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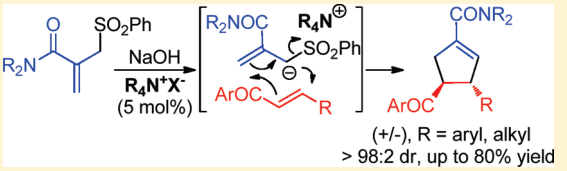
Highly Regio- and Diastereoselective Anionic [3 + 2] Cycloaddition under Phase Transfer Catalytic Conditions

Vincent Gembus, Svetlana Postikova, Vincent Levacher, and Jean-François Brière*

CNRS UMR COBRA, Université et INSA de Rouen, FR INC3M 3038, IRCOF (Research Institute in Fine Organic Chemistry), rue Tesnière, 76821 Mont Saint Aignan cedex, France

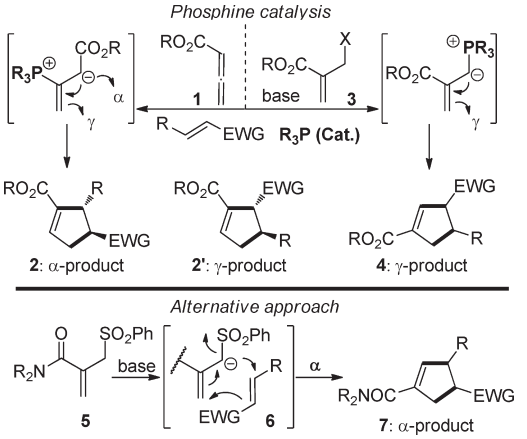
Supporting Information

ABSTRACT: A highly *trans* and regioselective anionic formal [3 + 2] cycloaddition was achieved with allylic sulfones having an MBH acrylamide backbone under phase transfer organocatalytic conditions giving rise to the formation of unprecedented densely substituted cyclopentene derivatives.



The regio- and stereoselective syntheses of chiral cyclopentenes and cyclopentane derivatives thereof have given rise to a great deal of research activity due to their presence within biologically relevant architectures.[1] The phosphine promoted [3 + 2] cycloaddition from β-substituted electron-poor alkenes emerged as a valuable organocatalytic methodology for the construction of such five-membered rings (Scheme 1).[2] In line with the so-called Lu's reaction,[2,3] starting from allenic esters **1**, several research teams achieved efficient diastereo- and enantioselective elaborations of cyclopentenes **2**. Interestingly, the regioselectivity outcome giving **2** versus **2′** (α- vs γ-addition pathway) could be controlled by the nature of phosphine catalyst.[4] To a lesser extent, the synthesis of a second class of cyclopentene regioisomer **4** was developed *via* a formal cycloaddition process involving Morita−Baylis−Hillman (MBH)[5] adducts **3** as starting material and a base through a γ-addition pathway.[2,6] However, the access to the third class of cyclopentene regioisomer **7** is rare. Only recently, Martín, García Ruano, and co-workers,[7] by means of allenylsulfones instead of allenylesters **1**, elegantly highlighted an abnormal regioselectivity of the Lu's [3 + 2] cycloaddition giving rise to bicylic derivatives **7** from chiral 5-alkoxyfuran-2(5*H*)-ones.[8] Alternatively, Beak and Burg pioneered in the 1980s a [3 + 2] annulation cascade on terminal enones **6** (R = H) triggered by the deprotonation of allylic sulfones of type **5** with a stoichiometric amount of lithium amides at low temperature (Scheme 1).[9] The electron-poor nature of the sulfone functional group secured both regioselective α-functionalization through an α-addition pathway and the cyclization step (S_N2' mechanism).[10] Unfortunately, these elegant stoichiometric annulations reaction conditions did not proceed with the less reactive β-substituted electron-deficient alkenes **6** and, hence, the regio- (α- vs γ-addition pathway) and diastereoselectivity outcomes (**7** with R ≠ H) have still to be addressed.[11] Then, we hypothesized that practical phase transfer catalytic (PTC)[12] conditions, although sparingly studied with allylic sulfones,[13,14] might overcome these limitations for the following reasons: (1) by generating a small amount of allylic anion nucleophile at higher temperature by an extractive process (biphasic system), preventing thereby the early decomposition of sulfones **5**, which are sensitive to polymerization; and (2) by forming a reactive "naked" anion having a large ammonium counterion showing an enhance reactivity during both the conjugated addition and the cyclization events in this likely stepwise process.[9]

Scheme 1. Formal [3 + 2] Cycloaddition



At the onset, we prepared allylic sufone starting materials **5a** and **5b**, making use of a straightforward MBH reaction/bromination sequence from commercially available acrylamides followed by a smooth addition reaction of $PhSO_2Na$ to the obtained allylic bromide intermediate (Scheme 2).[15]

Then, to our delight (Table 1, entries 2), a mixture of allylic sulfone **5a** and chalcone **6a** under the required (entry 1) phase transfer catalytic conditions (Cs_2CO_3 and *n*-Bu_4NBr, rt)

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Scheme 2. Formal [3 + 2] Cycloaddition

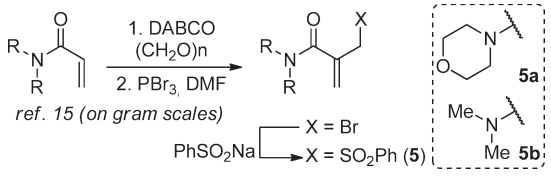
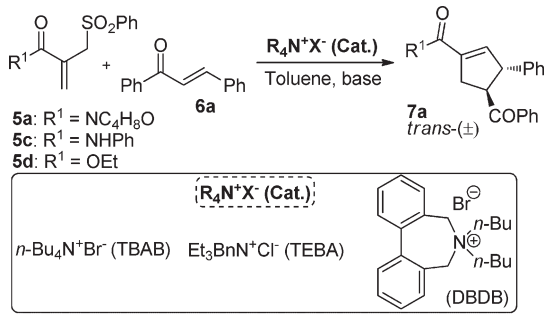


Table 1. Optimization of Reaction Conditions[a]

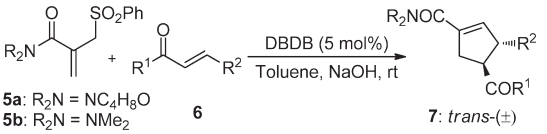


entry	sulfone	R_4NX	base	time (h)	yield (%)[b]	dr[d]
1	**5a**		Cs_2CO_3	15	0	
2	**5a**	TBAB (10)[e]	Cs_2CO_3	24	60	>98:2
3	**5c**	TBAB (10)[e]	NaOH	24	0	
4	**5d**	TBAB (10)[e]	NaOH	24	0	
5	**5a**	TBAB (10)[e]	NaOH	2	63	>98:2
6	**5a**	TEBA (10)[e]	NaOH	0.5	68	>98:2
7	**5a**	TEBA (10)[e]	NaOH	0.5	80[c]	>98:2
8	**5a**	DBDB (10)[e]	NaOH	0.5	88[c]	>98:2
9	**5a**	DBDB (5)[e]	NaOH	0.5	83[c]	>98:2

[a] Chalcone (1 equiv), allylic sulfone (1 equiv), base (2 equiv), toluene (0.2 M), rt. [b] NMR yield estimated by an internal standard. [c] 1.25 equiv of allylic sulfone **5a**. [d] *trans*:*cis* ratio determined on the basis of the ^{1}H NMR of the crude product. [e] Mole percent.

furnished the corresponding cyclopentene **7a** in 60% yield as one regioisomer and more than 98:2 diastereoisomeric ratio with respect to the crude ^{1}H NMR spectrum accuracy (see Supporting Information for further information). After purification by silica gel column chromatography, we were able to isolate only one stereoisomer beside polymers. The PTC approach not only provides user-friendly (tolerant of oxygen and moisture) and organocatalytic conditions for this undeveloped reaction[16] but also opens an entry to the regio- and *trans*-selective construction of novel cyclopentenes **7**. Further experiment demonstrated that the use of tertiary acrylamides was crucial for the success of this process considering that secondary acrylamide **5c** (entry 3) or acrylate **5d** (entry 4) decomposed before reacting with the enone **6a**.[17] It was found that stronger sodium hydroxide base reduced the reaction time (entry 2 vs 5). Furthermore, the use of an ammonium salt bearing a *N*-benzyl moiety like TEBA (entries 6) accelerated the reaction rate to afford a slightly improved yields of 68% within 30 min. In general, it was observed that the allylic sulfone **5a** partly polymerized instead of reacting completely with the remaining chalcone. Consequently, the use of sulfone **5a** in slight excess (1.25 equiv) with TEBA catalyst improved the yield to 80% (entry 7). Eventually, it was found that the readily

Table 2. Scope of the Reaction[a]



entry	sulfone	R^1	R^2	time (h)	yield (%)[b]	dr[c]
1	**5a**	Ph	Ph	2	80 (**7a**)	>98:2
2	**5d**	Ph	Ph	7	78 (**7b**)	>98:2
3	**5a**	4-ClC_6H_4	Ph	7	61 (**7c**)	>98:2
4	**5a**	4-$MeOC_6H_4$	Ph	8	69 (**7d**)	>98:2
5	**5a**	4-MeC_6H_4	Ph	24	63 (**7e**)	>98:2
6	**5a**	2-thienyl	Ph	4.5	66 (**7f**)	>98:2
7	**5a**	4-$NO_2C_6H_4$	Ph	4	67 (**7g**)[d]	>98:2
8	**5a**	Ph	4-ClC_6H_4	2.5	63 (**7h**)	>98:2
9	**5a**	Ph	4-$MeOC_6H_4$	24	66 (**7i**)	>98:2
10	**5a**	Ph	3-$MeOC_6H_4$	8.5	77 (**7j**)	>98:2
11	**5a**	Ph	2-MeC_6H_4	2	71 (**7k**)	>98:2
12	**5a**	Ph	*n*-pentyl	7	70 (**7l**)	>98:2
13	**5a**	OMe	Ph	24	0	
14	**5a**	OMe	H	24	0	

[a] Chalcone (0.5 mmol), allylic sulfone (1.25 equiv), NaOH (2 equiv), toluene (0.2 M), rt. [b] Isolated yield after silica gel column chromatography. [c] *trans*:*cis* ratio determined on the ^{1}H NMR of the crude product. [d] A mixture of toluene/THF (2:1) was used to solubilize the nitrochalcone.

available dibenzepinium catalyst DBDB was somewhat more efficient (entry 8) and allowed reduction of the amount of catalyst to 5 mol % (entry 9) while maintaining good catalytic performances.[18]

We selected these last conditions with 5 mol % of DBDB catalyst in order to probe the scope of this reaction (Table 2). The formal [3 + 2] cycloaddition was achieved with chalcone **6a** and acrylamides bearing either a morpholine **5a** or a dimethylamine moiety **5b** with 80% and 78% isolated yields, respectively (entries 1 and 2), allowing the introduction of chemical diversity on the amide part. Various chalcones **6** with electron-withdrawing (entries 3, 7−8) and electron-donating functional groups at *ortho*, *meta*, and *para* positions (entries 4, 5, and 9−11), together with heteroaromatic ring (entries 6) were transformed with 61% to 77% yields. An enone having an alkyl pendant underwent a smooth transformation into cyclopentene **7l** allowing the introduction of an alkyl group at C3 position (entry 12). In all cases, more than 98:2 *trans*:*cis* ratio was measured by ^{1}H NMR of the crude product. The PTC conditions were not capable of giving any product with acrylate showing a complementary reactivity profile to lithium allylic anion with unsaturated esters (entries 13 and 14).[9]

Then, the usefulness of these new cyclopentenes has valuable building blocks was investigated in a two-step sequence (Scheme 3). First of all, a chemo- and a highly diastereoselective reduction of **7c** into alcohol **8** was achieved with superhydride reductant. Next, the amide moiety underwent a selective 1,2-nucleophilic addition by phenyllithium afforded product **9**, showing thereby the ability of the morpholine amide moiety to serve as a ketone precursors. Pleasingly, the alcohol **8** was suited for X-ray crystal structure determination, providing an ultimate proof of the relative configuration of our five-membered ring structures (see Supporting Information).

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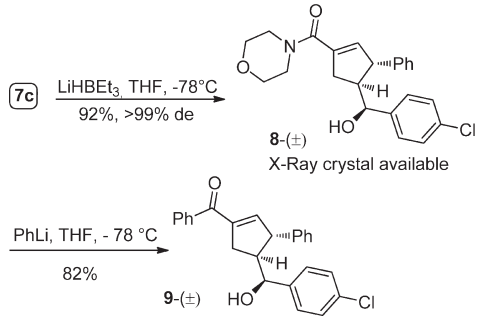
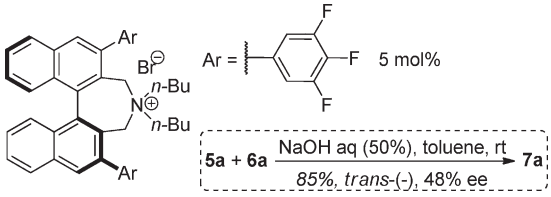
Scheme 3. Chemical Transformations of Cyclopentenes



Scheme 4. First Asymmetric Development with Maruoka's Catalyst



With these efficient diastereoselective PTC conditions in hands we were curious whether an enantioselective version would be feasible.[13,16] This would offer novel opportunities for the use of allylic sulfone **5** as a 3C allylic building block into asymmetric organocatalytic reactions. After some investigations (Scheme 4), we found that 4 mol % of the powerful Maruoka's catalyst[12a,b] effected a smooth stereoselective transformation of chalcone **6a** into the corresponding nonracemic cyclopentene **7a**, albeit in modest ee.[19] However, this promising result suggests that an enantioselective process should be allowed by means of better suited phase transfer catalysts.

In conclusion, the modified Beak's anionic [3 + 2] cycloaddition, under organocatalytic conditions, extended the methodology to β-enones leading to straightforward syntheses of unprecedented densely substituted cyclopentenes with high regio- and diastereoselectivity. This study also highlighted a significant rate acceleration under phase transfer catalytic conditions paving the way for asymmetric developments by means of suited chiral ammonium salts faced to allylic sulfone anions.

EXPERIMENTAL SECTION

The chalcones are commercially available or synthesized with respect to a literature procedure.[20]

Representative Procedure for the Synthesis of Allylic Sulfones 5. To a stirred solution of allylic bromide (see Scheme 1) derived from acrylamide[15] (9.8 mmol) in anhydrous methanol (5 mL) was added the sodium salt of benzenesulfinic acid (1.936 mg, 11.8 mmol). The mixture was heated in reflux for 2 h. After cooling, the mixture was concentrated *in vacuo*, and the residue was purified by flash column chromatography to furnish the corresponding sulfone.

1-Morpholino-2-(phenylsulfonylmethyl)prop-2-en-1-one ***5a***. Colorless viscous oil (567 mg, 92%); R_f = 0.18 (petroleum ether/EtOAc 1/2); IR (KBr) ν_{max} 1642, 1614, 1469, 1445, 1306, 1209, 1152, 1112, 1086, 1033 cm^{-1}; ^{1}H NMR (300 MHz; $CDCl_3$) δ 7.93−7.89 (2 H, m), 7.71−7.54 (3 H, m), 5.62 (1 H, s), 5.50 (1 H, s), 4.15 (2 H, d, J = 0.9 Hz), 3.71 (8 H, br s); ^{13}C NMR (75.4 MHz; $CDCl_3$) δ 168.2 (C), 139.2 (C), 134.2 (CH), 130.6 (C), 129.5 (C), 128.0 (C), 125.1 (CH_2), 66.8 (CH_2), 60.6 (CH_2), 48.5 (CH_2), 42.6 (CH_2); HRMS (ESI+) calcd for $C_{14}H_{18}NO_4S$ [M + H$^+$] 296.0957, found 296.0950.

N,N-Dimethyl-2-(phenylsulfonylmethyl)acrylamide ***5b***. Pale yellow solid (484.1 mg, 95%); mp = 105−107 °C; R_f = 0.15 (petroleum ether/EtOAc 1/2); IR (KBr) ν_{max} 1639, 1608, 1503, 1446, 1397, 1302, 1181, 1137, 1071, 961, 911, 770 cm^{-1}; ^{1}H NMR (300 MHz; $CDCl_3$) δ 7.92−7.87 (2 H, m), 7.68−7.62 (1 H, m), 7.59−7.52 (2 H, m), 5.61 (1 H, s), 5.49 (1 H, s), 4.17 (2 H, d, J = 0.7 Hz), 3.11 (3 H, br s), 2.89 (3 H, br s); ^{13}C NMR (75.4 MHz; $CDCl_3$) δ 169.0 (C), 139.2 (C), 134.0 (CH), 131.3 (C), 129.3 (CH), 128.1 (CH), 125.1 (C), 60.6 (CH_2), 39.6 (CH_2), 35.3 (CH_2); HRMS (ESI+) calcd for $C_{12}H_{16}NO_3S$ [M + H$^+$] 254.0851, found 254.0845.

6,6-Dibutyl-6,7-dihydro-5H-dibenzo[c,e]azepinium bromide (DBDB, Table 1). To a solution of 2,2′-bis(bromomethyl)-1,1′-biphenyl (340.1 mg, 1 mmol) in anhydrous CH_3CN (10 mL) were added *n*-Bu_2NH (0.17 mL, 1 mmol) and K_2CO_3 (691 mg, 5 mmol) at room temperature. After stirring at 80 °C for 15 h, the resulting mixture was cooled to room temperature and filtered through a pad of Celite with CH_2Cl_2. The filtrate was concentrated, and the crude solid was purified by precipitation (CH_2Cl_2/pentane) to give the ammonium salt (369 mg, 95%) as a white solid; mp = 165−167 °C; IR (KBr) ν_{max} 2970, 2947, 2874, 1474, 1452, 1379, 887, 795, 764 cm^{-1}; ^{1}H NMR (300 MHz; $CDCl_3$) δ 7.87 (2 H, d, J = 7.1 Hz), 7.69−7.52 (6 H, m), 4.89 (2 H, br s), 3.67 (6 H, br s), 1.94 (4 H, br s), 1.55−1.42 (4 H, m), 1.02 (6 H, t, J = 7.3 Hz); ^{13}C NMR (75.4 MHz; $CDCl_3$) δ 140.7 (C), 132.6 (CH), 131.2 (CH), 129.1 (CH), 128.4 (CH), 127.4 (C), 62.5 (CH_2), 58.9 (CH_2), 24.5 (CH_2), 19.9 (CH_2), 13.6 (CH_3); HRMS (ESI+) calcd for $C_{22}H_{30}N$ [M + H$^+$] 308.2378, found 308.2370.

Representative Procedure for the Formal [3 + 2] Cycloaddition (Table 2). To a stirred solution of sulfone **5** (0.625 mmol) and a chalcone (0.50 mmol) in toluene (2.5 mL) were added the ammonium salt catalyst (0.025 mmol) and pilled sodium hydroxide (40.0 mg, 1 mmol). The resulting mixture was vigorously stirred at room temperature until the disappearance of sulfone starting material on TLC. The mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were washed with water (2×) and brine and dried over $MgSO_4$. After filtration, the filtrate was concentrated *in vacuo* and purified by flash column chromatography on silica gel to furnish the corresponding cyclopentene as described in the following characterizations. *Remark*: the obtained oils tend to retain solvents such as AcOEt or CH_2Cl_2, so they have to be dried for a long period of time under vacuum.

Procedure for the asymmetric synthesis of cyclopentene 7a (Scheme 4). To a mixture of chalcone **6a** (20.8 mg, 0.1 mmol), sulfone **5a** (29.5 mg, 0.1 mmol), and Maruoka's ammonium salt (3.0 mg, 0.004 mmol) in toluene (500 μL) was added 50 μL of 50% NaOH aqueous solution. The heterogeneous solution was vigorously stirred for 2 h at room temperature. The mixture was diluted with water, and the organic layer was separated. The aqueous phase was extracted with ethyl acetate. Then, the combined organic layers were washed with water (2×) and brine and dried over $MgSO_4$. After filtration, the filtrate was concentrated *in vacuo* and purified by flash column chromatography (silica gel, petroleum ether/ethyl acetate) to afford **7a** (30.7 mg, 85% yield, 48% ee) as a colorless viscous oil. The ee of product **7a** was determined by HPLC analysis with a Chiralcel IA column, in a mixture of isopropyl alcohol/heptane (15/85), 1.0 mL per min, 230 nm giving 14.3 min (minor enantiomer), 17.6 min (major enantiomer).

*(4-Benzoyl-3-(3-methoxyphenyl)cyclopent-1-enyl)(morpholino)-methanone (****7a****).* Reaction time: 2 h; colorless viscous oil (144.4 mg, 80%); R_f = 0.39 (petroleum ether/EtOAc 1/1); IR (KBr) ν_{max} 3059, 2958, 2921, 2852, 1681, 1611, 1492, 1430, 1360, 1300, 1275, 1250, 1113, 1008 cm^{-1}; ^{1}H NMR (300 MHz; $CDCl_3$) δ 7.87−7.84 (2 H, m), 7.58−7.52 (1 H, m), 7.45−7.40 (2 H, m), 7.35−7.20 (5 H, m), 5.86 (1 H, dd, J = 4.1 Hz and J = 1.9 Hz), 4.52−4.49 (1 H, m), 4.08

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(1 H, dt, J = 9.6 Hz and J = 5.8 Hz), 3.70 (8 H, br s), 3.37−3.26 (1 H, m), 2.99−2.90 (1 H, m); ^{13}C NMR (75.4 MHz; $CDCl_3$) δ 200.0 (C), 167.0 (C), 143.0 (C), 136.6 (C), 135.8 (C), 134.0 (CH), 133.4 (CH), 129.0 (CH), 128.8 (CH), 128.7 (CH), 127.6 (CH), 127.2 (CH), 67.0 (CH_2), 54.7 (CH), 53.9 (CH), 47.6 (CH_2), 42.1 (CH_2), 38.5 (CH_2); HRMS (ESI+) calcd for $C_{23}H_{24}NO_3$ [M + H^+] 362.1756, found 362.1747.

*4-Benzoyl-N,N-dimethyl-3-phenylcyclopent-1-enecarboxamide (**7b**).* Reaction time: 7 h; colorless viscous oil (125.0 mg, 78%); R_f = 0.20 (petroleum ether/EtOAc 1/2); IR (KBr) ν_{max} 3054, 2924, 1680, 1614, 1492, 1448, 1396, 1243, 1182 cm^{-1}; ^{1}H NMR (300 MHz; $CDCl_3$) δ 7.87−7.85 (2 H, m), 7.58−7.52 (1 H, m), 7.45−7.40 (2 H, m), 7.35−7.22 (5 H, m), 5.91 (1 H, dd, J = 4.1 Hz and J = 1.9 Hz), 4.62−4.58 (1 H, m), 4.09 (1 H, dt, J = 12.2 Hz and J = 6.2 Hz), 3.38−3.28 (1 H, m), 3.18 (3 H, br s), 3.03 (3 H, br s), 2.98−2.90 (1 H, m); ^{13}C NMR (75.4 MHz; $CDCl_3$) δ 199.9 (C), 168.0 (C), 143.2 (C), 137.0 (C), 135.9 (C), 134.0 (CH), 133.2 (CH), 128.8 (CH), 128.7 (CH), 128.6 (CH), 127.6 (CH), 127.0 (CH), 54.3 (CH), 54.1 (CH), 38.8 (CH_3), 38.6 (CH_2), 35.0 (CH_3); HRMS (ESI+) calcd for $C_{21}H_{22}NO_2$ [M+H]+: 320.1651, found 320.1634.

*[4-(4-Chlorobenzoyl)-3-phenyl-1-cyclopenten-1-yl](4-morpholinyl) methanone (**7c**).* Reaction time: 7 h; viscous yellow oil (120 mg, 61%); R_f = 0.45 (petroleum ether/EtOAc 1/2); IR (KBr) ν_{max} 1681, 1611, 1431, 1360, 1275, 1253, 1114, 1091, 1011 cm^{-1}; ^{1}H NMR (300 MHz; $CDCl_3$) δ 7.80−7.75 (2 H, m), 7.41−7.36 (2 H, m), 7.35−7.27 (3 H, m), 7.21−7.17 (2 H, m), 5.83 (1 H, dd, J = 4.2 Hz and J = 1.9 Hz), 4.47−4.43 (1 H, m), 4.03 (1 H, dt, J = 9.4 Hz and J = 5.7 Hz), 3.70 (8 H, br s), 3.34−3.23 (1 H, m), 3.00−2.91 (1 H, m); ^{13}C NMR (75.4 MHz; $CDCl_3$) δ 198.8 (C), 166.9 (C), 142.8 (C), 140.0 (C), 136.7 (C), 134.2 (C), 133.9 (CH), 130.3 (CH), 129.1 (CH), 127.7 (CH), 127.4 (CH), 67.1 (CH_2), 54.9 (CH), 54.0 (CH), 47.5 (CH2), 42.4 (CH2), 38.4 (CH_2); HRMS (ESI+) calcd for $C_{23}H_{23}ClNO_3$ [M + H]$^+$ 396.1366, found 396.1350.

*[4-(4-Methoxybenzoyl)-3-phenyl-1-cyclopenten-1-yl](4-morpholinyl) methanone (**7d**).* Reaction time: 8 h; viscous oil (122 mg, 61%); R_f = 0.33 (petroleum ether/EtOAc 1/2); IR (KBr) ν_{max} 1674, 1600, 1511, 1432, 1361, 1252, 1170, 1113, 1020 cm^{-1}; ^{1}H NMR (300 MHz; $CDCl_3$) δ 7.87−7.82 (2 H, m), 7.36−7.27 (3 H, m), 7.25−7.21 (2 H, m), 6.93−6.88 (2 H, m), 5.86 (1 H, dd, J = 4.2 Hz and J = 2.1 Hz), 4.52−4.48 (1 H, m), 4.06 (1 H, dt, J = 9.4 Hz and J = 5.7 Hz), 3.86 (3 H, s), 3.71 (8 H, br s), 3.35−3.25 (1 H, m), 3.00−2.92 (1 H, m); ^{13}C NMR (75.4 MHz; $CDCl_3$) δ 198.5 (C), 167.0 (C), 163.7 (C), 143.1 (C), 136.7 (C), 133.9 (C), 131.0 (CH), 128.86 (CH), 128.78 (CH), 127.6 (CH), 127.1 (CH), 113.8 (CH), 66.9 (CH_2), 55.5 (CH_3), 54.9 (CH), 53.5 (CH), 47.3 (CH_2); 42.2 (CH_2); 38.5 (CH_2); HRMS (ESI+) calcd for $C_{24}H_{26}NO_4$ [M + H]$^+$ 392.1862, found 392.1843.

*[4-(4-Methylbenzoyl)-3-phenyl-1-cyclopenten-1-yl](4-morpholinyl) methanone (**7e**).* Reaction time: 24 h; colorless viscous oil (118 mg, 63%); R_f = 0.44 (petroleum ether/EtOAc 1/2); IR (KBr) ν_{max} 3031, 2958, 2921, 2853, 1677, 1608, 1455, 1431, 1274, 1252, 1114, 1010 cm^{-1}; ^{1}H NMR (300 MHz; $CDCl_3$) δ 7.80−7.72 (2 H, m), 7.34−7.20 (7 H, m), 5.84 (1 H, dd, J = 4.3 Hz and J = 2.0 Hz), 4.51−4.47 (1 H, m), 4.06 (1 H, dt, J = 9.4 Hz and J = 5.6 Hz), 3.69 (8 H, br s), 3.34−3.24 (1 H, m), 2.97−2.88 (1 H, m), 2.39 (3 H, s); ^{13}C NMR (75.4 MHz; $CDCl_3$) δ 199.6 (C), 167.0 (C), 144.3 (C), 143.0 (C), 136.7 (C), 133.9 (CH), 133.3 (C), 129.4 (CH), 128.9 (CH), 127.6 (CH), 127.2 (CH), 67.0 (CH_2), 54.7 (CH), 53.8 (CH), 47.5 (CH_2), 42.2 (CH_2), 38.5 (CH_2), 21.7 (CH_3); HRMS (ESI+) calcd for $C_{24}H_{26}NO_3$ [M + H^+] 376.1913, found 376.1895.

*4-Morpholinyl[3-phenyl-4-(2-thienylcarbonyl)-1-cyclopenten-1-yl] methanone (**7f**).* Reaction time: 4.5 h; colorless viscous oil (120 mg, 66%); R_f = 0.39 (petroleum ether/EtOAc 1/2); IR (KBr) ν_{max} 2919, 2852, 1656, 1614, 1455, 1429, 1414, 1273, 1251, 1130 cm^{-1}; ^{1}H NMR (300 MHz; $CDCl_3$) δ 7.65 (1 H, dd, J = 4.9 Hz and J = 1.0 Hz), 7.45 (1 H, dd, J = 3.8 Hz and J = 1.1 Hz), 7.34−7.19 (5 H, m), 7.06 (1 H, dd, J = 4.9 Hz and J = 3.8 Hz), 5.83 (1 H, dd, J = 4.3 Hz and J = 2.0 Hz), 4.47−4.44 (1 H, m), 3.93 (1 H, dt, J = 9.2 Hz and J = 5.6 Hz), 3.70 (8 H, br s), 3.33−3.22 (1 H, m), 3.05−2.97 (1 H, m); ^{13}C NMR (75.4 MHz; $CDCl_3$) δ 193.1 (C), 166.9 (C), 143.5 (C), 142.7 (C), 136.8 (C), 134.4 (CH), 133.5 (CH), 132.6 (CH), 128.9 (CH), 128.2 (CH), 127.5 (CH), 127.2 (CH), 67.1 (CH_2), 55.3 (CH), 55.1 (CH), 47.4 (CH_2), 41.7 (CH_2), 38.5 (CH_2); HRMS (ESI+) calcd for $C_{21}H_{22}NO_3S$ [M + H^+] 368.1320, found 368.1314.

*(4-(Morpholine-4-carbonyl)-2-phenylcyclopent-3-enyl)(4-nitrophenyl) methanone (**7g**).* Reaction time: 4 h; viscous yellow oil (136 mg, 67%); R_f = 0.32 (petroleum ether/EtOAc 1/2); IR (KBr) ν_{max} 1688, 1604, 1457, 1433, 1346, 1274, 1251, 1113, 1010 cm^{-1}; ^{1}H NMR (300 MHz; $CDCl_3$) δ 8.27−8.21 (2 H, m), 7.99−7.94 (2 H, m), 7.31−7.16 (5 H, m), 5.84 (1 H, dd, J = 3.9 Hz and J = 1.8 Hz), 4.47−4.41 (1 H, m), 4.08 (1 H, dt, J = 9.3 Hz and J = 5.7 Hz), 3.70 (8 H, br s), 3.35−3.25 (1 H, m), 3.04−2.95 (1 H, m); ^{13}C NMR (75.4 MHz; $CDCl_3$) δ 198.4 (C), 166.6 (C), 150.4 (C), 142.4 (C), 140.4 (C), 136.4 (C), 133.7 (CH), 129.8 (CH), 129.1 (CH), 127.6 (CH), 127.5 (CH), 123.9 (CH), 66.9 (CH_2), 54.9 (CH), 54.5 (CH), 47.4 (CH_2); 42.2 (CH_2); 38.0 (CH_2); HRMS (ESI+) calcd for $C_{23}H_{23}N_2O_5$ [M + H]$^+$ 407.1607, found 407.1593

*[4-Benzoyl-3-(4-chlorophenyl)-1-cyclopenten-1-yl](4-morpholinyl) methanone (**7h**).* Reaction time: 2.5 h; viscous yellow oil (125 mg, 63%); R_f = 0.43 (petroleum ether/EtOAc 1/2); IR (KBr) ν_{max} 1680, 1612, 1431, 1360, 1275, 1254, 1114, 1014 cm^{-1}; ^{1}H NMR (300 MHz; $CDCl_3$) δ 7.86−7.83 (2 H, m), 7.60−7.54 (1 H, m), 7.46−7.41 (2 H, m), 7.30−7.26 (2 H, m), 7.17−7.12 (2 H, m) 5.81 (1 H, dd, J = 4.3 Hz and J = 2.1 Hz), 4.52−4.48 (1 H, m), 4.03 (1 H, dt, J = 9.3 Hz and J = 5.9 Hz), 3.69 (8 H, br s), 3.36−3.26 (1 H, m), 2.96−2.87 (1 H, m); ^{13}C NMR (75.4 MHz; $CDCl_3$) δ 199.6 (C), 166.7 (C), 141.5 (C), 137.0 (C), 135.7 (C), 133.5 (C), 133.2 (CH), 132.9 (CH), 128.99 (CH), 128.92 (CH), 128.74 (CH), 128.70 (CH), 66.9 (CH_2), 53.9 (CH), 53.8 (CH), 47.6 (CH2), 42.1 (CH2), 38.4 (CH_2); HRMS (ESI+) calcd for $C_{23}H_{23}ClNO_3$ [M + H]$^+$ 396.1366, found 396.1361.

*[4-Benzoyl-3-(4-methoxyphenyl)-1-cyclopenten-1-yl](4-morpholinyl) methanone (**7i**).* Reaction time: 24 h; viscous oil (127 mg, 64%); R_f = 0.36 (petroleum ether/EtOAc 1/2); IR (KBr) ν_{max} 1682, 1608, 1512, 1428, 1361, 1273, 1248, 1113, 1008 cm^{-1}; ^{1}H NMR (300 MHz; $CDCl_3$) δ 7.87−7.84 (2 H, m), 7.58−7.52 (1 H, m), 7.45−7.40 (2 H, m), 7.15−7.10 (2 H, m), 6.87−6.82 (2 H, m), 5.81 (1 H, dd, J = 4.2 Hz and J = 1.9 Hz), 4.44−4.41 (1 H, m), 4.04 (1 H, dt, J = 9.4 Hz and J = 5.7 Hz), 3.79 (3 H, s), 3.70 (8 H, br s), 3.33−3.23 (1 H, m), 2.98−2.89 (1 H, m); ^{13}C NMR (75.4 MHz; $CDCl_3$) δ 200.1 (C), 167.1 (C), 158.8 (C), 136.4 (C), 135.9 (C), 135.0 (C), 134.2 (CH), 133.4 (CH), 128.8 (CH), 128.7 (CH), 128.6 (CH), 114.3 (CH), 67.0 (2CH_2), 55.4 (CH_3), 54.11 (CH), 54.08 (CH), 47.5 (CH_2); 42.1 (CH_2); 38.3 (CH_2); HRMS (ESI+) calcd for $C_{24}H_{26}NO_4$ 392.1862, found 392.1878.

*(4-Benzoyl-3-(3-methoxyphenyl)cyclopent-1-enyl)(morpholino) methanone (**7j**).* Reaction time: 8.5 h; colorless viscous oil (151 mg, 77%); R_f = 0.40 (petroleum ether/EtOAc 1/2); IR (KBr) ν_{max} 3059, 2958, 2919, 2863, 1681, 1605, 1485, 1432, 1276, 1253, 1158, 1114, 1044, 1007 cm^{-1}; ^{1}H NMR (300 MHz; $CDCl_3$) δ 7.87−7.84 (2 H, m), 7.58−7.52 (1 H, m), 7.45−7.40 (2 H, m), 7.22 (1 H, d, J = 7.5 Hz), 6.81−6.77 (2 H, m), 6.74−6.73 (1 H, m), 5.84 (1 H, dd, J = 4.1 Hz and J = 1.9 Hz), 4.52−4.48 (1 H, m), 4.09 (1 H, dt, J = 9.6 Hz and J = 5.9 Hz), 3.77 (3 H, s), 3.69 (8 H, br s), 3.52−3.25 (1 H, m), 2.97−2.88 (1 H, m); ^{13}C NMR (75.4 MHz; $CDCl_3$) δ 199.8 (C), 166.8 (C), 159.9 (C), 144.5 (C), 136.5 (C), 135.7 (C), 133.8 (CH), 133.3 (CH), 129.9 (CH), 128.7 (CH), 128.6 (CH), 119.7 (CH), 113.2 (CH), 112.4 (CH), 66.9 (CH_2), 55.2 (CH_3), 54.5 (CH), 53.7 (CH), 47.4 (CH_2), 42.0 (CH_2), 38.4 (CH_2); HRMS (ESI+) calcd for $C_{24}H_{26}NO_4$ [M + H^+] 392.1862, found 392.1854.

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*[4-Benzoyl-3-(2-methylphenyl)-1-cyclopenten-1-yl](4-morpholinyl) methanone (**7k**).* Reaction time: 2 h; colorless viscous oil (133.5 mg, 71%); R_f = 0.40 (petroleum ether/EtOAc 1/2); IR (KBr) ν_{max} 3059, 2958, 2914, 2855, 1680, 1611, 1429, 1358, 1275, 1251, 1113, 1019 cm^{-1}; ^1H NMR (300 MHz; $CDCl_3$) δ 7.84−7.81 (2 H, m), 7.57−7.51 (1 H, m), 7.43−7.38 (2 H, m), 7.23−7.09 (4 H, m), 5.83 (1 H, dd, J = 4.1 Hz and J = 1.9 Hz), 4.84−4.80 (1 H, m), 4.10−4.03 (1 H, m), 3.69 (8 H, br s), 3.42−3.31 (1 H, m), 2.93−2.85 (1 H, m), 2.17 (3 H, s); ^{13}C NMR (75.4 MHz; $CDCl_3$) δ 200.2 (C), 166.8 (C), 141.2 (C), 135.9 (C), 135.7 (C), 135.6 (C), 134.7 (CH), 133.3 (CH), 130.5 (CH), 128.7 (CH), 128.6 (CH), 127.2 (CH), 126.9 (CH), 126.6 (CH), 66.9 (CH_2), 53.0 (CH), 50.2 (CH), 47.3 (CH_2), 42.1 (CH_2), 38.8 (CH_2), 19.7 (CH_3); HRMS (ESI+) calcd for $C_{24}H_{26}NO_3$ $[M + H]^+$ 376.1913, found 376.1899.

*(4-Benzoyl-3-pentylcyclopent-1-enyl)(morpholino)methanone (**7l**).* Reaction time: 7 h; colorless viscous oil (124.6 mg, 70%); R_f = 0.42 (petroleum ether/EtOAc 1/2); IR (KBr) ν_{max} 2958, 2923, 2853, 1681, 1608, 1449, 1430, 1360, 1274, 1256, 1115, 1021 cm^{-1}; ^1H NMR (300 MHz; $CDCl_3$) δ 7.95−7.92 (2 H, m), 7.59−7.42 (3 H, m), 5.79 (1 H, dd, J = 3.9 Hz and J = 1.9 Hz), 3.77 (1 H, td, J = 9.4 Hz and J = 5.2 Hz), 3.64 (8 H, br s), 3.32−3.22 (1 H, m), 3.19−3.07 (1 H, m), 2.78−2.68 (1 H, m), 1.59−1.46 (2 H, m), 1.36−1.17 (6 H, m), 0.82 (3 H, t, J = 6.7 Hz); ^{13}C NMR (75.4 MHz; $CDCl_3$) δ 201.2 (C), 167.5 (C), 136.2 (C), 135.1 (C), 135.0 (CH), 133.2 (CH), 128.8 (CH), 128.5 (CH), 67.0 (CH_2), 50.4 (CH), 49.3 (CH), 47.4 (CH_2), 42.2 (CH_2), 38.2 (CH_2), 35.0 (CH_2), 31.8 (CH_2), 27.3 (CH_2), 22.5 (CH_2), 14.0 (CH_3); HRMS (ESI+) calcd for $C_{22}H_{30}NO_3$ $[M + H^+]$ 356.2226, found 356.2199.

*(4-((4-Chlorophenyl)(hydroxy)methyl)-3-phenylcyclopent-1-enyl)-(morpholino)methanone (**8**).* To a stirred solution of ketone **7c** (0.328 mmol) in anhydrous THF (3 mL) was added slowly a solution of $LiBEt_3H$ 1 M in THF (0.33 mL, 0.33 mmol) at −78 °C. The resulting mixture was magnetically stirred at this temperature until the disappearance of starting material on TLC. The mixture was quenched by addition of water, 30% aqueous solution of H_2O_2, and a saturated aqueous solution of NH_4Cl. The mixture was extracted with ethyl acetate three times, and the combined organic layers were washed with saturated aqueous solution of NH_4Cl (2×). After drying over $MgSO_4$, the filtrate was concentrated *in vacuo* and purified by flash column chromatography on silica gel to furnish the alcohol **8** as a white solid (120 mg, 92%); R_f = 0.16 (petroleum ether/EtOAc 1/3); mp = 179−181 °C; IR (KBr) ν_{max} 3289, 2930, 2852, 1642, 1589, 1460, 1435, 1279, 1116, 1080, 1038, 837 cm^{-1}; ^1H NMR (300 MHz; $CDCl_3$) δ 7.31−7.21 (7 H, m), 7.13−7.10 (2 H, m), 5.78−5.76 (1 H, m), 4.75 (1 H, br d, J = 7.2 Hz), 4.13−4.08 (1 H, m), 3.65 (8 H, br s), 2.75−2.61 (2 H, m), 2.52−2.42 (1 H, m), 1.89 (1 H, br s); ^{13}C NMR (75.4 MHz; $CDCl_3$) δ 167.5 (C), 144.3 (C), 141.5 (C), 136.9 (C), 135.3 (CH), 133.4 (C), 128.7 (CH), 128.6 (CH), 128.1 (CH), 127.6 (CH), 126.7 (CH), 77.0 (CH), 66.9 (CH_2), 54.7 (CH), 53.7 (CH), 47.4 (CH_2), 42.1 (CH_2), 37.3 (CH_2); HRMS (ESI+) calcd for $C_{23}H_{25}NO_3Cl$ $[M + H^+]$ 398.1523, found 398.1517. Crystals suitable for X-ray diffraction structure determination was obtained by slow evaporation of ethyl acetate (see Supporting Information).

*(4-((4-Chlorophenyl)(hydroxy)methyl)-3-phenylcyclopent-1-enyl)-(phenyl)methanone (**9**).* To a stirred solution of amide **8** (0.1 mmol) in THF (1 mL) was added slowly a solution of PhLi 2 M in dibutylether (0.1 mL, 0.2 mmol) at −78 °C. The resulting mixture was magnetically stirred at this temperature for 2 h. Then, a saturated aqueous solution of NH_4Cl was added dropwise at 0 °C. The resulting mixture was extracted with ethyl acetate three times, and the combined organic layers were washed with saturated aqueous solution of NH_4Cl (2×). After drying over $MgSO_4$ and filtration, the filtrate was concentrated *in vacuo* and purified by flash column chromatography on silica gel to furnish the ketone **9** as a white solid (32 mg, 82%); R_f = 0.41 (petroleum ether/EtOAc 3/1); mp < 50 °C; IR (KBr) ν_{max} 3400, 2919, 2863, 1631, 1594, 1485, 1446, 1360, 1281, 1089, 1013 cm^{-1}; ^1H NMR (300 MHz; $CDCl_3$) δ 7.76−7.71 (2 H, m), 7.51−7.45 (1H, m), 7.40−7.35 (2H, m), 7.30−7.17 (7 H, m), 7.13−7.10 (2 H, m), 6.40−6.38 (1 H, m), 4.72−4.70 (1 H, m), 4.25−4.23 (1 H, m), 2.89−2.74 (2 H, m), 2.62−2.49 (1 H, m), 1.87 (1 H, br s); ^{13}C NMR (75.4 MHz; $CDCl_3$) δ 193.9 (C), 148.0 (CH), 143.7 (C), 142.8 (C), 141.3 (C), 138.4 (C), 133.7 (C), 132.2 (CH), 129.0 (CH), 128.9 (CH), 128.8 (CH), 128.4 (CH), 128.1 (CH), 127.8 (CH), 126.9 (CH), 77.4 (CH), 55.9 (CH), 53.7 (CH), 35.0 (CH_2); HRMS (ESI+) calcd for $C_{25}H_{20}OCl$ $[M + H^+]$ 371.1203, found 371.1201.

■ ASSOCIATED CONTENT

Supporting Information. Copies of NMR spectra for all newly formed products and X-ray crystal data for compound **8** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author
*E-mail: jean-francois.briere@insa-rouen.fr.

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