DOI: 10.1002/ejoc.200700197

Efficient, Transition Metal Mediated, Sequential, Two- and Three-Component Coupling Reactions for the Synthesis of Highly Substituted Five-Membered Ring Carbocycles

Nicolas Coia,[a] Didier Bouyssi,[a] and Geneviève Balme*[a]

Keywords: Synthetic design / Multicomponent reactions / Methylenecyclopentanes / Arylidenecyclopentanes / Copper iodide / Palladium

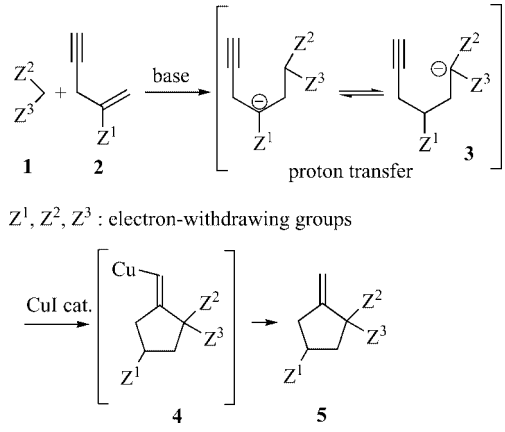
A Cu-catalysed method for the preparation of highly substituted methylenecyclopentanes, through a sequence involving a Michael addition of stabilized enolates to activated enynes followed by an intramolecular carbocupration reaction, is presented. This method was also successfully combined with a Pd-mediated coupling reaction to perform a new three-component reaction through a transmetallation pathway on the vinylcopper intermediate.

Introduction

The importance of natural products and pharmaceuticals containing the cyclopentyl moiety has led to the development of numerous synthetic methods to construct such structures in recent years.[1] In these synthetic approaches, several procedures based on the cyclisation of acetylenic substrates bearing a pendant nucleophile and leading to functionalised methylenecyclopentanes have been reported.[2] Among them, our group has recently developed a general method allowing for the cyclisation of a variety of δ-acetylenic stabilized carbanions with catalytic amounts of base and copper salts.[3] It occurred to us that the combination of this intramolecular cupration with an initial intermolecular Michael addition of a stabilized enolate **1** to an activated olefin such as **2** would provide a new procedure for the highly flexible synthesis of substituted methylenecyclopentanes. Another advantage of this [4+1] annulation approach is that, by the appropriate choice of the different electron-withdrawing substituents groups, the resulting cyclopentane derivatives could then be subjected to a number of further transformations.[4]

Results and Discussion

This [4+1] annulation strategy utilizes **1** and **2** as the one- and four-carbon components, respectively, and is based on a sequential Michael addition-cyclisation reaction (Scheme 1). Indeed, we envisioned that the Michael addition of an active methylene compound of type **1** such as malonate, malononitrile or methylcyanoacetate to the activated olefin **2** would lead to the expected stabilized intermediate **3** by proton transfer. This would be followed by a Cu-mediated cycloisomerisation of the resulting functionalised unactivated alkynes, leading to highly substituted methylenecyclopentanes **5**.

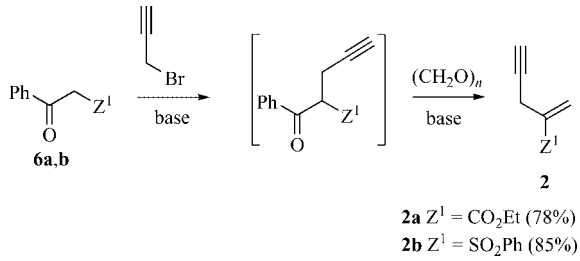


Scheme 1. Cu-catalysed synthesis of functionalised methylenecyclopentanes.

The two Michael acceptors **2a**,**b** were readily prepared in good yields by the reaction of the anions of the β-keto ester **6a** and the β-keto sulfone **6b**, respectively, with paraformaldehyde followed by an in situ deacylation according to a slight modification of known procedures (Scheme 2).[5]

First of all, we studied the [4+1] annulation reaction of unsaturated ester **2a** with the malonic enolate prepared from dimethyl malonate (**1a**) and potassium *tert*-butoxide in THF. The Michael addition was nearly complete, as observed by GC, after 3 h at 68 °C. However, a subsequent

[a] ICBMS, Institut de Chimie et Biochimie Moléculaires et Supramoléculaires, Université Lyon 1, CPE,
43 Boulevard du 11 Novembre 1918, 69622 Villeurbanne, France
Fax: +33-4-72431214
E-mail: balme@univ-lyon1.fr



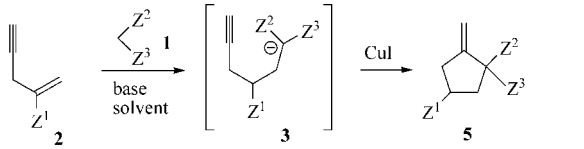
Scheme 2. Synthesis of Michael acceptors.

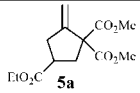
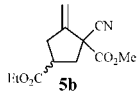
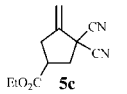
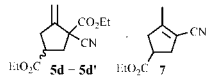
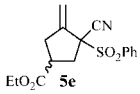
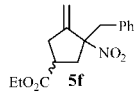
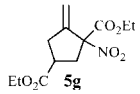
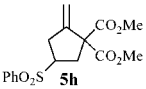
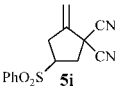
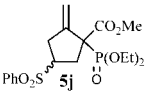
addition of a catalytic amount of CuI (10 mol-%) to the reaction mixture only resulted in a low conversion to **5a** even after prolonged heating at reflux temperature. When the same reaction was performed in the presence of stoichiometric amounts of CuI, the annulation process took place, and the resulting functionalised methylenecyclopentane **5a** was obtained in 53% isolated yield (Table 1, Entry 1). The addition of methylcyanoacetate (**1b**) to **2a** under identical reaction conditions gave **5b** in 48% yield as a mixture of diastereomers (Table 1, Entry 2). The major drawback of this procedure is that a stoichiometric amount of CuI was required. As a consequence, we started a systematic study concerning the development of a catalytic process for the Cu-mediated cyclisation reaction that was capable of producing a comparable yield of **5a** to that obtained by the stoichiometric route. Therefore, different bases (Cs_2CO_3, DBU, K_2CO_3, NaH, KH and *n*BuLi) and solvents (CH_3CN, DMSO and THF) were screened. The best results were obtained by the addition of **2a** to a CH_3CN solution of the preformed enolate [1.2 equiv. of dimethyl malonate (**1a**) and 1 equiv. of NaH]. After 5 h at 50 °C, CuI (10 mol-%) was added to the resulting Michael adduct. The reaction required 5 h to reach completion and gave rise to **5a** in 60% isolated yield (Table 1, Entry 3). These optimised conditions, applied to malononitrile (**1c**), afforded the related methylenecyclopentane analogue **5c** in 55% yield (Table 1, Entry 4). However, the reaction of ethyl cyanoacetate (**1d**) with **2a** gave rise to two different cyclised compounds, identified as the expected diastereomeric products **5d** and **5d′** and the decarboxylated[6] product **7** in 54% combined yield (1:1:1 mixture, Table 1, Entry 5). The isomeric ratios were based on the integrals of the ^1H NMR signals corresponding to the two exocyclic methylene protons observed in the crude reaction mixture.

The above conditions, applied to (phenylsulfonyl)acetonitrile (**1e**), resulted predominantly in the trienic dinitrile **8**, which probably results from the dimerisation of a vinylcarbene, which, in turn, arises from the vinylic copper intermediate **4e** (Scheme 3).[7] However, under a different set of conditions (with THF and DBU), the expected methylenecyclopentane **5e** was formed in 69% yield (Table 1, Entry 6).

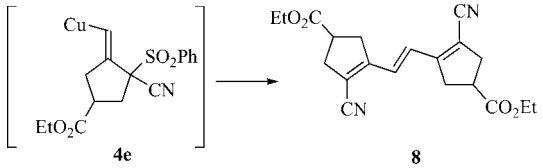
The Michael addition-cyclisation process was also tested with nitronate anions derived from phenylnitroethane (**1f**) and ethyl nitroacetate (**1g**). The Michael addition of the sodium salt of **1f** to **2a** in CH_3CN containing 1 equiv. of triethylbenzylammonium (TEBA) chloride followed by the

Table 1. Cu-mediated Michael addition-cyclisation.



Entry	Nucleophile (equiv.)	Michael acceptor, conditions[a]	Product	% Yield
1	$Z^2 = CO_2Me$ $Z^3 = CO_2Me$ **1a** (1.3 equiv.)	**2a** *t*BuOK 1.1 equiv. THF, reflux	 **5a**	53
2	$Z^2 = CN$ $Z^3 = CO_2Me$ **1b** (1.3 equiv.)	**2a** *t*BuOK 1.1 equiv. THF, reflux	 **5b**	48 (43:57)
3	**1a** (1.2 equiv.)	**2a** NaH 1 equiv. CH_3CN, 50 °C	**5a**	60
4	$Z^2 = CN$ $Z^3 = CN$ **1c** (1.2 equiv.)	**2a** NaH 1 equiv. THF, 50 °C	 **5c**	55
5	$Z^2 = CN$ $Z^3 = CO_2Et$ **1d** (1.2 equiv.)	**2a** NaH 1 equiv. CH_3CN, 50 °C	 **5d – 5d′** **7**	54[b]
6	$Z^2 = CN$ $Z^3 = SO_2Ph$ **1e** (1.2 equiv.)	**2a** DBU 1 equiv. THF, 50 °C	 **5e**	69 (60:40)
7	$Z^2 = CH_2Ph$ $Z^3 = NO_2$ **1f** (1.2 equiv.)	**2a** NaH 1 equiv. TEBA 1 equiv. CH_3CN, 50 °C	 **5f**	65 (75:25)
8	$Z^2 = CO_2Et$ $Z^3 = NO_2$ **1g** (3 equiv.)	**2a** DIPEA 3 equiv. TEAB 0.1 equiv. CH_3CN, 50 °C	 **5g**	55[c]
9	**1a** (2 equiv.)	**2b** NaH 1 equiv. THF, 50°C	 **5h**	89
10	**1c** (3 equiv.)	**2b** NaH 1 equiv. THF, 50 °C	 **5i**	46
11	$Z' = P(O)OEt_2$ $Z'' = CO_2Me$ **1h** (2 equiv.)	**2b** NaH 1 equiv. THF, 50 °C	 **5j**	65 (84:16)

[a] All reactions were performed with 10 mol-% of CuI as the catalyst, except for entries 1 and 2, where a stoichiometric quantity of CuI was added to the reaction medium. [b] Isolated as a mixture of three compounds [two diastereomers (**5d** and **5d′**) and **7** in a 1:1:1 ratio]. [c] Only one diastereomer was obtained.



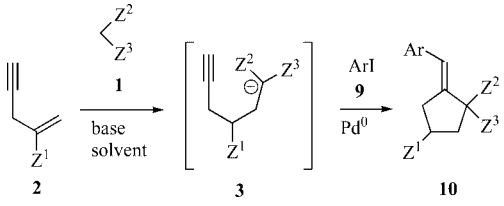
Scheme 3. Dimerisation of the vinylcopper intermediate.

addition of CuI afforded **5f** in 65% yield (Table 1, Entry 7). The presence of an ammonium salt, such as TEBA chloride, to dissolve the nitronate anion, was critical for the success of this reaction.

The attempted condensation of **2a** with ethyl nitroacetate (**1g**) as the nucleophilic moiety under the various reaction conditions described above failed to effect the desired Michael addition-cyclisation tandem reaction. Interestingly, with CH_3CN and the reaction conditions recently reported by Hammer and coworkers for the Michael addition of alkyl nitroacetates (DIPEA in the presence of a catalytic amount of tetraalkylammonium salt to increase the reactivity of the anion),[8] functionalised methylenecyclopentane **5g** was obtained in 55% yield (Table 1, Entry 8).

Since vinylic sulfones are versatile precursors for various functionalities,[9] this Michael addition-cyclisation tandem reaction was also developed on the unsaturated sulfone **2b**. Optimum conditions with dimethyl malonate (**1a**), malononitrile (**1c**) or methyl (diethoxyphoshoryl)acetate (**1h**) as nucleophilic moieties involved the Michael addition of a THF solution of the preformed enolate (2 equiv. of **1a** or **1h** or 3 equiv. of **1c** and 1 equiv. of NaH) to **2b** at 50 °C. The addition of 10 mol-% of CuI to the resulting Michael adduct gave rise to **5h**, **5i** and **5j** in 89%, 46% and 65% yield, respectively (Table 1, Entries 9–11).

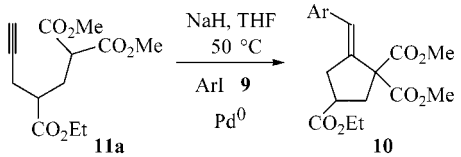
Having succeeded in the preparation of various functionalised methylenecyclopentanes, we next turned our attention to the development of a new three-component, domino, Michael addition-cyclisation-coupling process involving an organopalladium species as the promoter of the cyclisation reaction so as to introduce diversity onto the exocyclic unsaturation of the final ring (Scheme 4).[10]

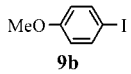


Scheme 4. Pd-mediated Michael addition-cyclisation-coupling reaction.

We first attempted the sequential Michael addition-cyclisation-coupling reaction in a one-pot procedure, with active methylene compound **1a**, unsaturated alkyne **2a** and iodobenzene (**9a**) as the precursor of the organopalladium species. Thus, the intermediate Michael adduct enolate **3a** (Z^1 = CO_2Et and Z^2, Z^3 = CO_2Me) was generated by the addition of 1 equiv. of dimethyl sodium malonate in CH_3CN to **2a**, followed by stirring of the mixture at 50 °C for 5 h. This was followed by the addition of iodobenzene **9a** (1.2 equiv.) and 5 mol-% of a Pd^0 complex, generated by the reduction of $PdCl_2(PPh_3)_2$ with *n*BuLi.[11] After 15 h at this temperature, the desired cycloadduct **10a** was isolated in low yield (17%) along with **5a** (17% yield). The attempted modification of this standard protocol to achieve acceptable yields of the desired cycloadduct was unsuccessful. Therefore, to test the feasibility of the overall transformation, we chose to examine the Pd-mediated cyclisation process on the isolated open-chain Michael adduct **11a** with an aryl iodide. After screening various solvents and bases, we found that the best results in this cyclisation-coupling reaction were achieved when the reaction of **11a** with **9a** was conducted in THF at 50 °C with $PdCl_2(PPh_3)_2$/*n*BuLi as the catalytic system and with NaH. The expected cyclised product **10a** was then isolated in 52% yield (Table 2, Entry 1). When these conditions were applied to **11a** and 1-iodo-4-methoxybenzene (**9b**), **10b** was obtained in 62% yield (Table 2, Entry 2). In this last case, the yield was improved to 94% yield with a slow addition procedure (syringe pump addition of the preformed sodium enolate derived from **11a** to 2.5 equiv. of **9b** in the presence of 5 mol-% of the Pd catalyst in THF at 50 °C, Table 2, Entry 3).

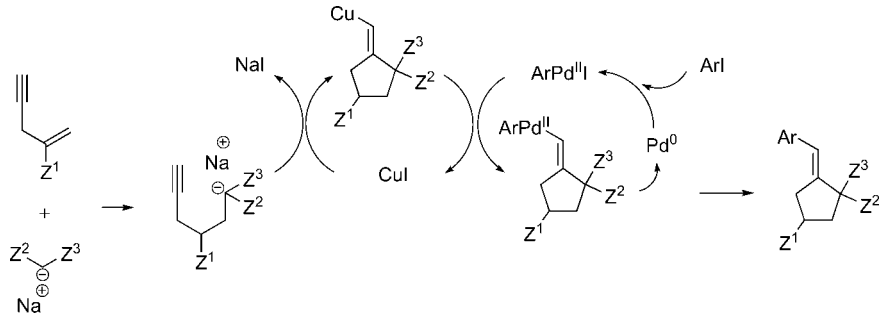
Table 2. Pd-mediated cyclisation-coupling reaction.



Entry	Aryl iodide 9	Product (% yield)
1	 9a	**10a** (52)
2	 9b	**10b** (62)
3	9b	**10b** (94)[a]

[a] Slow addition of sodium enolate with a syringe pump.

With these results in hand, we next attempted to effect the Michael addition and the subsequent cyclisation-coupling reaction in one operation with the precursors **1a**, **2a** and **9a**. After considerable experimentation, with slow addition techniques and varying the order of introduction of each starting material and the solvent, we found that the highest yield of cycloadduct **10a** that could be obtained from this one-pot cascade process was only 35%. The optimised reaction conditions involve the slow addition of the intermediate Michael adduct enolate (1 equiv.) at 50 °C to a THF solution of iodobenzene (1.2 equiv.) in the presence of dichlorobis(triphenylarsane)palladium [$PdCl_2(AsPh_3)_2$] as the catalyst (10 mol-%). Following these unfruitful efforts, we decided to investigate another strategy to access the targeted three-component adduct **10a** in a single operation. In our earlier studies, we had developed an efficient Pd/CuI-cocatalysed cyclisation-coupling reaction of linear unactivated alkynes bearing a stabilized nucleophile with 1-halogeno-1-alkynes.[12] The mechanism for this transformation was not clear but one could speculate that the cyclisation-coupling reaction proceeds through the formation of

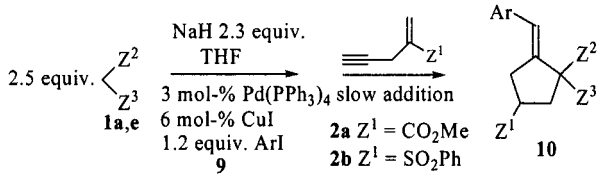


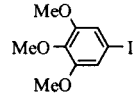
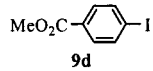
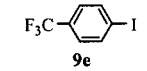
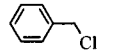
Scheme 5. Proposed mechanism for the Pd/Cu-mediated three-component condensation reaction.

a vinylcopper intermediate followed by a transmetallation pathway. On the basis of this study and of the successful results from the Cu-promoted Michael addition-cyclisation reaction described above, we decided to extend this Pd/Cu-cocatalysed methodology to the one-step preparation of compounds of type **10** (Scheme 5).

We were pleased to see that, in this way, it was possible to reach satisfactory results, and the highest yield was obtained with a slight excess of malonate. Thus, compound **10a** was obtained in 80% yield by the slow addition (over 2 h) of enyne **2a** (1 equiv.) to iodobenzene (**9a**, 1.2 equiv.), dimethyl malonate (**1a**, 2.5 equiv.), NaH (2.3 equiv.), ($Pd(PPh_3)_4$) as the catalyst (3 mol-%) and CuI (6 mol-%, Table 3, Entry 1). Having optimized conditions in hand, the generality of this process was investigated. In most entries, good yields were obtained for the Pd/Cu-cocatalysed three-component reaction with a wide range of electronically varied aryl iodides; no appreciable difference in the yield for the three-component reaction was observed with electron-donating groups or electron-withdrawing substituents on the aryl iodides (Table 3, Entries 2–5). We also investigated this Pd/Cu-cocatalysed three-component condensation reaction with benzyl chloride (**9f**) as the coupling reagent under our optimized reactions. We were pleased to observe a 50% yield of the desired three-component coupling product **10f** (Table 3, Entry 6). No trace of the benzylmalonate resulting from the reaction of the malonate anion with the chlorine derivative was isolated.[13] We have also examined the three-component reaction of iodobenzene (**9a**) and the unsaturated ester **2a** with (phenylsulfonyl)acetonitrile (**1e**) as the nucleophile. Under the optimal conditions described above, the reaction proceeded to give the target arylidenecyclopentane **10g** along with the undesired cyclic product **5e** resulting from the competitive two-component process. Several experiments indicated that the solvent was very important for this particular three-component condensation reaction. Thus, effecting the three-component reaction in a 2:1 mixture of THF/DMSO suppressed the formation of **5e** dramatically, and **10g** was isolated as an inseparable 7:3 mixture of two diastereomers in 50% yield (Table 3, Entry 7). This three-component condensation reaction was then extended to unsaturated sulfone **2b**, and the corresponding functionalised arylidenecyclopentanes were isolated in good to excellent yields with neutral, electron-rich or electron-deficient aryl iodides (Table 3, Entries 8–10).

Table 3. Pd/Cu-cocatalysed three-component condensation reaction.



Entry	Nucleophile and Michael acceptor	Aryl iodide ArI	Product	% Yield[a]
1	**1a** **2a**	**9a**	**10a**	80
2	**1a** **2a**	**9b**	**10b**	68
3	**1a** **2a**	 **9c**	**10c**	92
4	**1a** **2a**	 **9d**	**10d**	75
5	**1a** **2a**	 **9e**	**10e**	55
6	**1a** **2a**	 **9f**	**10f**	50
7	**1e** **2a**	**9a**	**10g**	50 (70:30)
8	**1a** **2b**	**9a**	**10h**	71
9	**1a** **2b**	**9d**	**10i**	59
10	**1a** **2b**	**9c**	**10j**	57

[a] All reactions were performed with 3 mol-% of $Pd(PPh_3)_4$ and 6 mol-% of CuI as the catalyst with NaH and THF except for Entry 7, where a 2:1 mixture of THF/DMSO was used.

Conclusions

In summary, we have developed efficient methods for the one-pot synthesis of a variety of methylenecyclopentanes and (arylmethylene)cyclopentanes containing useful functionalities from readily or commercially available starting materials. Further work is in progress to study the synthetic application of these new two-component and three-component condensation reactions.

Experimental Section

All reactions were carried out under a nitrogen atmosphere. ^1H and ^{13}C NMR spectra were recorded with a Bruker DRX 300 spectrometer. Chemical shifts are reported in δ values (ppm) relative to TMS for ^1H and to $CDCl_3$ for ^{13}C. Mass spectra were recorded with a Thermoquest Finnigan MAT 95 XL. In the case of diastereoisomeric mixtures, the chemical shifts for the minor isomer where determined from the relative intensities, and corresponding shifts are given in brackets.

Ethyl 2-Methylenepent-4-yn-1-oate (2a): Based on the protocol of Queignec et al.,[5b] in a 100 mL round-bottomed flask, propargyl bromide (80% in toluene, 7.1 mL, 63.7 mmol), NaI (2.17 g, 14.5 mmol) and ethyl benzoylacetate (10 mL, 58 mmol) were mixed, and K_2CO_3 (12 g, 86.9 mmol) was then added quickly. The resulting heterogeneous mixture was vigorously stirred for 24 h at room temp., giving a thick orange gum. Once diluted in dry THF (50 mL), this gum was mixed with paraformaldehyde (2.96 g, 96.4 mmol) and additional K_2CO_3 (8 g, 58 mmol), and the mixture was stirred for 9 d at 40 °C. The mixture was extracted by ethyl acetate (3 × 150 mL), and the organic layers were concentrated, giving the crude product, which was distilled under vacuum (35 °C/3 Torr) to afford pure **2a** as a pale yellow oil (6.27 g, 78% yield). NMR analysis was in accordance with literature data.

1-[(Pent-1-en-4-yn-2-yl)sulfonyl]benzene (2b): (Phenylsulfonyl)acetophenone (4 g, 15.4 mmol) and NaH (60% oil dispersion, 614 mg, 15.35 mmol) were mixed in CH_3CN (80 mL). Once the evolution of gas had stopped, propargyl bromide (80% in toluene, 2 mL, 18 mmol) and NaI (576 mg, 3.8 mmol) were added. The reaction mixture was then stirred at room temp. for 24 h before being concentrated under vacuum. The resulting gum was then diluted with dry THF (60 mL) and dry CH_2Cl_2 (20 mL), and NaH (60% oil dispersion, 614 mg, 15.35 mmol) was then added. Once gaseous evolution stopped, paraformaldehyde (1.4 g, 46.63 mmol) was added with vigorous stirring to avoid instant clotting. The resulting solution was stirred at room temp. for 48 h. The mixture was extracted with diethyl ether (4 × 200 mL), the organic layers were washed with brine (100 mL) and concentrated under vacuum, and the crude product was purified by flash chromatography on silica gel with petroleum ether/ethyl acetate (8:2) containing 4% of Et_3N to ensure good separation. Pure **2b** was obtained as a pale yellow oil, which turned brown rapidly (2.15 g, 68% yield). ^1H NMR (300 MHz, $CDCl_3$): δ = 2.21 (t, J = 2.5 Hz, 1 H, CH), 3.18 (td, J = 1.8 Hz, J = 2.5 Hz, 2 H, CH_2), 6.22 (dt, J = 0.6 Hz, J = 1.8 Hz, 1 H, CH), 6.50 (dt, J = 0.6 Hz, J = 1.8 Hz, 1 H, CH), 7.56 (tt, J = 1.4 Hz, J = 7.5 Hz, 2 H, CH), 7.63 (tt, J = 1.4 Hz, J = 7.5 Hz, 1 H, CH), 7.87 (dt, J = 7.5 Hz, J = 1.4 Hz, 2 H, CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.2 (CH_2), 73.5 (CH), 77.4 ($C_{quat.}$), 125.4 (CH_2), 128.3 (CH), 129.4 (CH), 133.9 (CH), 138.2 ($C_{quat.}$), 145.5 ($C_{quat.}$) ppm. HRMS (EI): calcd. for $C_{11}H_{10}O_2S$ $[M]^+$ 206.0402; found 206.0402.

1-Ethyl 3,3-Dimethyl 4-Methylenecyclopentane-1,3,3-tricarboxylate (5a): Under a nitrogen atmosphere, dimethylmalonate (**1a**, 100 µL, 0.868 mmol) and NaH (60% oil dispersion, 29 mg, 0.724 mmol) were mixed in CH_3CN (2 mL). The reaction mixture was vigorously stirred until hydrogen evolution stopped. Ethyl 2-methylenepent-4-yn-1-oic acid (**2a**, 100 mg, 0.724 mmol) was added, and the resulting solution was stirred at 50 °C for 5 h (TLC monitoring). CuI (13.8 mg, 0.072 mmol) was then added, and the reaction mixture was stirred for an additional 5 h at 50 °C. After removal of CuI by filtration through a short pad of silica gel (CH_2Cl_2) and concentration of the mixture, the crude product was purified by flash chromatography on silica gel with petroleum ether/diethyl ether (7:3) containing 4% Et_3N, to afford pure **5a** as a pale yellow oil (116 mg, 60% yield). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.28 (t, J = 7.1 Hz, 3 H, CH_3), 2.51 (dd, J = 10.7 Hz, J = 13.5 Hz, 1 H, CH), 2.73–2.78 (m, 3 H, CH), 2.97 (m, 1 H, CH), 3.77 (s, 3 H, OCH_3), 3.78 (s, 3 H, OCH_3), 4.16 (q, J = 7.1 Hz, 2 H, OCH_2), 5.25 (d, J = 2.15Hz, 1 H, CH), 5.30 (d, J = 2.15Hz, 1 H, CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (CH_3), 36.8 (CH_2), 38.4 (CH_2), 41.7 (CH), 52.8 (OCH_3), 52.9 (OCH_3), 60.6 ($C_{quat.}$), 62.9 (OCH_2), 113.2 (CH_2), 145.4 ($C_{quat.}$), 170.2 ($C_{quat.}$), 170.4 ($C_{quat.}$), 173.6 ($C_{quat.}$) ppm. HRMS (ESI): calcd. for $C_{13}H_{18}NaO_6$ $[M + Na]^+$ 293.1001; found 206.1002.

Ethyl 3,3-Dicyano-4-methylenecyclopentane-1-carboxylate (5c): With the same procedure as was described for the synthesis of **5a**, the reaction was performed with Michael acceptor **2a** (100 mg, 0.72 mmol). Purification by chromatography with petroleum ether/ethyl acetate (8:2) containing 2% of Et_3N afforded **4c** as a colourless oil (82 mg, 55% yield). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.28 (t, J = 7.1 Hz, 3 H, CH_3), 2.68 (dd, J = 9.7 Hz, J = 13.3 Hz, 1 H, CH), 2.85 (m, 3 H, CH), 3.20 (m, 1 H, CH), 4.19 (q, J = 7.1 Hz, 2 H, OCH_2), 5.49 (d, J = 2.0 Hz, 1 H, CH), 5.69 (d, J = 2.0 Hz, 1 H, CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (CH_3), 33.7 (CH_2), 38.1 ($C_{quat.}$), 41.3 (CH_2), 41.5 (CH), 61.7 (OCH_2), 114.6 (CN), 114.7 (CN), 116.2 (CH_2), 142.6 ($C_{quat.}$), 171.6 ($C_{quat.}$) ppm. HRMS (EI): calcd. for $C_{11}H_{12}N_2O_2$ $[M]^+$ 204.0899; found 204.0899.

Diethyl 1-Cyano-5-methylenecyclopentane-1,3-dicarboxylate (5d): With the same procedure as was described for the synthesis of **5a**, the Michael acceptor **2a** (200 mg, 1.45 mmol) was employed as the starting material. Purification of the reaction mixture by flash chromatography on silica gel with petroleum ether/CH_2Cl_2 (7:3) led to a 1:1:1 mixture of cyclisation diastereomers **5d** and **5d′** and monoester **7** (177 mg, 54% overall yield for the cyclization) as a colourless oil. ^1H NMR (300 MHz, $CDCl_3$, mixture of **5d** and **5d′**): δ = 1.19–1.27 (m, 6 H, CH_3), 2.50 (m, 2 H, CH), 2.66–2.90 (m, 3 H, CH), 3.00–3.22 (m, 3 H, CH), 4.18 (q, J = 7.1 Hz, J = 7.1 Hz, 4 H, 2 H, OCH_2), 4.28 (q, J = 7.1 Hz, J = 7.1 Hz, 2 H, OCH_2), 5.27 (s, 1 H, CH), 5.28 (s, 1 H, CH), 5.38 (s, 1 H, CH), 5.48 (s, 1 H, CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.7 (13.7) [CH_3], 14.5 (CH_3), 35.9 (CH_2), 39.7 (CH_2), 42.6 (CH), 61.5 (OCH_2), 63.6 (63.7) [OCH_2], 114.0 (114.2) [CN], 146.3 ($C_{quat.}$), 167.4 ($C_{quat.}$), 175.2 ($C_{quat.}$) ppm. HRMS (ESI): calcd. for $C_{13}H_{17}NO_4$ $[M]^+$ 251.1158; found 251.1155.

Ethyl 3-Cyano-4-methylcyclopent-3-ene-1-carboxylate (7): Compound **7** was isolated from an earlier attempt at the synthesis of **5d** with **2a** (200 mg, 1.45 mmol), Cs_2CO_3 (472 mg, 1.45 mmol), methyl cyanoacetate (**1b**, 128 µL, 1.45 mmol) and CuI (28 mg, 0.15 mmol) in dry DMF (3 mL). The reaction was stirred at 50 °C for 14 h. Purification by chromatography with petroleum ether/ethyl acetate (7:3) afforded pure **7** as a colourless oil (43 mg, 17% yield). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.27 (t, J = 7.1 Hz, 3 H, CH_3), 1.93 (s, 3 H, CH_3), 2.65–2.85 (m, 2 H, CH), 3.04 (m, 1 H, CH), 3.22 (m, 1 H, CH), 4.08 (q, J = 7.1 Hz, 2 H, CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (CH_3), 16.3 (CH_3), 37.2 (CH_2), 40.7 (CH_2), 50.0 (CH), 61.0 (CH_2), 106.8 ($C_{quat.}$), 116.0 (CN), 158.8 ($C_{quat.}$), 174.0 ($C_{quat.}$) ppm.

Ethyl 3-Cyano-4-methylene-3-(phenylsulfonyl)cyclopentanecarboxylate (5e): Michael acceptor **2a** (400 mg, 2.89 mmol), (phenylsulfonyl)acetonitrile (**1e**, 630 mg, 3.48 mmol) and DBU (436 µL, 2.89 mmol) were stirred together at 50 °C for 4 h under a nitrogen

atmosphere. CuI (55 mg, 0.29 mmol) was then added, and the reaction mixture was stirred overnight at 50 °C. After removal of CuI by filtration through a short pad of silica gel (CH_2Cl_2) and concentration of the resulting filtrate, the crude product was purified by flash chromatography on silica gel with petroleum ether/diethyl ether (8:2) to afford **5e** as a 3:5 mixture of two diastereomers (635.2 mg, 69% yield) and as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$ mixture of the two diastereomers): δ = 1.28 (q, J = 7.1 Hz, 3 H, CH_3), 2.53–2.62 (m, 0.5 H, CH), 2.68–2.93 (m, 2 H, CH_2), 2.95–3.14, (m, 2 H, CH_2), 3.38–3.51 (m, 0.5 H, CH), 4.17 (q, J = 7.1 Hz, 1.2 H, OCH_2), 4.20 (q, J = 7.1 Hz, 0.8 H, OCH_2), 5.15–5.19 (m, 0.6 H, CH), 5.30 (m, 0.3 H, CH), 5.45 (m, 0.6 H, CH), 5.49 (m, 0.3 H, CH), 7.60–7.68 (m, 2 H, CH), 7.74–7.81 (m, 1 H, CH), 7.99–8.06 (m, 2 H, CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.2 (14.3) [CH_3], 37.1 (35.8) [CH_2], 36.9 (36.8) [CH_2], 41.6 (41.9) [CH], 61.4 (61.5) [OCH_2], 69.5 (68.2) [$C_{quat.}$], 116.8 (113.4) [CN], 118.9 (118.8) [CH_2] 129.2 (129.3) [CH], 131.3 (131.2) [CH], 133.0 (133.7) [$C_{quat.}$], 135.4 (135.3) [CH], 141.4 (141.6) [$C_{quat.}$], 173.0 (171.8) [$C_{quat.}$] ppm. HRMS (EI): calcd. for $C_{16}H_{17}NO_4S$ [M]$^+$ 319.0878; found 319.0879.

3-Benzyl-4-methylene-3-nitrocyclopentyl Propionate (5f): With the same procedure as was described for the synthesis of **5a**, the Michael acceptor **2a** (200 mg, 1.45 mmol) was employed as the starting material. The Michael addition step was performed with additional TEBA chloride (330 mg, 1.45 mmol). Purification by chromatography with petroleum ether/diethyl ether (9:1) containing 4% of Et_3N afforded **5f** as an inseparable 3:1 mixture of two diastereomers (210 mg, 50% yield) and as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$ mixture of the two diastereomers): δ = 1.16 (t, J = 7.1 Hz, 1 H, CH_3), 1.18 (t, J = 7.2 Hz, 3 H, CH_3), 2.09 (dd, J = 11.5 Hz, J = 14.6 Hz, 1 H, CH), 2.27–2.38 (m, 3.3 H, CH), 2.41–2.81 (m, 4.2 H, CH), 2.97 (d, J = 14.3 Hz, 1 H, CH), 3.05–3.10 (m, 1 H, CH), 3.63 (pseudo-t, J = 12.9 Hz, 0.33 H, CH), 3.79 (d, J = 14.3 Hz, 1.3 H, CH), 4.05 (q, J = 7.1 Hz, 0.3 H, OCH_2), 4.07 (q, J = 7.2 Hz, 2 H, OCH_2), 5.33 (dd, J = 1.9 Hz, J = 2.5 Hz, 1.33 H, CH), 5.56 (m, 0.33 H, CH), 5.66 (ddd, J = 0.6 Hz, J = 1.9 Hz, J = 2.8 Hz, 1 H, CH), 7.06 (m, 2.5 H, CH), 7.20 (m, 3.9 H, CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (14.0) [CH_3], 36.1 (35.3) [CH_2], 38.5 (37.4) [CH_2], 41.1 (40.2) [$C_{quat.}$], 43.9 (44.2) [CH_2], 60.7 (60.8) [OCH_2], 97.9 (96.6) [$C_{quat.}$], 113.5 (112.7) [CH_2], 127.4 (127.5) [CH], 128.5 (CH), 129.6 (129.9) [CH], 134.6 (134.3) [$C_{quat.}$], 148.1 ($C_{quat.}$), 173.9 (173.1) [$C_{quat.}$] ppm. HRMS (EI): calcd. for $C_{16}H_{19}NO_4$ [M]$^+$ 290.1392; found 290.1390.

3-Ethyl 1-Ethyl 5-Methylene-1-nitrocyclopentane-1,3-dicarboxylate (5g): Michael acceptor **2a** (200 mg, 1.45 mmol), ethyl nitroacetate (**1g**, 482 μL, 4.34 mmol), DIPEA (720 μL, 4.34 mmol) and tetraethylammonium bromide (31.5 mg, 0.15 mmol) were mixed together in CH_3CN (6 mL) and stirred at room temp. for 24 h under a nitrogen atmosphere. CuI (28 mg, 0.15 mmol) was then added, and the mixture was stirred at room temp. for an additional 24 h. The reaction mixture was then filtered through silica gel and purified by chromatography with petroleum ether/diethyl ether (8:2) to afford **5g** as a single diastereomer (216 mg, 55% yield) and as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.25 (dt, J = 0.5 Hz, J = 7.1 Hz, 3 H, CH_3), 1.28 (dt, J = 0.5 Hz, J = 7.1 Hz, 3 H, CH_3), 2.74 (m, 2 H, CH_2), 2.89 (m, 1 H, CH), 3.02 (m, 2 H, CH_2), 4.15 (dq, J = 0.5 Hz, J = 7.2 Hz, 2 H, OCH_2), 4.28 (dq, J = 0.5 Hz, J = 7.1 Hz, 2 H, OCH_2), 5.52 (t, J = 2.1 Hz, 1 H, CH), 5.63 (d, J = 2.1 Hz, 1 H, CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9 (13.9) [CH_3], 14.2 (14.2) [CH_3], 35.8 (33.8) [CH_2], 40.2 (39.2) [CH_2], 41.0 (39.7) [CH], 61.2 (61.4) [OCH_2], 63.2 (63.3) [OCH_2], 98.7 (100.8) [$C_{quat.}$], 118.0 (118.0) [CH_2], 142.6 (142.5) [$C_{quat.}$], 165.2 (161.9) [$C_{quat.}$], 172.9 (172.3) [$C_{quat.}$] ppm. HRMS (ESI): calcd. for $C_{15}H_{17}NNaO_4$ [M + Na]$^+$ 294.0954; found 294.0955.

Dimethyl 2-Methylene-4-(phenylsulfonyl)cyclopentane-1,1-dicarboxylate (5h): Compound **5h** was prepared by a procedure analogous to that used for **4a** except that 2 equiv. of the nucleophile in THF were used. The reaction was performed with the Michael acceptor **2b** (500 mg, 2.42 mmol). Purification by chromatography with petroleum ether/ethyl acetate (8:2) afforded **5h** as a pale yellow oil (709 mg, 86% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.23 (dt, J = 1.3 Hz, J = 7.3 Hz, 1 H, CH), 2.67 (m, 3 H, CH), 2.93 (m, 1 H, CH), 3.69 (s, 3 H, OCH_3), 3.75 (s, 3 H, OCH_3), 5.29 (s, 1 H, CH), 5.39 (s, 1 H, CH), 7.57 (t, J = 7.4 Hz, 2 H, CH), 7.67 (t, J = 7.4 Hz, 1 H, CH), 7.89 (d, J = 8.1 Hz, 2 H, CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 33.9 (CH_2), 34.0 (CH_2), 52.9 (OCH_2), 53.1 (OCH_2), 61.0 (CH_2), 62.5 ($C_{quat.}$), 114.5 (CH_2), 128.2 (CH), 129.2 (CH), 133.9 (CH), 137.9 ($C_{quat.}$), 142.7 ($C_{quat.}$), 169.0 ($C_{quat.}$), 169.6 ($C_{quat.}$) ppm. HRMS (ESI): calcd. for $C_{16}H_{18}NaO_6S$ [M + Na]$^+$ 361.0722; found 361.07219.

2-Methylene-4-(phenylsulfonyl)cyclopentane-1,1-dicarbonitrile (5i): Compound **5i** was prepared with the same procedure as was described for the synthesis of **5a** except that 2 equiv. of the nucleophile in THF were used. The reaction was performed with Michael acceptor **2b** (150 mg, 0.73 mmol) and gave pure product (197 mg, 46% yield) as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.87 (tdd, J = 2.1 Hz, J = 9.0 Hz, J = 17.4 Hz, 2 H, CH), 3.08 (tdd, J = 2.4 Hz, J = 9.0 Hz, J = 17.4 Hz, 1 H, CH), 3.8 (m, 1 H, CH), 5.53 (q, J = 2.2 Hz, 1 H, CH), 5.73 (q, J = 2.2 Hz, 1 H, CH), 7.63 (td, J = 3.8 Hz, J = 7.2 Hz, 2 H, CH), 7.73 (dd, J = 7.0 Hz, J = 14.0 Hz, 1 H, CH), 7.90 (dd, J = 2.3 Hz, J = 7.9 Hz, 2 H, CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 31.1 (CH_2), 38.3 (CH_2), 38.4 ($C_{quat.}$), 60.5 (CH), 113.6 (CN), 113.9 (CN), 117.4 (CH_2), 128.5 (CH), 129.9 (CH), 134.8 (CH), 137.2 ($C_{quat.}$), 140.3 ($C_{quat.}$) ppm. HRMS (EI): calcd. for $[C_{14}H_{12}N_2O_2S]^+$ 272.0619; found 272.0619.

Ethyl 1-(Diethoxyphosphoryl)-2-methylene-4-(phenylsulfonyl)cyclopentane-1-carboxylate (5j): Compound **5j** was prepared with the same procedure as was described for the synthesis of **5a** except that 2 equiv. of the nucleophile in THF were used. The reaction was performed with Michael acceptor **2b**. Purification by chromatography with petroleum ether/acetone (9:1) afforded **5j** as an inseparable 5:1 mixture of two diastereomers (135 mg, 65% yield) and as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.23 (m, 9 H, phosphoryl-CH_3 and carboxy-CH_3), 2.62 (dd, J = 9.4 Hz, J = 14.0 Hz, 2.6 H, CH_2), 2.88 (m, 1.2 H, CH), 3.65 (m, 0.8 H, CH), 3.88 (m, 0.2 H, CH), 4.12 (dd, J = 5.4 Hz, J = 8.9 Hz, 6 H, OCH_2), 5.23 (s, 1 H, CH), 5.51 (s, 0.8 H, CH), 5.59 (s, 0.2 H, CH), 7.54 (dd, J = 7.0 Hz, J = 1.3 Hz, 2 H, CH), 7.63 (dd, J = 7.0 Hz, J = 7.4 Hz, 1 H, CH), 7.86 (dd, J = 1.3 Hz, J = 7.4 Hz, 2 H, CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, major isomer): δ = 13.8 (CH_3), 16.2 (d, J = 6.29 Hz, CH_3), 16.3 (d, J = 6.1 Hz, CH_3), 34.0 (d, J = 0.5 Hz, CH_2), 35.3 (d, J = 5.8 Hz, CH_2) 56.7 (d, J = 146 Hz, $C_{quat.}$), 62.2 (CH), 62.9 (d, J = 7.2 Hz, OCH_2), 63.8 (d, J = 6.8 Hz, OCH_2), 114.5 (d, J = 6.38 Hz, CH_2), 128.3 (CH), 129.3 (CH), 133.9 (CH), 138.0 ($C_{quat.}$), 142.4 (d, J = 6.15 Hz, $C_{quat.}$), 168.9 (d, J = 1.2 Hz, $C_{quat.}$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, minor isomer): δ = 13.9 (CH_3), 16.2 (d, J = 6.29 Hz, CH_3), 16.3 (d, J = 6.1 Hz, CH_3), 33.4 (d, J = 3.4 Hz, CH_2), 34.4 (d, J = 3.2 Hz, CH_2), 57.9 (d, J = 137.9 Hz, $C_{quat.}$), 61.2 (CH), 63.3 (d, J = 7.4 Hz, OCH_2), 64.0 (d, J = 7.4 Hz, OCH_2), 114.5 (d, J = 8.47 Hz, CH_2), 128.3 (CH), 129.3 (CH), 133.8 (CH), 138.2 ($C_{quat.}$), 141.4 (d, J = 9.9 Hz, $C_{quat.}$), 168.1 (d, J = 3.6 Hz, $C_{quat.}$) ppm. HRMS (ESI): calcd. for $C_{19}H_{27}NaO_7PS$ [M + Na]$^+$ 453.1113; found 453.1114.

General Procedure for the Three-Component Reactions: In a round-bottomed flask, the nucleophile (2.5 equiv.) was deprotonated by NaH (60% oil dispersion, 2.3 equiv.) in dry THF (2.4 mL/mmol of NaH). Once the gaseous evolution stopped, the mixture was degassed by sparging with nitrogen. Aryl iodide (1.2 equiv.), CuI (0.06 equiv.) and $Pd(PPh_3)_4$ (0.03 equiv.) were then added, and the mixture was stirred at 50 °C. A solution of the Michael acceptor (1 equiv.) in THF (3 mL/mmol of acceptor) was then added over 2 h at 50 °C. Once the addition was complete, the mixture was heated for an additional 12 h at 50 °C. After filtration of the mixture through silica gel, the filtrate was concentrated under vacuum, and the crude material was purified by chromatography on silica gel with the appropriate solvent (see the details for each compound below).

(*E*)-1-Ethyl 3,3-Dimethyl 4-Benzylidenecyclopentane-1,3,3-tricarboxylate (10a): The reaction was performed with Michael acceptor **2a** (100 mg, 0.72 mmol). Purification by chromatography with petroleum ether/diethyl ether (8:2) containing 4% of Et_3N gave **10a** (200.5 mg, 80% yield) as a pale yellow oil. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.27 (t, J = 7.1 Hz, 3 H, CH_3), 2.52 (dd, J = 10.6 Hz, J = 13.0 Hz, 1 H, CH), 2.77 (m, 1 H, CH), 2.90–3.10 (m, 3 H, CH), 3.78 (s, 6 H, OCH_3), 4.16 (q, J = 7.1 Hz, 2 H, OCH_2), 6.74 (m, 1 H, CH), 7.25 (m, 1 H, CH), 7.32–7.35 (m, 4 H, CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.3 (CH_3), 35.3 (CH_2), 38.2 (CH_2), 42.9 (CH), 53.1 (OCH_3), 53.2 (OCH_3), 61.0 (OCH_2), 64.8 ($C_{quat.}$), 127.3 (CH), 128.4 (CH), 128.8 (CH), 128.9 (CH), 137.1 ($C_{quat.}$), 138.0 ($C_{quat.}$), 170.7 ($C_{quat.}$), 170.9 ($C_{quat.}$), 173.9 ($C_{quat.}$) ppm. HRMS (ESI): calcd. for $C_{19}H_{22}NaO_6$ $[M + Na]^+$ 369.1314; found 369.1313.

(*E*)-1-Ethyl 3,3-Dimethyl 4-(4-Methoxybenzylidene)cyclopentane-1,3,3-tricarboxylate (10b): The reaction was performed with Michael acceptor **2a** (100 mg, 0.72 mmol). Purification by chromatography with petroleum ether/diethyl ether (9:1) containing 4% of Et_3N gave **10b** (200 mg, 80% yield) as an orange oil. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.27 (t, J = 7.1 Hz, 3 H, CH_3), 2.50 (dd, J = 10.5 Hz, J = 13.1 Hz, 1 H, CH), 2.75 (ddd, J = 1.6 Hz, J = 6.1 Hz, J = 13.1 Hz, 1 H, CH), 2.97 (m, 3 H, CH), 3.77 (s, 6 H), 3.81 (s, 3 H, OCH_3), 4.17 (dq, J = 1.6 Hz, J = 7.1 Hz, 2 H, OCH_2), 6.67 (s, 1 H, CH), 6.88 (d, J = 8.8 Hz, 2 H, CH), 7.27 (d, J = 8.8 Hz, 2 H, CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.3 (CH_3), 35.2 (CH_2), 38.2 (CH_2), 42.9 (CH), 53.1 (OCH_3), 53.2 (OCH_3), 55.4 (OCH_3), 60.9 (OCH_2), 64.7 ($C_{quat.}$), 113.8 (CH), 128.2 (CH), 129.9 ($C_{quat.}$), 130.2 (CH), 135.7 ($C_{quat.}$), 158.8 ($C_{quat.}$), 170.9 5 ($C_{quat.}$), 171.0 ($C_{quat.}$), 174.0 ($C_{quat.}$) ppm. HRMS (ESI): calcd. for $C_{20}H_{24}NaO_7$ $[M + Na]^+$ 399.1420; found 399.1420.

(*E*)-1-Ethyl 3,3-Dimethyl 4-(3,4,5-Trimethoxybenzylidene)cyclopentane-1,3,3-tricarboxylate (10c): The reaction was performed with Michael acceptor **2a** (200 mg, 1.45 mmol). Purification by chromatography with petroleum ether/ethyl acetate (7:3) gave **10c** (585 mg, 92% yield) as a dark red oil. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.21 (t, J = 7.1 Hz, 3 H, CH_3), 2.47 (dd, J = 10.3 Hz, J = 13.1 Hz, 1 H, CH), 2.71 (m, 1 H, CH), 2.93 (m, 3 H, CH), 3.72 (s, 6 H, OCH_3), 3.78 (s, 3 H, OCH_3), 3.80 (s, 6 H, OCH_3), 4.10 (q, J = 7.1 Hz, 2 H, OCH_2), 6.49 (s, 2 H, CH), 6.61 (s, 1 H, CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (CH_3), 35.0 (CH_2), 38.0 (CH_2), 42.6 (CH), 53.0 (OCH_3), 53.1 (OCH_3), 56.1 (OCH_3), 60.8 (OCH_3), 64.6 (OCH_3), 106.0 (CH), 128.6 (CH), 132.7 ($C_{quat.}$), 137.2 ($C_{quat.}$), 137.3 ($C_{quat.}$), 149.8 ($C_{quat.}$), 152.9 ($C_{quat.}$), 170.5 ($C_{quat.}$), 170.7 ($C_{quat.}$), 173.7 ($C_{quat.}$) ppm. HRMS (ESI): calcd. for $C_{22}H_{28}NaO_9$ $[M + Na]^+$ 459.1631; found 459.1629.

(*E*)-1-Ethyl 3,3-Dimethyl 4-[4-(Methoxycarbonyl)benzylidene]cyclopentane-1,3,3-tricarboxylate (10d): The reaction was performed with Michael acceptor **2a** (200 mg, 1.45 mmol). Purification by chromatography with petroleum ether/ethyl acetate (85:15) gave **10d** (441 mg, 75% yield) as a dark red oil. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.27 (t, J = 7.1 Hz, 3 H, CH_3), 2.52 (ddd, J = 1.0 Hz, J = 9.0 Hz, J = 12.8 Hz, 1 H, CH), 2.78 (m, 1 H, CH), 3.00 (m, 3 H, CH), 3.79 (s, 6 H, OCH_3), 3.91 (s, 3 H, OCH_3), 4.16 (dq, J = 1.2 Hz, J = 7.1 Hz, 2 H, OCH_2), 6.78 (s, 1 H, CH), 7.38 (d, J = 8.4 Hz, 2 H, CH), 8.00 (d, J = 8.4 Hz, 2 H, CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.3 (CH_3), 35.4 (CH_2), 38.1 (CH_2), 42.8 (CH), 52.2 (OCH_3), 53.2 (OCH_3), 53.3 (OCH_3), 61.1 (OCH_2), 70.3 ($C_{quat.}$), 128.0 (CH), 128.6 (CH), 128.8 ($C_{quat.}$), 129.7 (CH), 140.7 ($C_{quat.}$), 141.6 ($C_{quat.}$), 166.9 ($C_{quat.}$), 170.4 ($C_{quat.}$), 170.6 ($C_{quat.}$), 173.8 ($C_{quat.}$) ppm. HRMS (ESI): calcd. for $C_{21}H_{24}NaO_8$ $[M + Na]^+$ 427.1369; found 427.1367.

(*E*)-1-Ethyl 3,3-Dimethyl 4-[4-(Trifluoromethyl)benzylidene]cyclopentane-1,3,3-tricarboxylate (10e): The reaction was performed with Michael acceptor **2a** (200 mg, 1.45 mmol). Purification by chromatography with petroleum ether/ethyl acetate (9:1) gave **10e** (332 mg, 55% yield) as a pale yellow oil. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.20 (t, J = 7.2 Hz, 3 H, CH_3), 2.50 (dd, J = 10.0 Hz, J = 12.8 Hz, 1 H, CH), 2.72 (m, 2 H, CH), 2.94 (m, 2 H, CH), 3.72 (s, 6 H, OCH_3), 4.10 (q, J = 7.2 Hz, 2 H, OCH_2), 6.75 (s, 1 H, CH), 7.39 (d, J = 7.5 Hz, 2 H, CH), 7.52 (d, J = 7.5 Hz, 2 H, CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.2 (CH_3), 35.2 (CH_2), 38.1 (CH_2), 42.7 (CH), 53.1 (OCH_3), 53.3 (OCH_3), 61.0 (OCH_2), 64.8 ($C_{quat.}$), 123.8 (dd, J = 241.2 Hz, J = 513.1 Hz, CF_3), 125.3 (q, J = 3.8 Hz, CH), 127.7 (CH), 128.9 ($C_{quat.}$), 140.6 (q, J = 1.4 Hz, CH), 140.8 ($C_{quat.}$), 146.0 ($C_{quat.}$), 170.4 ($C_{quat.}$), 170.5 ($C_{quat.}$), 173.6 ($C_{quat.}$) ppm. HRMS (ESI): calcd. for $C_{20}H_{21}F_3NaO_6$ $[M + Na]^+$ 415.1368; found 415.1368.

(*E*)-1-Ethyl 3,3-Dimethyl 4-(2-Phenylethylidene)cyclopentane-1,3,3-tricarboxylate (10f): The reaction was performed with Michael acceptor **2a** (150 mg, 1.1 mmol). Purification by chromatography with petroleum ether/diethyl ether (8:2) gave **10f** (196 mg, 50% yield) as an orange oil. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.33 (t, J = 7.1 Hz, 3 H, CH_3), 2.58 (dd, J = 11.1 Hz, J = 13.0 Hz, 1 H, CH), 2.68–2.95 (m, 3 H, CH), 3.07 (m, 1 H, CH), 3.49 (s, 1 H, CH), 3.51 (s, 1 H, CH), 3.79 (s, 6 H, OCH_3), 4.22 (q, J = 7.1 Hz, 2 H, OCH_2), 6.00 (m, J = 7.4 Hz, 1 H, CH), 7.24 (m, J = 1.6 Hz, 2 H, CH), 7.34 (m, J = 7.1 Hz, J = 7.8 Hz, 3 H, CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.2 (CH_3), 33.0 (CH_2), 35.6 (CH_2), 38.4 (CH_2), 41.8 (CH), 52.8 (OCH_3), 52.9 (OCH_3), 60.7 (CH_2), 63.4 ($C_{quat.}$), 126.0 (CH), 127.3 (CH), 128.2 (CH), 128.4 (CH), 137.6 ($C_{quat.}$), 139.8 ($C_{quat.}$), 170.6 ($C_{quat.}$), 170.9 ($C_{quat.}$), 173.9 ($C_{quat.}$) ppm. HRMS (ESI): calcd. for $C_{20}H_{24}O_6$ $[M + Na]^+$ 360.1573; found 360.1570.

(*E*)-Ethyl 4-Benzylidene-3-cyano-3-(phenylsulfonyl)cyclopentanecarboxylate (10g): The reaction was performed with Michael acceptor **2a** (100 mg, 0.48 mmol). THF/DMSO (2:1) was used instead of pure THF. Purification by chromatography with petroleum ether/ethyl acetate (8:2) afforded **10g** as a 0.45:1 mixture of diastereomers (143 mg, 50% yield) and as a brown oil. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.15 (t, J = 7.1 Hz, 1.35 H, CH_3), 1.19 (t, J = 7.1 Hz, 3 H, CH_3), 2.53 (dd, J = 5.8 Hz, J = 12.0 Hz, 1 H, CH), 2.63 (dd, J = 9.7 Hz, J = 14.9 Hz, 0.45 H, CH), 2.89–3.08 (m, 4.35 H, CH), 3.19 (ddd, J = 2.6 Hz, J = 9.5 Hz, J = 17.4 Hz, 1 H, CH), 3.53 (tt, J = 7.5 Hz, J = 9.6 Hz, 0.45 H, CH), 4.01 (dd, J = 6.2 Hz, J = 13.3 Hz, 1.0 H, 0.9 H, OCH_2), 4.11 (t, J = 7.1 Hz, 2 H, OCH_2), 6.24 (t, J = 2.5 Hz, 0.45 H, CH), 6.51 (s, 1 H, CH), 7.12–7.30 (m, 7.25 H, CH), 7.46–7.53 (m, 2.9 H, CH), 7.62–7.68 (m, 1.45 H, CH), 7.89–7.96 (m, 2.9 H, CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (14.1) [CH_3], 34.2 (34.1) [CH_2], 35.5 (35.5) [CH_2], 42.7 (42.2)

[CH], 61.4 (61.3) [OCH_2], 70.2 (71.9) [$C_{quat.}$], 117.0 (116.8) [CN], 128.5 (128.6) [CH], 128.6 (128.6) [CH], 129.1 (129.0) [CH], 129.2 (129.1) [CH], 131.0 (131.1) [CH], 132.8 (132.6) [$C_{quat.}$], 133.1 (133.2) [$C_{quat.}$], 133.4 (133.3) [CH], 135.0 (134.9) [$C_{quat.}$], 135.3 (135.2) [CH], 171.8 (173.0) [$C_{quat.}$] ppm. HRMS (ESI): calcd. for $C_{22}H_{21}NNaO_4S$ $[M + Na]^+$ 418.1089; found 418.1089.

(*E*)-Dimethyl 2-Benzylidene-4-(phenylsulfonyl)cyclopentane-1,1-dicarboxylate (10h): The reaction was performed with Michael acceptor **2b** (300 mg, 2.2 mmol). Purification by chromatography with petroleum ether/ethyl acetate (8:2) gave **10h** (427 mg, 71% yield) as a brown oil. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.6 (d, J = 10 Hz, 1 H, CH), 2.95 (ddd, J = 1.3 Hz, J = 7.7 Hz, J = 16.5 Hz, 1 H, CH), 3.11 (ddd, J = 3.1 Hz, J = 10 Hz, J = 16.5 Hz, 1 H, CH), 3.66 (s, 3 H, OCH_3), 3.69 (m, 1 H, CH), 3.71 (s, 3 H, OCH_3), 6.73 (t, J = 1.9 Hz, 1 H, CH), 7.16–7.23 (m, 3 H, CH), 7.27 (m, 2 H, CH), 7.50 (m, 1 H, CH), 7.60 (m, 2 H, CH), 7.85 (m, 2 H, CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 32.0 (CH_2), 35.3 (CH_2), 53.2 (OCH_3), 53.3 (OCH_3), 62.1 ($C_{quat.}$), 64.1 (CH), 127.5 (CH), 128.3 (CH), 128.4 (CH), 128.6 (CH), 129.4 (CH), 129.9 (CH), 134.0 (CH), 134.9 ($C_{quat.}$), 136.3 ($C_{quat.}$), 138.1 ($C_{quat.}$), 169.5 ($C_{quat.}$), 170.2 ($C_{quat.}$) ppm. HRMS (ESI): calcd. for $C_{22}H_{22}NaO_6S$ $[M + Na]^+$ 437.1035; found 437.1034.

(*E*)-Dimethyl 2-(3,4,5-Trimethoxybenzylidene)-4-(phenylsulfonyl)cyclopentane-1,1-dicarboxylate (10i): The reaction was performed with Michael acceptor **2b** (200 mg, 1 mmol). Purification by chromatography with petroleum ether/ethyl acetate (7:3) gave **10i** (319 mg, 65% yield) as a brown oil. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.64 (d, J = 9.1 Hz, 2 H, CH), 2.88 (dd, J = 7.1 Hz, J = 16.5 Hz, 1 H, CH), 3.07 (ddd, J = 2.9 Hz, J = 10.4 Hz, J = 16.2 Hz, 1 H, CH), 3.67 (s, 3 H), 3.70 (m, 1 H, CH), 3.72 (s, 3 H), 3.74 (pseudo-s, 9 H, OCH_3), 6.40 (s, 2 H, CH), 6.65 (s, 1 H, CH), 7.49 (t, J = 7.5 Hz, 1 H, CH), 7.59 (t, J = 7.4 Hz, 1 H, CH), 7.84 (d, J = 7.3 Hz, 1 H, CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 32.4 (CH_2), 34.6 (CH_2), 53.0 (OCH_3), 53.2 (OCH_3), 55.8 (OCH_3), 60.6 (OCH_3), 61.9 (OCH_3), 63.9 ($C_{quat.}$), 105.7 (CH), 128.0 (CH), 129.2 (CH), 129.6 (CH), 131.8 ($C_{quat.}$), 133.9 (CH), 134.1 ($C_{quat.}$), 137.3 ($C_{quat.}$), 138.0 ($C_{quat.}$), 152.8 ($C_{quat.}$), 169.3 ($C_{quat.}$), 169.9 ($C_{quat.}$) ppm.

(*E*)-Dimethyl 2-[4-(Methoxycarbonyl)benzylidene]-4-(phenylsulfonyl)-cyclopentane-1,1 dicarboxylate (10j): The reaction was performed with Michael acceptor **2b** (200 mg, 1 mmol). Purification by chromatography with petroleum ether/ethyl acetate (7:3) gave **10j** (325 mg, 71% yield) as an orange oil. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.62 (d, J = 9.0 Hz, 2 H, CH), 2.92 (m, 1 H, CH), 3.15 (ddd, J = 2.3 Hz, J = 10.1 Hz, J = 16.2 Hz, 1 H, CH), 3.68 (s, 3 H, OCH_3), 3.70 (m, 1 H, CH), 3.73 (s, 3 H, OCH_3), 3.84 (s, 3 H, OCH_3), 6.79 (s, 1 H), 7.28 (d, J = 8.3 Hz, 2 H), 7.56 (td, J = 7.1 Hz, J = 14.8 Hz, 3 H), 7.85 (d, J = 7.6 Hz, 2 H), 7.94 (d, J = 7.6 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 32.0 (CH_2), 35.0 (CH_2), 52.0 (OCH_3), 53.2 (OCH_3), 53.3 (OCH_3), 61.9 (CH), 64.1 ($C_{quat.}$), 128.2 (CH), 128.4 (CH), 128.9 (CH), 129.4 (CH), 129.5 (CH), 134.0 (CH), 137.4 ($C_{quat.}$), 137.9 ($C_{quat.}$), 140.6 ($C_{quat.}$), 166.4 ($C_{quat.}$), 169.1 ($C_{quat.}$), 169.8 ($C_{quat.}$) ppm.

Acknowledgments

N. C. wishes to thank the Ministère de l'Education Nationale, de la Recherche et de la Technologie for a fellowship.

[1] For selected references, see:a) B. M. Trost, A. B. Pinkerton, *J. Org. Chem.* **2001**, *66*, 7714; b) D. F. Taber, H. Yu, C. D. Incarvito, A. L. Rheingold, *J. Am. Chem. Soc.* **1998**, *120*, 13285; c) G. A. Molander, E. D. Dowdy, H. Schumann, *J. Org. Chem.* **1998**, *63*, 3386; d) A. Hassner, E. Ghera, T. Yechezkel, V. Kleiman, T. Balasubramanian, D. Ostercamp, *Pure Appl. Chem.* **2000**, *72*, 1671; e) M. Mikolajczyk, M. Mikina, R. Zurawinski, *Pure Appl. Chem.* **1999**, *71*, 473.

[2] a) Palladium-catalyzed: N. Monteiro, J. Gore, G. Balme, *Tetrahedron* **1992**, *48*, 10103; b) Molybdenum-catalyzed: F. E. McDonald, T. C. Olson, *Tetrahedron Lett.* **1997**, *38*, 7691; c) Cobalt/light-catalyzed: J.-L. Renaud, C. Aubert, M. Malacria, *Tetrahedron* **1999**, *55*, 5113; d) Gold(I)-catalyzed: J. Kennedy-Smith, S. T. Staben, F. D. Toste, *J. Am. Chem. Soc.* **2004**, *126*, 4526; e) Rhenium-catalyzed: Y. Kuninobu, A. Kawata, K. Takai, *Org. Lett.* **2005**, *7*, 4823; f) Nickel(II)-catalyzed: Q. Gao, B.-F. Zheng, J.-H. Li, D. Yang, *Org. Lett.* **2005**, *7*, 2185.

[3] D. Bouyssi, N. Monteiro, G. Balme, *Tetrahedron Lett.* **1999**, *40*, 1297.

[4] Only a few [4+1] annulation strategies have been reported. For example, see:a) J. L. Loebach, D. M. Bennet, R. L. Danheiser, *J. Am. Chem. Soc.* **1998**, *120*, 9690; b) T. Hudlicky, M. G. Natchus, G. Sinai-Zingde, *J. Org. Chem.* **1987**, *52*, 4641; c) K. Takasu, H. Ohsato, J.-I. Kuroyanagi, M. Ihara, *J. Org. Chem.* **2002**, *67*, 6001; d) M. Murakami, K. Itami, Y. Ito, *J. Am. Chem. Soc.* **1999**, *121*, 4130; e) S. V. Gagnier, R. C. Larock, *J. Am. Chem. Soc.* **2003**, *125*, 4804.

[5] a) V. T. Ravikumar, S. Swaminathan, K. Rajagopalan, *Tetrahedron Lett.* **1984**, *25*, 6045; b) R. Gueignec, B. Kirschleger, F. Lambert, M. Aboutaj, *Synth. Commun.* **1988**, *18*, 1213.

[6] A similar demethoxycarbonylation was recently observed during a Pd-catalyzed tandem cyclization-coupling reaction of conjugated enynes bearing a methyl cyanoacetate as the nucleophile. See: T. Lomberget, D. Bouyssi, G. Balme, *Synlett* **2002**, 1439.

[7] N. Monteiro, G. Balme, J. Gore, *Synlett* **1992**, 227.

[8] Y. Fu, L. G. J. Hammarström, T. J. Miller, F. R. Fronczek, M. L. McLaughlin, R. P. Hammer, *J. Org. Chem.* **2001**, *66*, 7118.

[9] For reviews on the chemistry of sulfones:a) S. Patai, Z. Rappoport, C. Stirling in *The Chemistry of sulfones and sulfoxides*, Wiley, Chichester, **1988**; b) B. M. Trost, *Bull. Chem. Soc. Jpn.* **1988**, *61*, 107; c) N. S. Simpkins in *Sulfones in Organic Synthesis*, Pergamon Press, Oxford, **1993**; d) S. Patei, Z. Rappoport in *The Synthesis of sulfones, Sulfoxides and Cyclic Sulphides*, Wiley, Chichester, **1994**; e) C. M. Rayner, *Contemp. Org. Synth.* **1994**, *1*, 191; f) C. M. Rayner, *Contemp. Org. Synth.* **1995**, *2*, 409; g) C. M. Rayner, *Contemp. Org. Synth.* **1996**, *3*, 499; h) R. Chinchilla, C. Nájera, *Recent Res. Devel. Org. Chem.* **1997**, *1*, 437; i) Nájera, J. M. Sansano, *Recent Res. Devel. Org. Chem.* **1998**, *2*, 637; j) C. Nájera, M. Yus, *Tetrahedron* **1999**, *55*, 10547; k) E. N. Prilezhaeva, *Russ. Chem. Rev.* **2000**, *69*, 367.

[10] a) G. Balme, D. Bouyssi, T. Lomberget, N. Monteiro, *Synthesis* **2003**, 2115; b) G. Balme, E. Bossharth, N. Monteiro, *Eur. J. Org. Chem.* **2003**, 4101; c) G. Balme, D. Bouyssi, N. Monteiro, in *Handbook of Organopalladium Chemistry for Organic Synthesis* (Ed.: E.-I. Negishi), Wiley, New York, **2002**, vol. 2, pp. 2245–2265; d) G. Balme, D. Bouyssi, N. Monteiro, *Pure Appl. Chem.* **2006**, *78*, 231.

[11] We have already reported the high efficiency of this Pd^0 source in a related cyclisation-coupling reaction; see: M. Bottex, M. Cavicchioli, B. Hartmann, N. Monteiro, G. Balme, *J. Org. Chem.* **2001**, *66*, 175.

[12] D. Bouyssi, G. Balme, J. Gore, *Tetrahedron Lett.* **1991**, *32*, 6541.

[13] A subsequent control experiment revealed that treatment of the preformed enolate of **1a** with 1 equiv. of NaH with benzyl chloride in THF at 50 °C for 7 h led mainly to the recovery of unreacted substrates.

Received: March 6, 2007
Published Online: May 22, 2007

