occasion of his 80th birthday

Abstract

Treatment of substituted pent-4-en-2-ones and phenylacetylene with samarium diiodide in a mixture of THF and HMPA yielded 3-methyl-1-phenylcyclopent-1-en-3-ols that rapidly dehydrated and underwent [1,5] hydrogen migrations to afford substituted cyclopentadienes. The mechanism involved ketyl radical anions, generated from the unsaturated ketones by SmI_2, initially adding to the alkyne. The resulting vinyl type radicals cyclised in the preferred 5-*exo*-mode to produce cyclopentenylmethyl radicals that were reduced to the corresponding anions and abstracted a proton from *t*-BuOH. The overall process amounted to a novel free-radical [3+2]-annulation.

Keywords: Cyclopentadienes, novel annulation, hemolytic annulation, but-3-en-1-ones, alkynes, samarium diiodide

Introduction

The concept of a novel homolytic annulation process, involving unsaturated radicals and alkenes or alkynes, has been turned into a reality by several research groups in the last few years. Essentially, the process is a two-stage cascade consisting of the intermolecular addition of a radical, containing an appropriately placed unsaturated group, to a radical acceptor, followed by intramolecular ring closure of the resulting adduct radical. Most frequently, the initial radical is a but-3-en-1-yl (homoallyl) **1**, but-3-yn-1-yl, or analogous species, that adds (**A**) to a double or triple bond (A=B) to produce a hex-5-en-1-yl type of radical **2**. The latter is well adapted to rapidly cyclise in the allowed 5-*exo*-mode ($\mathbf{C^{5x}}$) to produce a cyclopentane derivative **3**.
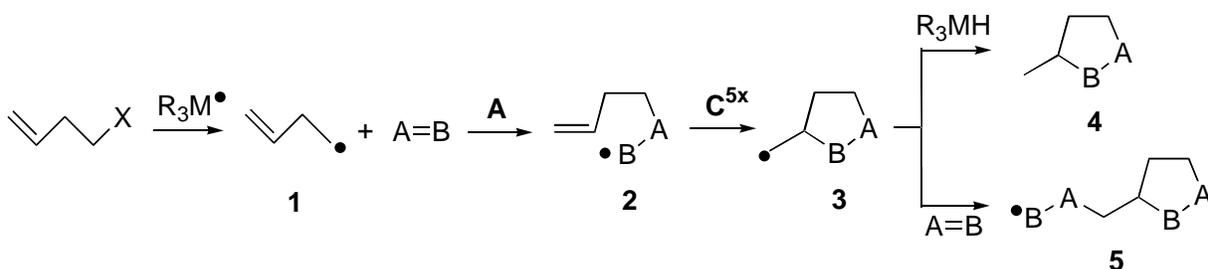
Scheme 1. Archetype free radical annulations and the problem of oligomerisation.

This 2-stage sequence [**AC^{5x}**] amounts to a [3 + 2]-annulation[1] and has obvious potential for the synthesis of cyclopentanes, di- and triquinanes.

Successful homolytic annulation sequences of various types have been reported,[2-4] but a basic problem with this process is that the cyclised radical **3** is rather similar in reactivity to the initial radical **1**. Radical **3** may, therefore, add to more acceptor (AB) to produce oligomeric radical **5**, rather than abstract hydrogen from the metal hydride (R$_3$MH) to produce the desired product **4**. Ways of circumventing this problem include differentiating the propagating radicals sterically,[5,6] or electronically,[7-10] and arranging for the ring closure step to take place onto an aromatic ring.[11-13]

Samarium(II) iodide appeared to be a promising reagent for mediating radical annulations. Reaction of SmI$_2$ with a but-3-en-1-one **6** was expected to generate a ketyl radical anion **7** that should be nucleophilic. Intermolecular addition to a triple bond should, therefore, take place efficiently to generate vinyl radical **8** and hence, after a **C^{5x}** ring closure, cycloalkenylmethyl type radical **9**. Radicals **7**, **8** and **9** are ketyl, vinyl and alkyl types respectively, so these different electronic characters should lead to a sharp difference in reactivity, hence ensuring that oligomerisation is unimportant.
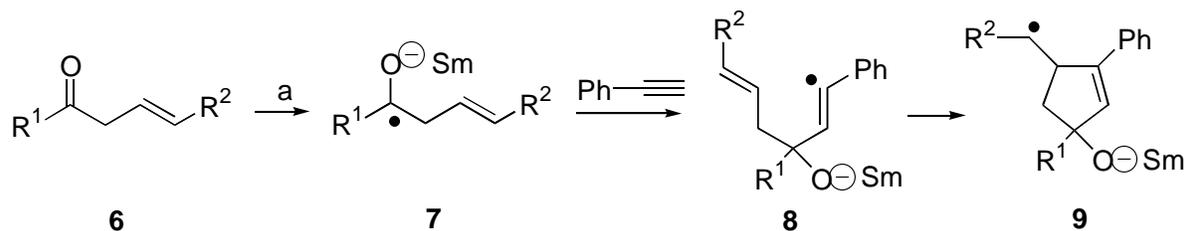
Scheme 2. (a) SmI$_2$, HMPA, *t*-BuOH, THF.

To test the practicality of this annulation sequence a short series of functionalised but-3-en-1-ones was prepared and reacted under various sets of conditions.[14,15]

Results and Discussion

The simplest suitable ketone, pent-4-en-2-one **6a** was prepared via an organozinc intermediate that underwent addition to a nitrile (Scheme 3).[16] Work-up proved to be problematic due to the volatility of product, the similar boiling points of starting materials and product and, most seriously, to the instability of the product with respect to the α,β-unsaturated isomer, pent-3-en-2-one **10a**. Repeated careful distillation gave **6a** in 39% yield. Unfortunately, isomerisation to **10a** occurred rapidly, so **6a** had to be prepared immediately prior to use. Hept-1-en-4-one **6b** was made by the same technique, in the hope that purification would be easier. Distillation was again difficult, but the higher boiling point of **6b** compared to **6a** meant that column chromatography could be utilised. Chromatography on silica had previously been avoided because it was suspected that isomerisation would take place on the column. This surmise proved to be unfounded and **6b** was isolated in 40% yield. Disappointingly, isomerisation to **10b** occurred on standing for 24 hours, again necessitating use of **6b** immediately upon preparation.

It was thought that isomerisation might be prevented if an aromatic substituent R^2 was introduced. The simple route to 5-phenylpent-4-en-2-one **6c** shown in Scheme 3 was chosen.[17] A Knoevenagel condensation yielded 3-styryl-pentane-2,4-dione which was converted to **6c** with of zinc acetate dihydrate in 65% yield. Gratifyingly, **6c** proved to be stable, and could be kept on the bench indefinitely.

$R^1-C\equiv N$ + Br—R^2 →(a) R^1—C(=O)—R^2 → R^1—C(=O)—R^2

6, a R^1 = Me, R^2 = H, 39%   **10**
   b R^1 = n-Pr, R^2 = H, 40%

6c, 65%
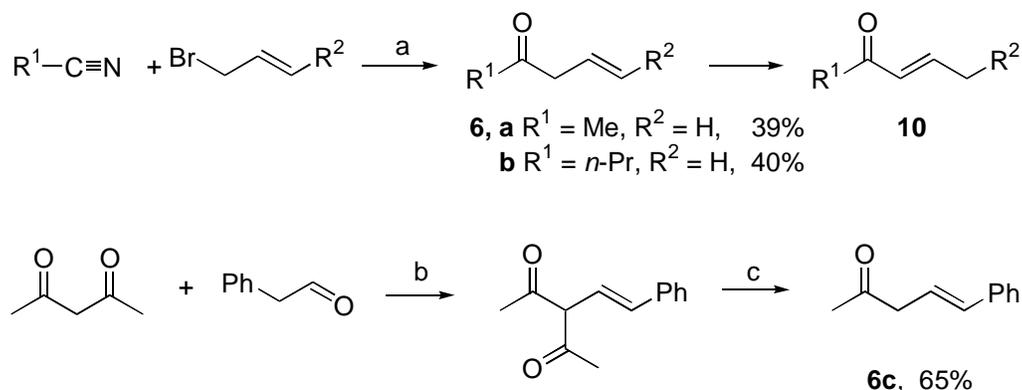
Scheme 3. (a) Zn/Ag, Et$_2$O, THF followed by H$_2$O. (b) Cat. piperidine (19%) (c) Zn(OAc)$_2$.2H$_2$O, MeOH.

Before attempting any annulations, the addition stage of the process was tested separately by carrying out an intermolecular coupling of phenylacetylene with benzylacetone **11** (Scheme 4).[18] Samarium(II) iodide was added to phenylacetylene in t-butanol and HMPA followed by addition of the benzylacetone. 1,5-Diphenyl-3-methylpent-1-en-3-ol **12** was obtained in 36% yield, after chromatography.
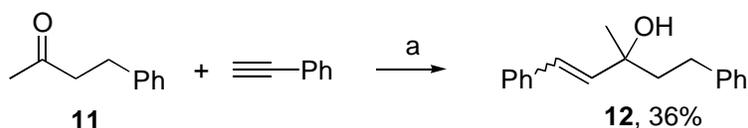
Scheme 4. (a) SmI_2, THF, HMPA, t-BuOH.

Subsequently the annulation sequence shown in Scheme 2 above was tested for each of **6a-c**. Isolation and purification of the final products was problematic because of the almost identical R_F values of the product and starting material in whichever solvent system was used. The annulation with **6a** was successful, although pure product could not be isolated. NMR spectroscopy indicated that the annulated product **13a** had been formed; there was a characteristic singlet at 5.95 ppm in the ^{1}H NMR spectrum, corresponding to an uncoupled alkenyl proton. GC/MS analysis indicated that **13a** dehydrated very easily to afford cyclopentadiene **15a**. Treatment of **6b** with SmI_2 under similar conditions yielded what was believed to be **13b**. Addition of this material to deuteriochloroform resulted in the formation of a cloudy emulsion due to the expulsion of water. NMR analysis of the dried material indicated that **13b** dehydrated with concomitant thermal rearrangement to give the thermodynamically more stable cyclopentadiene **15b** (Scheme 5). Mass spectrometry of the initial material (i.e. product that had not been added to deuteriochloroform) verified this, but indicated that some enol **13b** was present, even under the operating conditions of the mass spectrometer. The overall yield was 27%.
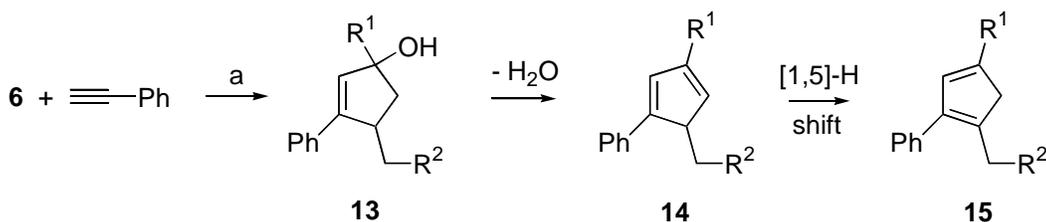
Scheme 5. (a) SmI_2, THF, MeOH, HMPA.

Use of the more stable precursor enone **6c** again led to annulated product. Employment of DMPU as a co-solvent in place of the highly toxic HMPA[19,20] greatly slowed the reaction. After 3 days of stirring, the reaction mixture was still deep blue. NMR analysis revealed that there was a substantial amount of starting material left in the mixture. Use of HMPA as the co-solvent resulted in complete reaction in under a minute. Unfortunately, purification by repeated column chromatography was not successful, but GC/MS analysis indicated that the annulated product had been formed. It was suspected that loss of product was occurring during column chromatography because cyclopentadienes readily undergo Diels-Alder dimerisation reactions, and it is possible that this was causing the difficulties in separation and low perceived yields.

Samarium(II) iodide was found to be a suitable mediator of radical annulations. The success of the sequence was due to the difference in reactivity of the propagating radicals. The ketyl radicals generated were highly reactive, and intermolecular addition did not require a large excess of radical acceptor. Oligomerisation did not occur because the final alkyl radical was much less reactive. When the product was a cyclopent-2-enol, as in the examples studied here, dehydration occurred, followed by a concomitant [1,5]-H shift forming a thermodynamically more stable cyclopentadiene derivative. The less than excellent yields were probably a consequence of difficulties encountered in purification, and the dimerisation of the product cyclopentadienes. HMPA was found to be a superior co-solvent to DMPU in the annulation sequences.

Experimental Section

General Procedures. ^{1}H NMR spectra were obtained using a Bruker AM 300 MHz spectrometer unless otherwise stated, in which case the spectrum was obtained using a Varian Gemini 200 MHz spectrometer. ^{13}C NMR spectra were run at 75 MHz using the Bruker mentioned above. All samples were dissolved in deuteriochloroform, with tetramethylsilane as an internal standard. Coupling constants are given in Hz. GC/MS analysis was carried out using a Finnigan Incos 50 quadrupole mass spectrometer interfaced with a Hewlett-Packard HP5890 capillary gas chromatograph fitted with a column coated with methylsilicone as the stationary phase. Petroleum ether (PE) refers to the fraction boiling between 40 and 60˚C unless otherwise stated. Column chromatography was performed using BDH silica gel (40 - 63 mm).

Materials. Were purchased from Aldrich, Avocado or Lancaster. THF and diethyl ether were distilled under nitrogen from sodium benzophenone ketyl prior to use. Samarium diiodide (Aldrich) was a 0.1 M solution in THF. Acetylacetone was distilled prior to use. Other organic compounds were used as received.

Pent-4-en-2-one (6a).[16] Allyl bromide (32.4 g; 23.2 mL; 0.27 mol) was added, over a period of 2.5 hours, to a mixture of acetonitrile (8.2 g; 10.4 mL, 0.2 mol) and zinc-silver couple[17] (filings: 18 g; 0.27 mol) in THF (5 mL) and ether (45 mL). The mixture was stirred overnight, then poured into a mixture of ether (100 mL), saturated aqueous ammonium chloride solution (200 mL) and ice water (100 g). The mixture was stirred for 10 minutes, then the aqueous layer was separated and extracted with ether. The combined organic layers were dried ($MgSO_4$), then the solvents were removed by distillation at room temperature. Careful bulb to bulb distillation (105˚C @ 760 mmHg) yielded pure pent-4-en-2-one as a colourless oil (6.59 g; 39%). ^{1}H NMR δ (200 MHz) 2.17 (3H, s, CH_3), 3.29 (2H, d, J = 6.6, $C(O)CH_2$), 5.07-5.23 (2H, m, $=CH_2$), 5.80-6.08 (1H, m, -CH=).

Hept-1-en-4-one (6b).[16] Allyl bromide (17.51 g; 12.25 mL; 0.146 mol) was added, over a period of 2.5 hours, to a mixture of butyronitrile (7.46 g; 0.108 mol) and zinc-silver couple (powder:

9.46 g) in ether (27 mL). The mixture was stirred overnight, then poured into a mixture of ether (100 mL), saturated aqueous ammonium chloride solution (200 mL) and ice water (100 g). The mixture was stirred for 10 minutes, then the aqueous layer was separated and extracted with ether (3 x 75 mL). The combined organic layers were dried ($MgSO_4$) and concentrated at room temperature. Column chromatography (PE̅DCM, with contact time of product on silica kept as short as possible) yielded hept-1-en-4-one as a colourless oil (4.82 g; 40%). ^{1}H-NMR δ 0.92 (3H, t, J = 7.4, CH_3), 1.60 (2H, m, CH_2Me), 2.42 (2H, t, J = 7.4, CH_2CH_2CO), 3.16 (2H, d, J = 6.9, COCH_2CH=), 5.11-5.20 (2H, m, =CH_2), 5.86-5.98 (1H, m, CH=CH_2).

3-Styrylpentane-2,4-dione.[17,21] Pentane-2,4-dione (10.01g; 0.1 mol), phenylacetaldehyde (1.20 g; 0.1 mol) and piperidine (0.1 g) were stirred for 24 h at room temperature. DCM (100 mL) was added, and the mixture was washed with 5% HCl (50 mL) and water (50 mL), then dried ($MgSO_4$), and concentrated. Column chromatograpy (PE/EtOAc) yielded the title compound (3.80 g; 19%). ^{1}H-NMR δ 1.73 (6H, s, CH_3), 6.42 (1H, d, J = 16.2, CH=), 6.75 (1H, d J = 16.2, CH=), 7.26-7.45 (5H, m, ArH). ^{13}C-NMR δ 24.3, 111.6, 123.0, 126.3, 127.9, 128.9, 134.5, 137.3, 191.5.

1-Phenylpent-1-en-4-one (6c).[17] 3-Styrylpentane-2,4-dione (0.80 g; 3.96 mmol) and zinc acetate dihydrate (0.02 g) were refluxed in methanol for 24 hours. Bulb to bulb distillation yielded **6c** (60˚C @ 0.04 mmHg) as a pale yellow oil (0.41 g; 65%). ^{1}H-NMR δ 2.24 (3H, s, CH_3), 3.35 (2H, d, CH_2), 6.25-6.55 (2H, m, CH=CH), 7.18-7.45 (5H, m, ArH).

1,5-Diphenyl-3-methylpent-1-en-3-ol (12). To a flame dried 3-necked flask, purged with nitrogen, was added a solution of samarium(II) iodide in THF (0.1M; 41 mL; 4.1 mmol) followed by phenylacetylene (330 μl; 3 mmol), HMPA (5 mL), *t*-butanol (480 μl; 5 mmol), and benzylacetone (300 μl; 2 mmol). The mixture was decoloured, so more samarium(II) iodide solution was added (15 mL; 1.5 mmol), then the mixture was stirred for 20 minutes. 3% HCl was added (50 drops), followed by hexane (30 mL) and silica gel (10g). The mixture was filtered, and the filtrate allowed to stand. An inorganic solid precipitated, and the mixture was filtered again. HMPA was removed by bulb to bulb distillation under vacuum, and the remaining material was purified by column chromatography (hexane/ether 1/1) to give *trans*-1,5-diphenyl-3-methylpent-1-en-3-ol (0.155 g; 28%) as pure material, and *cis*-1,5-diphenyl-3-methylpent-1-en-3-ol (0.035 g; 8%) which contained a small amount of benzylacetone impurity. *trans*-1,5-Diphenyl-3-methylpent-1-en-3-ol: ^{1}H-NMR (200 MHz) δ 1.5 (3H, s, CH_3), 1.60 (1H, s, OH), 1.95 (2H, m, CH_2CH$_2$Ph), 2.7 (2H, m, PhCH$_2$), 6.33 (1H, d, J = 16.1, HC=), 6.65 (1H, d, J = 16.1, HC=) 7.2-7.5 (10H, m, ArH). ^{13}C-NMR δ 29.1, 31.1, 45.5, 73.8, 126.4, 127.1, 128.1, 128.9 (x 2), 129.0, 136.9, 137.5, 142.9. (Found M^+ 252.1505. $C_{18}H_{20}O$ requires M, 252.1514). *cis*-1,5-Diphenyl-3-methylpent-1-en-3-ol: ^{1}H-NMR δ 1.42 (3H, s, CH_3), 1.63 (1H, bs, OH), 1.84-1.96 (2H, m, CH_2CH$_2$Ph), 2.80-2.95 (2H, m, CH$_2$Ph), 5.75 (1H, d, J = 12.7, HC=), 6.60 (1H, d, J = 12.8, HC=), 7.15-7.37 (10H, m, ArH). ^{13}C-NMR δ 30.2, 31.1, 46.0, 75.1, 126.2, 126.7, 127.6, 128.7, 128.8, 128.9, 129.0, 129.3, 137.9, 138.8, 143.0.

Samarium(II) iodide mediated annulation of pent-4-en-2-one and phenylacetylene. To a flame dried 3-necked flask, purged with nitrogen, was added a solution of samarium(II) iodide in THF (0.1M; 41 mL; 4.1 mmol) followed by phenylacetylene (330 μl; 3 mmol), HMPA (5 mL), *t*-butanol (480 μl; 5 mmol), and pent-4-en-2-one (300 μl; 2 mmol). The mixture was decoloured, so more samarium(II) iodide solution was added (15 mL; 1.5 mmol), then the mixture was stirred for 20 minutes. 3% HCl was added (50 drops), followed by hexane (30 mL) and silica gel (10g). The mixture was filtered, and the filtrate allowed to stand. An inorganic solid precipitated, and the mixture was filtered again. The mixture was partially purified by repeated column chromatography to afford 1,4-dimethyl-3-phenylcyclopent-2-en-1-ol **13a**, ^{1}H-NMR δ 1.2 (3H, d, CH$_3$), 1.5 (3H, s, CH$_3$), 1.65 (bs, OH), 2.45 (2H, m), 3.45 (1H, m), 5.97 (1H, s), 7.20-7.50 (5H, m, ArH); ^{13}C-NMR δ 21.1, 28.3, 37.1, 48.7, 127.2, 128.2, 129.3, 129.4, 149.7. The mixture was also analysed by GC/MS which showed that dehydration to give (3,5-dimethyl-cyclopenta-1,4-dienyl)-benzene **15a** occurred very readily, *m/z* (relative intensity) 170 (68), 155 (100), 128 (50), 115 (46), 91 (68), 77 (61), 51 (53), 39 (63).

Samarium diiodide mediated annulation of hept-1-en-4-one and phenylacetylene: synthesis of 1-methyl-2-phenyl-4-propylcyclopentadiene (15b). To a flame dried 3-necked flask, purged with nitrogen, was added HMPA (5 mL), *t*-butanol (0.56 g; 7.5 mmol), phenylacetylene (0.51 g; 5 mmol), and hept-1-en-4-one (0.34 g; 3 mmol) followed by a solution of samarium(II) iodide in THF (0.1M; 60 mL; 6 mmol). The mixture was kept at −20˚C overnight, then a saturated aqueous solution of ammonium chloride was added (50 mL). The mixture was separated, and the aqueous layer extracted with ether (5 x 30 mL). The combined organic extracts were washed with water (50 mL) and brine (50 mL), then dried (MgSO$_4$) and concentrated. The mixture was purified by column chromatography (hexane/ether 3/1). Addition of isolated product to CDCl$_3$ resulted in the formation of water droplets. The solution was dried over 4 Å molecular sieves to give 1-methyl-2-phenyl-4-propylcyclopentadiene **15b** (0.22 g; 27%) as an oil. ^{1}H-NMR δ 0.95 (3H, t, *J* = 7.3, C*H*$_2$Me), 1.59 (2H, m, MeC*H*$_2$), 2.11 (3H, s, CH$_3$), 2.35 (2H, t, *J* = 7.6, EtC*H*$_2$), 3.00 (2H, s, ring CH$_2$), 6.26 (1H, s, CH=), 7.21-7.39 (5H, m, ArH). ^{13}C-NMR δ 14.1 (CH$_3$), 14.7 (CH$_3$), 22.8 (CH$_2$), 32.9 (CH$_2$), 49.0 (CH$_2$), 126.2 (CH), 127.8 (CH), 128.2 (CH), 129.1 (CH), 135.4, 137.3, 139.2, 146.4 (all C). The product before addition to CDCl$_3$ was analysed by mass spectrometry, but dehydration took place under these conditions to give **15b** *m/z* (relative intensity) 198 (M$^+$) (39), 183 (22), 173 (100), 169 (39), 155 (10), 141 (10), 129 (9), 128 (10) 115 (10), 91 (16). (Found: M$^+$ 198.1401. C$_{15}$H$_{18}$ requires *M*, 198.1409). A small amount, ca. 1%, of **13b** was still present as indicated by the spectra.

Samarium diiodide mediated annulation of 1-phenylpent-1-en-4-one and phenylacetylene. To a flame dried 3-necked flask, purged with nitrogen, was added a solution of samarium(II) iodide in THF (0.1M; 50 mL; 5.0 mmol) followed by phenylacetylene (330 μl; 3 mmol), DMPU (5 mL), *t*-butanol (480 μl; 5 mmol), and 1-phenylpent-1-en-4-one (0.32 g; 2 mmol). The mixture was stirred for 3 days under nitrogen, after which the mixture was still deep blue, then a saturated aqueous solution of sodium hydrogen carbonate was added (50 mL), and the mixture extracted with ether (3 x 30 mL), dried (MgSO$_4$) and concentrated. NMR and GC/MS analysis indicated that there was still a substantial amount of 1-phenylpent-1-en-4-one present. Repeated

column chromatography (hexane/ether and hexane/ethyl acetate) failed to isolate pure annulated product, but GC/MS indicated that **15c** had been formed (*ca.* 30 %), *m/z* (relative intensity) 246 (M^+, 100), 160 (45), 155 (95), 145 (56), 117 (93), 115 (59), 91 (64), 43 (44). (Found: M^+ 246.1402. $C_{19}H_{18}$ requires *M*, 246.1409). The reaction was repeated as above using HMPA instead of DMPU as co-solvent. The reaction was complete in under a minute, and no 1-phenylpent-1-en-4-one remained in the reaction mixture.

Acknowledgements

References and Notes

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