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Tandem reactions catalyzed by lanthanide iodides. Part 1: Tandem Mukaiyama–Michael iminoaldol reactions

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Abstract—Samarium diiodide, as well as lanthanide triiodides catalyze a one-pot procedure allowing to perform sequentially the Mukaiyama–Michael addition of a ketene silyl acetal on a cyclic α,β-unsaturated ketone, followed by the addition of a glyoxylic, aromatic or heteroaromatic imine. According to the nature of the silyl group the adducts resulting from this tandem process are isolated as ketones or as enoxysilanes. The presence of a coordinating group on the imine increases the rate of the reaction.

1. Introduction

Tandem or cascade reactions allowing the formation of several bonds by one-pot procedures afford useful methodologies for the preparation of complex molecules as they allow the reduction of the number of steps, but also the diminution of costs and of waste production. They are thus the focus of growing interest and the concern of several reviews.[1] Amongst the panel of tandem reactions reported in the literature, a large part is devoted to radical or anionic reactions and/or to intramolecular reactions allowing the rapid formation of cyclic or polycyclic molecules.[2] The use of metal catalysts which afford the possibility to modulate stereo and/or enantioselectivities has been more recently developed in sequences of tandem reactions.[3] Lewis acids catalyze a variety of three-component reactions, which involve the successive formation of two bonds with one catalyst.[4] Lanthanide and scandium triflates are useful catalysts for three-component reactions involving the in situ preparation of an imine followed by a carbon–carbon bond formation.[5] Michael–aldol sequences leading to the consecutive formation of two carbon–carbon bonds in three-component reactions are well known.[6] Michael additions of an organometallic on α,β-unsaturated ketones followed by aldolisation of the intermediate have been widely employed for the synthesis of prostaglandins. Lewis acids, especially $Cu(OTf)_2$ associated to chiral ligands are highly enantioselective catalysts for 1,4-additions of alkyl zinc on α,β-unsaturated ketones and the stereochemistry of the tandem adducts is thus controlled, while heterobimetallic ALB complex $[Li_3Al(binol)_3]$ is an effective catalyst for asymmetric tandem Michael–aldol reactions.[7] An alternative method for creating two carbon–carbon bonds by a one-pot procedure is to realize a Michael addition of silylated derivatives on α,β-unsaturated ketones leading to an enoxysilane as the intermediate which reacts in an aldol or a second Michael reaction.[8] These tandem reactions require the use of a Lewis acid as catalyst which is a trityl salt in most cases, while the second step involves an aldehyde or an α,β-unsaturated ketone. To the best of our knowledge, imino aldol reaction consecutive to a Michael reaction in tandem sequences has not been much studied.[9] Three-component reaction via tandem Michael iminoaldol reaction has been reported, but it involves the use of different Lewis acids for the two steps of the sequence, $SbCl_5–Sn(OTf)_2$ for the Michael addition and $Sc(OTf)_3$ for the iminoaldol reaction.[10] Double nucleophilic addition of ketene silyl acetals on α,β-unsaturated aldimines promoted by aluminium chloride has been also reported.[11]

The use of samarium diiodide as a precatalyst for a variety of Lewis acid-catalyzed reactions has been the topic of our previous investigations.[12] We have first described Mukaiyama aldol or Michael reactions,[13] cycloaddition reactions,[14] or enolization of ketones,[15] performed with catalytic amounts of samarium diiodide or other lanthanide iodides. We have further found that samarium diiodide can catalyze successively two reactions in a one-pot procedure, a Michael reaction on cyclic α,β-unsaturated ketones followed by an aldol reaction.[16] In all these reactions, an aldehyde or a ketone was used as the electrophile. Recently, we studied the reactivity of imines in similar reactions and reported on aza Diels–Alder as well as Mannich reactions catalyzed by samarium diiodide.[17] Especially imines react with acyclic or cyclic enoxysilanes to yield β-aminoketones

Keywords: Samarium diiodide; Catalysis; Imines; Michael reaction; Mannich reaction; Tandem reaction.
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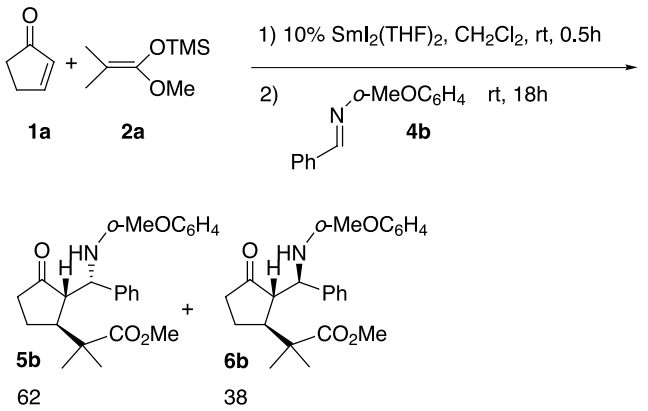
under mild conditions. This prompted us to examine the possibility to realize successively a Michael addition of ketene silyl acetal on α,β-unsaturated ketones leading to enoxysilanes followed by a Mannich reaction in a one-pot procedure. We have already reported our first results concerning tandem Michael–Mannich reactions using samarium diiodide as the sole catalyst.[18] We describe now our extensive study and especially the influence of the nature of ketene silyl acetal and imine on the Mannich step and on the structure of tandem adducts.

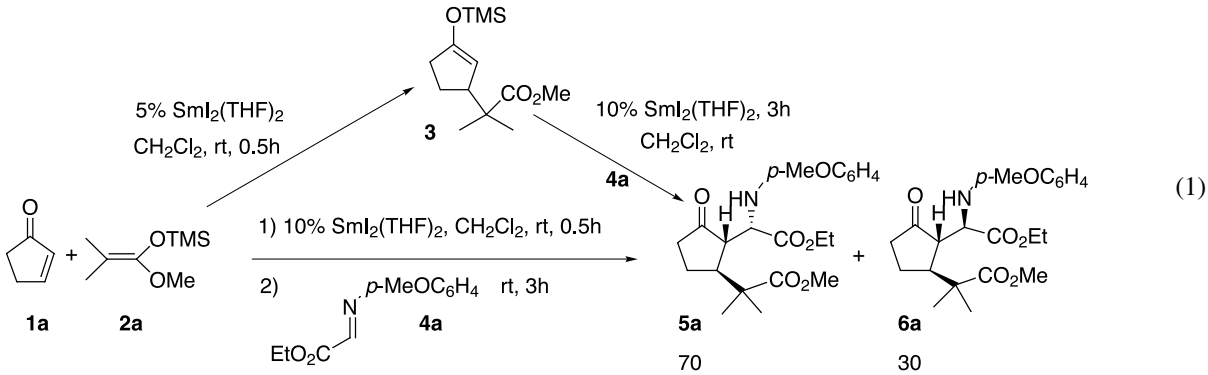
2. Results and discussion

We examined first the influence of various parameters on two tandem sequences considered as test reactions for optimizing the experimental procedure. We selected for Michael reaction cyclopenten-2-one **1a** and the commercially available ketene silyl acetal **2a**, which yield readily the enoxysilane **3** in the presence of catalytic amounts of samarium diiodide as was formerly shown.[13] For the Mannich step, *N-para*-anisyl ethyl glyoxylic imine **4a** and *N-ortho*-anisyl benzyl imine **4b** were chosen as we have already found their reactivity towards cyclic enoxysilanes to give β-aminoketones in the presence of catalytic amounts of samarium diiodide.[17] As was previously reported, in the reaction involving imine **4a** either the two consecutive reactions, or the tandem one-pot reaction afforded similar results (Eq. 1).[18] In the former procedure, the enoxysilane **3** resulting of the Michael addition was isolated, and its reaction with imine **4a** in the presence of 10% equiv. $SmI_2(THF)_2$, at room temperature, led to a product isolated in 44% yield as a diastereomeric mixture of **5a** and **6a**. The structure and configurational assignments and ratio were done after column chromatography separation on basis of NMR experiments (see below) as **5a** and **6a**, (**5a/6a**: 71/29). The one-pot reaction was realized by successive additions of ketene silyl acetal **2a** and cyclopenten-2-one **1a** on a suspension of samarium diiodide (10 mol%), in methylene chloride and after half-hour reaction time, at room temperature, the glyoxylic imine **4a** was added. Tandem adducts **5a** and **6a** were isolated in 50% yield and 70/30 diastereomeric ratio **5a/6a**, close to that obtained for the two steps procedure (Table 1, entry 1). We similarly realized a tandem sequence using **1**, **2**, *N-ortho*-anisyl benzyl imine **4b** and samarium diiodide (10 mol%) in methylene chloride, at room temperature, and isolated the adducts as a mixture of diastereoisomers **5b** and **6b** which could not be separated, in 45% yield (**5b/6b**: 62/38), (Eq. 2, entry 7).



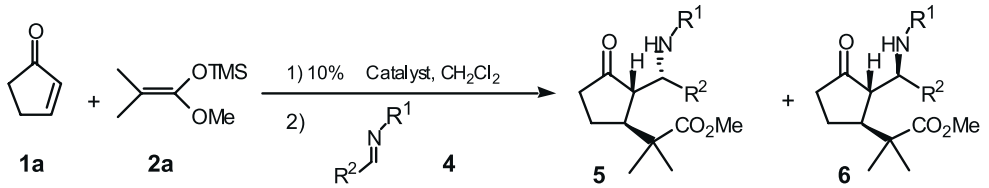
(2)

In the course of previous studies concerning the tandem Mukaiyama–Michael aldol reactions, we found that a decrease of temperature resulted in an increase of both yield, by suppression of by-products, and of stereoselectivity. Effect of temperature was thus examined on the two tandem sequences described in Eqs. 1 and 2. For the reactions with glyoxylic imine **4a** leading to adducts **5a** and **6a**, a decrease of temperature afforded a slight increase in diastereoselectivity (entries 1–4) together with an increase in yield down to −55 °C (81%, entry 3) which gave the best result. At lower temperature (−78 °C, entry 4) the yield decreased in spite of a longer reaction time. For reactions involving imine **4b**, from room temperature to −40 °C, no significant change in stereoselectivity could be detected (entries 7–9), while lower temperature resulted in the highest stereoselectivity (**5b/6b**: 80/20) albeit with a lower yield as with imine **4a** (entry 10). For this reaction, optimal temperature appears to be 0 °C (entry 8). As we precedently noticed for other reactions involving the use of samarium diiodide in catalytic amounts, the change of colour of the reaction mixtures from blue to yellow after the addition of substrates indicates that the actual catalytic species is trivalent. A comparative study of a variety of divalent and trivalent lanthanides as catalysts for aldol reaction did not allow to detect any difference in the rate of the reaction,[13] whereas for Mukaiyama Michael–aldol tandem reactions only $YbI_3(THF)_3$ and $LaI_3(DME)_2$ have exhibited an activity and selectivity similar to that of $SmI_2(THF)_2$.[16] Ytterbium and lanthanum triiodides were thus compared to



(1)

Table 1. Tandem Michael imino–aldol reactions, influence of reaction temperature and of catalyst

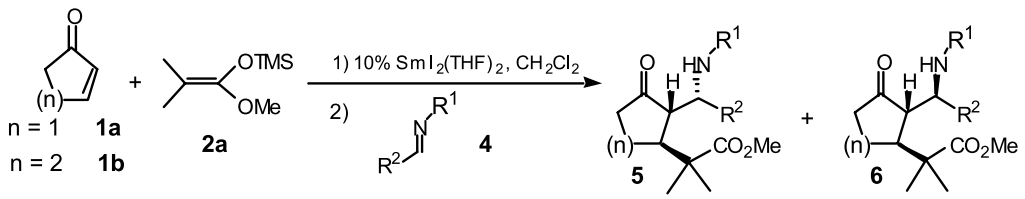


Entry	Catalyst	Imine			T (°C)	t (h)	Product		
			R^1	R^2				Yield (%)[a,b]	**5/6**[c]
1	$SmI_2(THF)_2$	**4a**	*p*-$MeOC_6H_4$	CO_2Et	rt	3	**5a+6a**	50	70/30
2	$SmI_2(THF)_2$	**4a**	*p*-$MeOC_6H_4$	CO_2Et	−30	3	**5a+6a**	76	70/30
3	$SmI_2(THF)_2$	**4a**	*p*-$MeOC_6H_4$	CO_2Et	−55	18	**5a+6a**	81	78/22
4	$SmI_2(THF)_2$	**4a**	*p*-$MeOC_6H_4$	CO_2Et	−78	46	**5a+6a**	70[d]	85/15
5	$YbI_3(THF)_3$	**4a**	*p*-$MeOC_6H_4$	CO_2Et	−30	4	**5a+6a**	60[d]	66/34
6	$LaI_3(DME)_2$	**4a**	*p*-$MeOC_6H_4$	CO_2Et	−30	4	**5a+6a**	45[d]	60/40
7	$SmI_2(THF)_2$	**4b**	Ph	*o*-$MeOC_6H_4$	rt	18	**5b+6b**	45	62/38
8	$SmI_2(THF)_2$	**4b**	Ph	*o*-$MeOC_6H_4$	0	24	**5b+6b**	53	65/35
9	$SmI_2(THF)_2$	**4b**	Ph	*o*-$MeOC_6H_4$	−40	24	**5b+6b**	54	62/38
10	$SmI_2(THF)_2$	**4b**	Ph	*o*-$MeOC_6H_4$	−78	46	**5b+6b**	30	80/20
11	$YbI_3(THF)_3$	**4b**	Ph	*o*-$MeOC_6H_4$	−30	24	**5b+6b**	45	60/40
12	$LaI_3(DME)_2$	**4b**	Ph	*o*-$MeOC_6H_4$	−30	24	**5b+6b**	50	70/30

[a] 10% $SmI_2(THF)_2$ in 10 mL CH_2Cl_2; ratio **1/2/4**: 1/1.5/1.3.
[b] Isolated yield of analytical pure product.
[c] Diastereoisomer ratio measured by ^1H NMR in crude product.
[d] Yield in crude product.

samarium diiodide for both test tandem Michael–iminoaldol reactions. For the tandem sequence leading to **5a** and **6a**, at −30 °C, yield and selectivity were higher with samarium diiodide than with both trivalent lanthanide iodides (entries 2, 5, 6). In the case of reactions leading to **5b** and **6b**, the three catalysts led to similar results, with close values for the stereomer ratios **5b/6b** and a slighty higher yield given by samarium diiodide at −40 °C (entries, 9, 11, 12). Scandium triflate which is known to display a high activity as a Lewis acid catalyst,[19] has been tested for the tandem Michael–iminoaldol reaction involving glyoxylic imine **4a**. Its catalytic activity was similar to that of samarium diiodide, but the adducts **5a** and **6a** were formed together with decomposition products which could not be separated by purification. Similar trend has been observed upon attempts to catalyze Mukaiyama Michael–aldol reactions by scandium

Table 2. Tandem Michael imino–aldol reactions catalyzed by samarium diiodide



Entry	Ketone	Imine			T (°C)	t (h)	Product		
			R^1	R^2				Yield[a,b] (%)	**5/6**[c]
1	**1a**	**4a**	*p*-$MeOC_6H_4$	CO_2Et	−55	18	**5a+6a**	81	78/22
2	**1a**	**4b**	*o*-$MeOC_6H_4$	Ph	−40	24	**5b+6b**	54	62/38
3	**1a**	**4c**	Ph	Ph	0	24	**5c+6c**	47	71/29
4	**1a**	**4c**	Ph	Ph	−50	36	**5c+6c**	47	74/26
5	**1a**	**4d**	Ph	*p*-$CF_3C_6H_4$	0	24	**5d+6d**	42	50/50
6	**1a**	**4d**	Ph	*p*-$CF_3C_6H_4$	−50	24	**5d+6d**	50	59/41
7	**1a**	**4e**	Ph	*p*-$MeOC_6H_4$	rt	48		0	
8	**1a**	**4f**	*o*-$MeOC_6H_4$	*p*-$CF_3C_6H_4$	−40	24	**5f+6f**	66	83/17
9	**1a**	**4g**	*o*-$MeOC_6H_4$	*p*-$MeOC_6H_4$	0	41	**5g+6g**	37	62/38
10	**1a**	**4h**	*o*-$MeOC_6H_4$	2-Furfuryl	0	68	**5h+6h**	36	75/25
11	**1b**	**4a**	*p*-$MeOC_6H_4$	CO_2Et	0	24	**5i+6i**	46	86/14
12	**1b**	**4b**	*o*-$MeOC_6H_4$	Ph	rt	48		0	

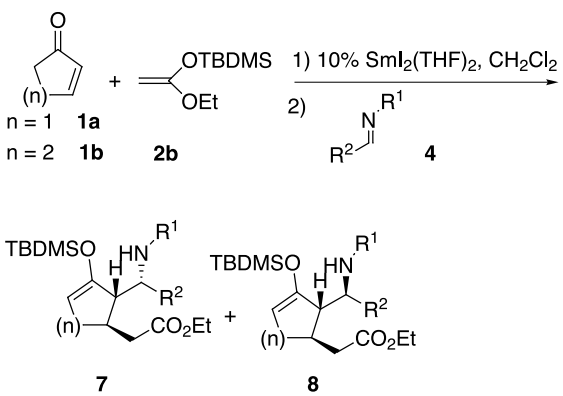
[a] 10% $SmI_2(THF)_2$ in 10 mL CH_2Cl_2; ratio **1/2/4**: 1/1.5/1.3.
[b] Isolated yield of analytical pure product.
[c] Diastereoisomer ratios measured by ^1H NMR in the crude product.

triflate.[16] Samarium diiodide will be used in the following of this study since it is commercially available or easy to prepare,[20] and furnishes higher yields than the other lanthanide iodides.

The scope of the reaction was next examined aiming at the determination of the nature of imines that can be employed in the second step of the tandem sequence, the Mannich reaction. The results are gathered in Table 2. As indicated above, we first tested the imines **4a** and **4b**, which contain a coordinating group either on the carbon, or on the nitrogen group of the imine. This choice was dictated by our precedent results indicating that other imines such as *N*-phenyl benzylidene imine were unreactive towards enoxysilanes in the presence of samarium diiodide.[18] After having established the possibility to realize the tandem Michael–Mannich sequence with coordinating imines, we tried to extend the reaction to the non-coordinating *N*-phenyl benzylidene imine **4c**. Contrary to our expectations, this imine afforded the tandem adducts **5c** and **6c** (entry 3). A decrease in the temperature of the reaction did not bring any benefit on yield or selectivity (entry 4). The use of imine **4d** with an attracting group on the substituent of the carbon led to the adducts **5d** and **6d** in similar yield than with **4c** but lower selectivity (entries 3–6), while, with an electron donor group (imine **4e**), reaction did not afford the tandem adducts (entry 7). We compared the two latter imines with imines **4f** and **4g** which bear the coordinating *o*-anisyl group as substituent of the nitrogen atom. Comparison of **4d** and **4f** (entries 6 and 8) indicates that the presence of the coordinating group brings an increase in yield and selectivity. Tandem adducts were obtained from imine **4g** (entry 9) while **4e** was unreactive, which also reveals beneficial effect of the *o*-anisyl substituent on the imine. Furfuryl imine **4h** allowed isolation of tandem adducts albeit in low yield (entry 10). Influence of the size of the cycle was then examined and a low reactivity for the Mannich reaction was found in the case of cyclohexen-2-one (entries 11 and 12). The use of glyoxylic imine **4a** led to the mixture of tandem adducts **5i** and **6i** in moderate yield and high selectivity while no tandem product was obtained with the aromatic coordinating imine **4b**. This result can be explained by the lower reactivity of the six-membered ring enoxysilane resulting of the Michael addition towards imines compared to the similar five-membered ring enoxysilane.

Tandem products resulting of reaction of **1a**, **2a** and **4a** have been isolated after chromatography on silica gel as a mixture of two stereoisomers which have been separated after a second chromatography on alumina. 2D NMR experiments COSY and NOESY analysis of the major stereoisomer revealed a *trans* stereochemistry for the two lateral chains and *syn* situation for the iminoaldolisation products, as shown for **5a**. The other stereoisomer **6a** was assigned as the *anti* iminoaldolisation product. For the other tandem products assignments of stereomers have been done by comparison with **5a** and **6a**. Isomer **5** and **6** observed in all cases in the absence of other stereomers, are the result of the *anti* approach of imine on the cycle. Obtention of structure **5** with *syn* configuration as the major one is similar to the results reported in the case of the tandem Michael iminoaldol reaction.[16]

Our next aim was to extend these tandem reactions to another ketene silyl acetal. We thus studied the reaction of glyoxylic imine **4a** on enoxysilane formed by reaction of **2b** with cyclopenten-2-one in a one-pot procedure. To our surprise, we observed that Mannich reaction took place but the adducts did not had a similar structure than in reactions described above. Instead of ketones, the tandem adducts were isolated as the corresponding enoxysilanes (Eq. 3, Table 3). On the basis of ^{1}H, ^{13}C and 2D NMR analyses, the compounds isolated after purification on alumina have been identified as regioisomers **7** and **8** showing the less substituted double bond and the two chains in *trans* stereochemical situation. The major isomer was identified as **7**, with configuration *syn* for the carbons of the bond formed in the iminoaldolisation step, like in tandem reactions described above leading to β-aminoketones. The diastereoisomeric ratio **7/8** was evaluated by integration of ^{1}H NMR spectra. The enoxysilane obtained by reaction of ketene silyl acetal **2b** on cyclopenten-2-one was more reactive towards imine than the corresponding six-membered ring enoxysilane: reactions were performed at 0 °C with imines **4a** and **4h** for cyclopenten-2-one (entries 1 and 2) while only imine **4a** afforded the tandem products with cyclohexen-2-one (entries 3 and 4). Enolization of ketones catalyzed by lanthanide iodides was already observed. We had described that ketones could be transformed in the corresponding trimethylsilyl enoxysilanes by reaction with ketene silyl acetal **2a** in the presence of samarium diiodide or other lanthanide iodides.[15] In the reactions reported here, the transformation of the ketones into enoxysilanes seems to be related to the presence of a *tert*-butyldimethylsilyl group. We tested then the ketene silyl acetal **2c** derived from phenyl acetate substituted with a trimethylsilyl group. The tandem reaction involving **1a**, **2c** and **4a** was realized by the usual one-pot procedure at 0 °C and furnished the adducts as ketones **5j** and/or **6j** in moderate yield (Eq. 4). However we could not assign the stereomers and thus the selectivity of the reaction was not evaluated. The dependence of the structures of reaction products with the nature of the silyl group prompted us to investigate the samarium diiodide Mannich reaction of enoxysilanes bearing a *tert*-butyldimethylsilyl group with imines. We have indeed found that in this case also reactions products are isolated as enoxysilanes and not as ketones. These results as well as mechanistic pathways will be presented in the following paper.[21]

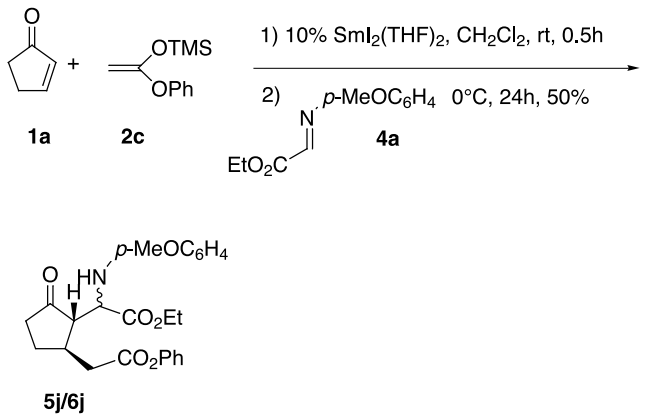


(3)

Table 3. Tandem Michael imino–aldol reactions catalyzed by samarium diiodide involving **2b**

Entry	Ketone	Imine			T (°C)	t (h)	Product		
			R^1	R^2				Yield[a,b] (%)	**7/8**[c]
1	**1a**	**4a**	*p*-$MeOC_6H_4$	CO_2Et	0	24	**7a+8a**	82	69/31
2	**1a**	**4h**	*o*-$MeOC_6H_4$	2-Furfuryl	0	68	**7b+8b**	60	82/18
3	**1b**	**4a**	*p*-$MeOC_6H_4$	CO_2Et	20	24	**7c+8c**	58	75/25
4	**1b**	**4h**	*o*-$MeOC_6H_4$	2-furfuryl	20	24		0	

[a] 10% $SmI_2(THF)_2$ in 10 mL CH_2Cl_2; Ratio **1/2/4**: 1/1.5/1.3.
[b] Isolated yield of analytical pure product.
[c] Diastereoisomer ratios measured by ^1H NMR in the crude product.



(4)

In summary we have shown that samarium diiodide catalyzes the formation of two carbon–carbon bonds by successive Michael and Mannich reactions on α,β-unsaturated cyclic ketones to afford β-aminoketones or β-aminoenoxysilanes, depending upon the nature of the silyl group used as substituent of nucleophile in the Michael reaction. The rates and the yields of the tandem Michael–Mannich reactions are increased by the presence of a chelating group, either on the carbon, or on the nitrogen of imine. To the best of our knowledge, no other catalyst has been described for such sequences of tandem reactions. Since the removal of *N*-*o*-anisyl or *N*-*p*-anisyl groups on Mannich products has been already described,[22] samarium diiodide-catalyzed tandem Michael–Mannich reactions should give access to different β-aminoketones or lactams. Recently, we reported that iodo samarium binaphthoxides are enantioselective catalysts for Diels–Alder reactions[23] and moreover for Mannich reactions.[24] We are currently investigating the use of these catalysts for asymmetric tandem reactions.

3. Experimental

3.1. General

All manipulations were carried out under an argon atmosphere using standard Schlenk or glovebox techniques. CH_2Cl_2 was distilled from CaH_2 and degassed immediately prior to use. The method for preparing $SmI_2(THF)_2$ has been previously described,[25] as well as $LaI_3(DME)_2$ and $YbI_3(THF)_3$ prepared from La or Yb powder and iodine.[26] Silyl ketene acetal **2a** was purchased from Aldrich, **2b** and **2c** were prepared according to literature procedure.[27] Bruker AM 250 and AM 400 spectrometers, operating at 250 and 400 MHz for ^1H, 62.5 and 100.8 MHz for ^{13}C, were used for the NMR spectra. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane for spectra in $CDCl_3$. Infrared spectra were recorded as Nujol mulls using NaCl plates on a Perkin–Elmer 1000 FT-IR spectrometer and are reported in cm^{-1}. HRMS were measured with a Perkin–Elmer Finnigan-Mat 955 spectrometer. Flash chromatography was realized using 230–400 mesh silica gel desactivated by Et_3N or neutral alumina using heptane/ethyl acetate mixtures as eluents.

3.2. Typical procedure for the synthesis of tandem products 5 and 6

In a Schlenk tube, a solution of SmI_2 in THF (0.1 M, 1 mL, 0.1 mmol) was carefully evaporated in vacuo to give $SmI_2(THF)_2$ as a blue powder, (alternatively $SmI_2(THF)_2$ (55 mg, 0.1 mmol) was weighed in a glovebox). Then CH_2Cl_2 (4 mL), 1-methoxy-2-methyl-1-trimethylsilyloxy-propene **2a** (203 μL, 1 mmol) and cyclopenten-2-one **1a** (125 μL, 1.5 mmol) were successively added under argon. The resulting yellow solution was then stirred for 0.5 h at room temperature, while the formation of enoxysilane **3** was monitored by GC and reaction mixture was cooled at −55 °C. A solution of imine **4a** (270 mg, 1.3 mmol) in CH_2Cl_2 (7 mL) was then added. After 18 h stirring at the same temperature, the reaction mixture was hydrolyzed and extracted by CH_2Cl_2. The crude product was purified on silica gel desactivated by Et_3N (heptane/AcOEt: 85/15) to give a mixture of **5a+6a**, (317 mg, 81%, **5a/6a**, 78/22). Column chromatography on neutral alumina allowed to separate each of diastereoisomers **5a** and **6a** pure.

3.2.1. 2-Methyl-2-[3-oxo-2-{(*N*-4-methoxyphenylamino)-ethoxycarbonyl-methyl}-cyclopentyl] propanoic acid methyl ester (*syn* 5a) and *anti* 6a. *syn* **5a**. ^1H NMR (250 MHz, $CDCl_3$, δ (ppm)): 6.73 (d, 2H, J=7.5 Hz), 6.66 (d, 2H, J=7.5 Hz), 4.59 (d, 1H, J=10 Hz), 4.35 (dd, 1H, J=10, 3.4 Hz), 4.10 (q, 2H, J=7.3 Hz), 3.70 (s, 3H), 3.65 (s, 3H), 2.64 (q, 1H, J=7.8 Hz), 2.52 (dd, 1H, J=7.5, 3.4 Hz), 2.26 (m, 2H), 2.09 (m, 1H), 1.64 (m, 1H), 1.23 (t, 3H, J=7.3 Hz), 1.17 (s, 3H), 1.15 (s, 3H). ^{13}C NMR: (62.5 MHz, $CDCl_3$, δ (ppm)): 219.56, 177.64, 172.36, 153.16, 140.73, 116.43, 114.66, 61.39, 60.02, 55.61, 52.09, 51.65, 44.82, 44.64, 37.75, 24.16, 22.86, 21.12, 14.05. FTIR (NaCl) (cm^{-1}): 3374, 1731. HRMS: calcd for $C_{21}H_{29}NNaO_6$ (M^++Na): 414.1892, found: 414.1892.

anti **6a**. ^1H NMR (250 MHz, $CDCl_3$, δ (ppm)): 6.75 (d, 2H, J=8.7 Hz), 6.62 (d, 2H, J=8.7 Hz), 4.59 (d, 1H, J=10 Hz),

4.28 (dd, 1H, J=10, 2.9 Hz), 4.18 (q, 2H, J=7.3 Hz), 3.71 (s, 3H), 3.59 (s, 3H), 2.77 (dd, 1H, J=7.5, 2.9 Hz), 2.64 (q, 1H, J=7.5 Hz), 2.26 (m, 2H), 2.09 (m, 1H), 1.64 (m, 1H), 1.24 (t, 3H, J=7.3 Hz), 1.17 (s, 3H), 1.12 (s, 3H). ^{13}C NMR: (62.5 MHz, $CDCl_3$, δ (ppm)): 218.21, 177.58, 171.79, 152.93, 140.66, 115.43, 114.79, 61.55, 58.45, 55.59, 52.49, 51.96, 45.27, 44.80, 37.75, 23.83, 22.72, 21.62, 14.06. HRMS: calcd for $C_{21}H_{29}NNaO_6$ (M^++Na): 414.1892, found: 414.1895.

3.2.2. 2-Methyl-2-[3-oxo-2-{α-(*N*-2-methoxyphenyl-amino)-benzyl}-cyclopentyl] propanoic acid methyl ester (mixture of diastereomers, *syn* 5b+*anti* 6b). *syn* **5b**+*anti* **6b**. ^{1}H NMR (200 MHz, $CDCl_3$, δ (ppm)): 7.35–7.16 (m, 5H), 6.72 (m, 1H), 6.57 (m, 2H), 6.29 (m, 1H), 5.98 (l, 0.62H, *syn* **5b**), 5.29 (l, 0.38H, *anti* **6b**), 4.61 (l, 1H), 3.90 (s, 1.86H, *syn* **5b**), 3.87 (s, 1.14H, *anti* **6b**), 3.63 (s, 1.86H, *syn* **5b**), 3.56 (s, 1.14H, *anti* **6b**), 2.69 (m, 1H), 2.52 (m, 1H), 2.10 (m, 1H), 1.65 (m, 3H), 1.11 (s, 3H), 1.09 (s, 3H). ^{13}C NMR: (62.5 MHz, $CDCl_3$, δ (ppm)): 221.05, 177.32, 146.82, 139.61, 136.07, 128.42, 127.44, 127.01, 120.83, 116.40, 110.65, 109.27, 58.96, 55.48, 54.63, 51.84, 45.33, 45.01, 38.82, 23.23, 22.41, 22.31. FTIR (NaCl) (cm^{-1}): 3410, 1726. HRMS: calcd for $C_{24}H_{29}NNaO_4$ (M^++Na): 418.1994, found: 418.1995.

3.2.3. 2-Methyl-2-[3-oxo-2-{α-(*N*-phenylamino)-benzyl}-cyclopentyl] propanoic acid methyl ester (mixture of diastereomers, *syn* 5c+*anti* 6c). *syn* **5c**+*anti* **6c**. ^{1}H NMR (250 MHz, $CDCl_3$, δ (ppm)): 7.27 (m, 5H), 7.03 (m, 2H), 6.58 (m, 1H), 6.49 (m, 2H), 5.67 (l, 0.74H, *syn* **5c**), 5.05 (l, 0.26H, *anti* **6c**), 4.52 (l, 1H), 3.65 (s, 2.22H, *syn* **5c**), 3.57 (s, 0.78H, *anti* **6c**), 2.57 (m, 1H), 2.07 (m, 2H), 1.54 (m, 3H), 1.18 (s, 2.22H, *syn* **5c**), 1.13 (s, 2.22H, *syn* **5c**), 1.01 (s, 0.78H, *anti* **6c**), 0.96 (s, 0.78H, *anti* **6c**). ^{13}C NMR: (62.5 MHz, $CDCl_3$, δ (ppm)): 221.64, 220.39, 177.90, 177.49, 146.81, 146.28, 140.71, 139.49, 129.03, 128.99, 128.61, 128.54, 127.72, 127.59, 127.21, 117.24, 117.46, 113.49, 113.37, 59.28, 58.30, 57.07, 54.24, 52.04, 52.00, 45.66, 45.39, 45.32, 44.98, 39.21, 37.26, 23.98 23.79, 22.18, 22.03, 21.82, 21.62. FTIR (NaCl) (cm^{-1}): 3386, 1728. HRMS: calcd for $C_{23}H_{27}NNaO_3$ (M^++Na): 388.1889, found: 388.1889.

3.2.4. 2-Methyl-2-[3-oxo-2-{α-(*N*-phenylamino)-4-trifluoromethyl-benzyl}-cyclopentyl] propanoic acid methyl ester (mixture of diastereomers, *syn* 5d+*anti* 6d). *syn* **5d**+*anti* **6d**. ^{1}H NMR (250 MHz, $CDCl_3$, δ (ppm)): 7.47 (m, 4H), 7.05 (m, 2H), 6.63 (m, 1H), 6.47 (m, 2H), 5.75 (l, 0.59H, *syn* **5d**), 5.04 (l, 0.41H, *anti* **6d**), 4.61 (l, 1H), 3.68 (s, 1.77H, *syn* **5d**), 3.59 (s, 1.23H, *anti* **6d**), 2.68 (m, 1H), 2.52 (m, 1H), 2.14 (m, 1H), 1.59 (m, 3H), 1.22 (s, 1.77H, *syn* **5d**), 1.15 (s, 1.77H, *syn* **5d**), 1.09 (s, 1.23H, *anti* **6d**), 1.03 (s, 1.23H, *anti* **6d**). ^{13}C NMR: (62.5 MHz, $CDCl_3$, δ (ppm)): 220.48, 192.33, 177.57, 145.88, 129.19, 128.23, 127.64, 125.53, 117.69, 113.30, 58.54, 54.19, 52.14, 45.20, 45.19, 39.17, 24.15, 22.16, 21.55. ^{19}F NMR: (235 MHz, $CDCl_3$, δ (ppm)): −63.74 (*syn* **5d**), −63.66 (*anti* **6d**). FTIR (NaCl) (cm^{-1}): 3383, 1727. HRMS: calcd for $C_{24}H_{26}F_3NNaO_3$ (M^++Na): 456.1762, found: 456.1761.

3.2.5. 2-Methyl-2-[3-oxo-2-{α-(*N*-2-methoxyphenyl-amino)-4-trifluoromethyl-benzyl}-cyclopentyl] propanoic acid methyl ester (mixture of diastereomers, *syn* 5f+*anti* 6f). *syn* **5f**+*anti* **6f**. ^{1}H NMR (250 MHz, $CDCl_3$, δ (ppm)): 7.53 (d, 2H, J=8.3 Hz), 7.40 (d, 2H, J=8.3 Hz), 6.74 (m, 1H), 6.61 (m, 2H), 6.20 (m, 1H), 6.01 (l, 1H), 4.69 (l, 1H), 3.91 (s, 2.49H, *syn* **5f**), 3.88 (s, 0.51H, *anti* **6f**), 3.65 (s, 2.49H, *syn* **5f**), 3.58 (s, 0.51H, *anti* **6f**), 2.71 (m, 1H), 2.53 (m, 1H), 2.18 (m, 1H), 1.67 (m, 3H), 1.14 (s, 3H), 1.10 (s, 3H). ^{13}C NMR: (62.5 MHz, $CDCl_3$, δ (ppm)): 220.48, 177.42, 146.96, 144.18, 135.66, 128.04, 127.48, 125.49, 120.93, 117.06, 110.68, 109.49, 58.47, 55.60, 54.56, 52.05, 45.31, 44.92, 38.86, 23.57, 22.50, 22.03. ^{19}F NMR: (235 MHz, $CDCl_3$, δ (ppm)): −63.63 (*anti* **6f**), −63.69 (*syn* **5f**). FTIR (NaCl) (cm^{-1}): 3396, 1727. HRMS: calcd for $C_{25}H_{28}F_3NNaO_4$ (M^++Na): 486.1869, found 486.1868.

3.2.6. 2-Methyl-2-[3-oxo-2-{α-(*N*-2-methoxyphenyl-amino)-4-methoxy-benzyl}-cyclopentyl] propanoic acid methyl ester (mixture of diastereomers, *syn* 5g+*anti* 6g). *syn* **5g**+*anti* **6g**. ^{1}H NMR (250 MHz, $CDCl_3$, δ (ppm)): 7.20 (m, 2H), 6.76 (m, 3H), 6.56 (m, 2H), 6.27 (m, 1H), 6.00 (d, 0.62H, J=8.8 Hz, *syn* **5g**), 5.26 (d, 0.38H, J=5.4 Hz, *anti* **6g**), 4.53 (m, 1H), 3.89 (s, 1.86H, *syn* **5g**), 3.87 (s, 1.14H, *anti* **6g**), 3.74 (s, 1.14H, *anti* **6g**), 3.72 (s, 1.86H, *syn* **5g**), 3.65 (s, 1.86H, *syn* **5g**), 3.58 (s, 1.14H, *anti* **6g**), 2.66 (m, 1H), 2.52 (m, 1H), 2.30–1.95 (m, 2H), 1.78–1.52 (m, 2H), 1.14 (s, 3H), 1.11 (s, 3H). ^{13}C NMR: (62.5 MHz, $CDCl_3$, δ (ppm)): 221.24, 220.23, 177.35, 177.08, 158.70, 146.84, 136.59, 136.12, 132.46, 131.41, 128.53, 128.04, 120.87, 120.81, 116.60, 116.29, 113.80, 113.74, 110.87, 110.65, 109.27, 58.40, 56.69, 55.48, 55.43, 55.02, 54.98, 54.60, 51.82, 51.68, 45.42, 45.30, 45.22, 45.13, 40.31, 38.94, 38.72, 37.18, 23.28, 23.15, 22.54, 22.46. FTIR (NaCl) (cm^{-1}): 3396, 1727. HRMS: calcd for $C_{25}H_{31}NNaO_5$: (M^++Na) 448.2100, found: 448.2100.

3.2.7. 2-Methyl-2-[3-oxo-2-{(*N*-2-methoxyphenylamino)-(2-furfuryl)-methyl}-cyclopentyl] propanoic acid methyl ester (mixture of diastereomers, *syn* 5h+*anti* 6h). (*syn* **5h**+*anti* **6h**). ^{1}H NMR (250 MHz, $CDCl_3$, δ (ppm)): 7.32 (m, 0.25H, *anti* **6h**), 7.28 (m, 0.75H, *syn* **5h**), 6.77 (m, 2H, *syn*+*anti*), 6.65 (m, 1H, *syn*+*anti*), 6.51 (m, 1H, *syn*+*anti*), 6.28 (m, 0.25H, *anti* **6h**), 6.23 (m, 0.75H, *syn* **5h**), 6.17 (m, 0.25H, *anti* **6h**), 6.14 (m, 0.75H, *syn* **5h**), 5.75 (d, J=10.3 Hz, 1H, *syn*+*anti*), 4.95–4.88 (m, 0.25H, *anti* **6h**), 4.81 (dd, J_1=10.3 Hz, J_2=4.3 Hz, 0.75H, *syn* **5h**), 3.87 (s, 2.25H, *syn* **5h**), 3.85 (s, 0.75H, *anti* **6h**), 3.66 (s, 2.25H, *syn* **5h**), 3.57 (s, 0.75H, *anti* **6h**), 2.83–2.79 (m, 0.25H, *anti* **6h**), 2.71–2.67 (m, 0.75H, *syn* **5h**), 2.57–2.49 (m, 1H, *syn*+*anti*), 2.30–1.94 (m, 3H, *syn*+*anti*), 1.78–1.62 (m, 1H, *syn*+*anti*), 1.19 (s, 0.75H, *anti* **6h**), 1.18 (s, 0.75H, *anti* **6h**), 1.17 (s, 2.25H, *syn* **5h**), 1.14 (s, 2.25H, *syn* **5h**). ^{13}C NMR (62.9 MHz, $CDCl_3$, δ (ppm)): 220.35, 177.43, 153.34, 147.31, 141.48, 136.11, 120.94, 117.26, 110.93, 110.36, 109.73, 107.78, 55.58, 55.14, 52.88, 51.78, 45.64, 45.18, 40.40, 38.80, 38.31, 37.61, 30.87, 29.61, 24.38, 23.42, 22.63, 21.19. FTIR (CCl_4,) (cm^{-1}): 3392, 1733. HRMS: calcd for $C_{22}H_{27}NNaO_5$ (M^++Na): 408.1787, found: 408.1788.

3.2.8. 2-Methyl-2-[3-oxo-2-{(*N*-4-methoxyphenylamino)-ethoxycarbonyl-methyl}-cyclohexyl] propanoic acid methyl ester (mixture of diastereomers, *syn* 5i+*anti* 6i). *syn* **5i**+*anti* **6i**. ^{1}H NMR: (250 MHz, $CDCl_3$, δ (ppm)): 6.73

(m, 2H), 6.60 (m, 2H), 4.07 (m, 3H), 3.71 (s, 2.58, *syn* **5i**), 3.70 (s, 0.42H, *anti* **6i**), 3.61 (s, 2.58H, *syn* **5i**), 3.47 (s, 0.42H, *anti* **6i**), 2.66 (m, 2H), 2.53 (m, 1H), 2.27 (m, 1H), 1.88 (m, 3H), 1.52 (m, 1H), 1.19–1.13 (m, 9H). ^{13}C NMR: (62.5 MHz, $CDCl_3$, δ (ppm)): 212.12, 177.81, 172.48, 152.95, 140.74, 115.67, 114.66, 61.18, 60.42, 55.49, 55.00, 51.70, 45.85, 43.79, 39.48, 24.11, 23.88, 22.54, 21.39, 13.88. FTIR (NaCl) (cm^{-1}): 3360, 1728. HRMS: calcd for $C_{22}H_{31}NNaO_6$ (M^++Na): 428.2049, found: 428.2045.

3.2.9. [3-Oxo-2-{(*N*-4-methoxyphenylamino)-ethoxycarbonyl-methyl}-cyclopentyl] acetic acid phenyl ester (*syn* 5j+*anti* 6j). *syn* **5j**+*anti* **6j**. ^{1}H NMR (250 MHz, $CDCl_3$, δ (ppm)): 7.36 (m, 2H), 7.07 (m, 2H), 6.73 (s, 5H), 4.52 (l, 1H), 4.39 (l, 1H), 4.12 (q, 2H, J=7.32 Hz), 3.71 (s, 3H), 2.90–2.19 (m, 6H), 1.73–1.58 (m, 2H), 1.18 (t, 3H, J=7.32 Hz). ^{13}C NMR (62.9 MHz, $CDCl_3$, δ (ppm)): 216.77, 173.12, 170.57, 153.28, 150.34, 140.87, 129.41, 125.96, 121.41, 116.70, 114.60, 61.49, 57.85, 56.20, 55.54, 38.60, 37.79, 34.32, 27.27, 14.01. FTIR (film, NaCl) (cm^{-1}): 3373, 1749. HRMS calcd for $C_{24}H_{27}NNaO_6$ (M^++Na): 448.1735, found: 448.1736.

3.3. Typical procedure for the synthesis of tandem products 7 and 8

In a Schlenk tube, a solution of SmI_2 in THF (0.1 M, 1 mL, 0.1 mmol) was carefully evaporated in vacuo to give $SmI_2(THF)_2$ as a blue powder, (alternatively $SmI_2(THF)_2$ (55 mg, 0.1 mmol) was weighed in a glovebox). Then 1-ethoxy-1-*tert*-butyldimethylsilyloxyethene **2b** (202 mg, 1 mmol) in solution in CH_2Cl_2 (4 mL), and cyclopenten-2-one **1a** (125 μL, 1.5 mmol) were successively added under argon. The resulting yellow solution was then stirred for 0.5 h at room temperature, while the formation of enoxysilane was monitored by GC and reaction mixture was cooled at 0 °C. A solution of imine **4a** (270 mg, 1.3 mmol) in CH_2Cl_2 (7 mL) was then added. After 24 h stirring at the same temperature, the reaction mixture was hydrolyzed and extracted by CH_2Cl_2. The crude product was purified on alumina (heptane/AcOEt: 90/10) to give a mixture of **7a**+**8a**, (403 mg, 82%, **7a/8a**, 69/31). Diastereoisomer **7a** was then isolated form the mixture **7a**+**8a** by chromatography on alumina plate.

3.3.1. (5-Ethoxycarbonylmethyl-2-*tert*-butyldimethylsilyloxy-cyclopent-2-enyl)-(4-methoxyphenylamino) acetic acid ethyl ester (mixture of diastereomers, *syn* 7a+*anti* 8a). *syn* **7a**. ^{1}H NMR (400 MHz, $CDCl_3$, δ (ppm)): 6.71 (d, J=8.8 Hz, 2H), 6.57 (d, J=8.8 Hz, 2H), 4.88 (bs, 1H), 4.59 (bs, 1H), 4.24 (bs, 1H), 4.13 (m, 4H), 3.70 (s, 3H), 2.70 (m, 2H), 2.56 (m, 1H), 2.56 (m, 2H), 1.88 (m, 1H), 1.22 (m, 6H), 0.91 (s, 9H), 0.16 (s, 3H), 0.12 (s, 3H). ^{13}C NMR (62.9 MHz, $CDCl_3$, δ (ppm)): 173.32, 172.48, 152.48, 151.95, 141.58, 115.14, 114.62, 102.08, 60.93, 60.35, 59.42, 55.67, 54.10, 41.10, 34.17, 33.00, 25.67, 18.04, 14.23, −4.86, −4.97. FTIR (NaCl) (cm^{-1}): 3396, 1736, 1645. HRMS: calcd for $C_{26}H_{41}NNaO_6Si$: 514.2597, found: 514.2600.

syn **7a**+*anti* **8a**. ^{1}H NMR (200 MHz, $CDCl_3$, δ (ppm)): 6.73 (m, 2H, *syn*+*anti*), 6.57 (m, 2H, *syn*+*anti*), 4.88 (l, 0.31H, *anti* **8a**), 4.59 (l, 0.69H, *syn* **7a**), 4.24–4.06 (m, 5H, *syn*+*anti*), 3.71 (s, 0.93H, *anti* **8a**), 3.70 (s, 2.07H, *syn* **7a**), 2.76–1.59 (m, 8H, *syn*+*anti*), 1.27–1.18 (m, 6H, *syn*+*anti*), 0.92 (s, 2.79H, *anti* **8a**), 0.91 (s, 6.21H, *syn* **7a**), 0.18 (s, 0.93H, *anti* **8a**), 0.02 (s, 0.93H, *anti* **8a**), 0.15 (s, 2.07H, *syn* **7a**), 0.12 (s, 2.07H, *syn* **7a**).

3.3.2. [2-{(*N*-2-Methoxyphenylamino)-(2-furfuryl)-methyl}-3-*tert*-butyldimethylsilyloxy-cyclopent-3-enyl] acetic acid ethyl ester (mixture of diastereomers, *syn* 7b+*anti* 8b). *syn* **7b**+*anti* **8b**. ^{1}H NMR (250 MHz, $CDCl_3$ δ (ppm)): 7.32 (m, 0.82H, *syn* **7b**), 7.28 (m, 0.18H, *anti* **8b**), 6.71 (m, 2H, *syn*+*anti*), 6.59 (m, 1H, *syn*+*anti*), 6.44 (m, 1H, *syn*+*anti*), 6.25 (m, 1H, *syn*+*anti*), 6.17 (m, 1H, *syn*+*anti*), 4.95 (d, J=6.0 Hz, 0.18H, *anti* **8b**), 4.66 (m, 1H, *syn*+*anti*), 4.55 (d, J=1.5 Hz, 0.82H, *syn* **7b**), 4.07 (q, J=7.3 Hz, 2H, *syn*+*anti*), 3.85 (s, 0.54H, *anti* **8b**), 3.80 (s, 2.46H, *syn* **7b**), 2.85 (m, 1H, *syn*+*anti*), 2.65–2.37 (m, 2H, *syn*+*anti*), 2.19–2.03 (m, 2H, *syn*+*anti*), 1.89–1.79 (m, 1H, *syn*+*anti*), 1.21 (t, J=7.3 Hz, 3H, *syn*+*anti*), 0.88 (s, 1.62H, *anti* **8b**), 0.84 (s, 7.38H, *syn* **7b**), 0.14 (s, 3H, *syn*+*anti*), 0.01 (s, 3H, *syn*+*anti*). ^{13}C NMR (62.9 MHz, $CDCl_3$, δ (ppm)): 172.61, 155.13, 152.25, 146.75, 141.20, 137.32, 120.98, 116.41, 110.65, 110.32, 109.04, 106.76, 101.86, 60.18, 55.33, 55.12, 53.12, 40.82, 33.96, 33.23, 25.31, 18.00, 14.19, −4.89, −5.49. FTIR (CCl_4) (cm^{-1}): 3432, 1736, 1648. HRMS calcd for $C_{27}H_{39}NNaO_5Si$ (M^++Na): 508.2495, found: 508.2496.

3.3.3. (6-Ethoxycarbonylmethyl-2-*tert*-butyldimethylsilyloxy-cyclohex-2-enyl)-(4-methoxyphenylamino) acetic acid ethyl ester (mixture of diastereomers, *syn* 7c+*anti* 8c). *syn* **7c**+*anti* **8c**. ^{1}H NMR (400 MHz, $CDCl_3$, δ (ppm)): 6.72 (m, 2H, *syn*+*anti*), 6.60 (m, 2H, *syn*+*anti*), 5.24 (m, 1H, *syn*+*anti*), 4.99 (t, J=3.7 Hz, 0.75H, *syn* **7c**), 4.95 (t, J=3.7 Hz, 0.25H, *anti* **8c**), 4.24 (bs, 1H, *syn*+*anti*), 4.19–4.03 (m, 4H, *syn*+*anti*), 3.70 (s, 3H, *syn*+*anti*), 2.53–2.42 (m, 1H, *syn*+*anti*), 2.41–2.30 (m, 1H, *syn*+*anti*), 2.30–2.17 (m, 3H, *syn*+*anti*), 2.07–1.99 (m, 1H, *syn*+*anti*), 1.90–1.84 (m, 1H, *syn*+*anti*), 1.40–1.34 (m, 1H, *syn*+*anti*), 1.25–1.18 (m, 6H, *syn*+*anti*), 0.98–0.94 (m, 9H, *syn*+*anti*), 0.22–0.14 (m, 6H, *syn*+*anti*). ^{13}C NMR (62.9 MHz, $CDCl_3$, δ (ppm)): 173.76, 172.69, 152.54, 147.43, 142.02, 115.54, 114.60, 106.40, 104.83, 61.04, 60.34, 55.67, 47.08, 38.21, 31.15, 25.74, 24.01, 21.00, 20.32, 14.21, −4.18, −4.86. FTIR (NaCl) (cm^{-1}): 3392, 1732, 1669. HRMS calcd for $C_{27}H_{43}NaO_6Si$ (M^++Na): 528.2764, found: 528.2757.

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