Organic Process Research & Development **2010,** *14,* 687–691

One-Pot Synthesis of Optically Active β-Amino-α-methylene Carbonyl Derivatives From α-Amidosulfones Using Quinine-Based Phase-Transfer Catalysts

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Abstract:

Optically active β-amino-α-methylene carbonyl derivatives (aza-Morita–Baylis–Hillman adducts) were prepared using a one-pot protocol involving an enantioselective Mannich reaction catalyzed by various quinine-based catalysts, followed by a Horner olefination.

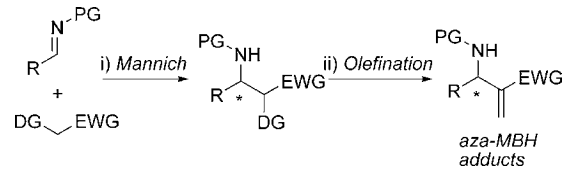
Introduction

α-Alkylidene-β-amino carbonyl derivatives are very versatile intermediates in organic synthesis.[1] These particular allylic amines are usually named as aza-Morita–Baylis–Hillman (aza-MBH) adducts, after the most common route used for their preparation. The aza-MBH reaction has in fact witnessed tremendous advances in the past few years, especially directed to catalytic asymmetric protocols.[2] In contrast, less attention has been paid to alternative approaches leading to these synthetically relevant compounds in enantioenriched form.[3] In this context, an attractive conceivable route involves a Mannich-type addition of an enolizable compound equipped with a suitable directing group (DG), such as a phosphonium or a sulfonyl moiety, able to undergo an olefination process after the Mannich addition has taken place (Scheme 1). The role of this directing group is two-fold: besides furnishing the synthetic handle necessary for the olefination, its electron-withdrawing properties facilitate the enolization process by acidifying the methylene moiety. As a result, the Mannich reaction may proceed under very mild and convenient conditions, overcoming some of the typical limitations of aza-MBH reactions, i.e. the presence of a tosyl protecting group at the imine nitrogen and difficult employment of imines derived from aliphatic enolizable aldehydes.[2]

In 2008, Chen and co-workers reported a very efficient asymmetric Mannich-type addition of stabilized α-triphenylphosphonium ester ylides to *N*-Boc imines, catalyzed by a bis-thiourea organocatalyst, wherein quenching the reaction with formalin furnished the corresponding aza-MBH adducts with outstanding results.[4] More recently,[5] we described arylsulfonylacetates as suitable reaction partners in an asymmetric Mannich-type reaction with *N*-Boc and *N*-Cbz imines under PTC (phase-transfer catalysis) conditions.[6] Thanks to the use of excess inorganic base in the PTC procedure, *N*-Boc and *N*-Cbz imines could be generated in situ from the corresponding α-amidosulfones[7] (avoiding isolation and storage of imines which are troublesome when derived from aliphatic enolizable aldehydes). However, the overall procedure leading to the aza-MBH adducts was complicated by the requirement of purification by filtration through silica gel, followed by a solvent switch and the addition of a different inorganic base, before the Julia–Kocienski olefination step.

Envisioning the possibility of obtaining the target aza-MBH adducts with a one-pot protocol by using a Wittig-type olefination instead of the Julia–Kocienski process, we set our

Scheme 1. **Mannich–olefination approach to aza-MBH adducts. DG = directing group. PG = protecting group. EWG = electron-withdrawing group**



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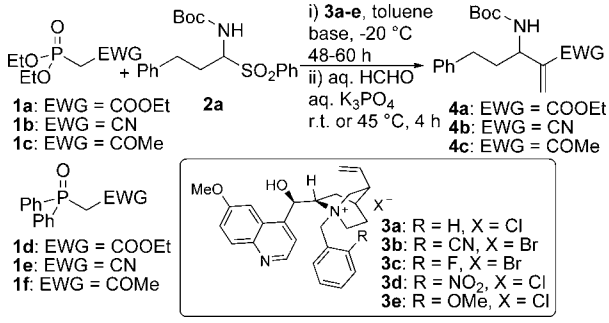
10.1021/op1000308
Published on Web 03/24/2010

Table 1. **Selected optimization results from the screening of Mannich donors 1, catalysts 3, and reaction conditions[a]**



entry	Mannich donor **1**	cat. **3**	base[b] (equiv)	conv.[c] (%)	aza-MBH adduct **4**	ee[d] (%)
1	**1a**	**3a**	aq 50% K_3PO_4 (10)	>90	**4a**	19
2	**1b**	**3a**	aq 50% K_2CO_3 (10)	>90	**4b**	25
3	**1c**	**3a**	aq 50% K_2CO_3 (10)	>90	**4c**	61
4	**1d**	**3a**	aq 50% K_3PO_4 (10)	<10	**4a**	–
5	**1e**	**3a**	aq 50% K_2CO_3 (10)	>90	**4b**	45
6	**1f**	**3a**	aq 50% K_2CO_3 (10)	75	**4c**	92
7	**1f**	**3b**	aq 50% K_2CO_3 (10)	70	**4c**	91
8	**1f**	**3c**	aq 50% K_2CO_3 (10)	75	**4c**	88
9	**1f**	**3d**	aq 50% K_2CO_3 (10)	55	**4c**	84
10	**1f**	**3e**	aq 50% K_2CO_3 (10)	80	**4c**	94
11[e]	**1f**	**3e**	aq 50% K_2CO_3 (10)	85	**4c**	94
12	**1f**	**3e**	Cs_2CO_3 (2.5)	90	**4c**	81
13	**1f**	**3a**	aq 50% K_3PO_4 (5)	>90	**4c**	77
14[f]	**1f**	**3e**	aq 50% K_3PO_4 (5)	90	**4c**	94

[a] Conditions: **2a** (0.05 mmol), **1a**−**f** (0.075 mmol), **3a**−**e** (0.0050 mmol, 10 mol %), in toluene (0.50 mL), base, −20 °C, 48−60 h; then aq 37% HCHO (0.25 mmol), and aq 50% K_3PO_4 (20 equiv for **1e**, **f**), rt for **1a**−**c**, 45 °C for **1e**, **f**, 4 h. [b] Base used in the Mannich step. [c] Refers to the Mannich step. Estimated by TLC and/or ^{1}H NMR sctroscopy. [d] Ee of **4**, determined by chiral stationary phase HPLC. [e] 0.25 mL of toluene was used. [f] toluene/CH_2Cl_2 7:3 mixture (0.25 mL) and 0.055 mmol of donor **1f** (1.1 equiv) were used.

focus on phosphonates and phosphine oxides as directing groups in Mannich donors.[8] Herein, we report our preliminary results on this new approach to aza-MBH adducts, which combines the operational simplicity of a one-pot procedure with the convenience of the direct use of α-amidosulfones in PTC Mannich reactions.

Results and Discussion

At the outset of our studies, phosphonate derivatives were chosen for several reasons. Many are commercially available, the phosphonate moiety should lower the pK_a of the methylene group at its α-position,[9] and Horner−Wadsworth−Emmons olefinations have been demonstrated to be feasible under PTC conditions.[10] Accordingly, triethyl phosphonoacetate **1a** was reacted with α-amidosulfone **2a** in toluene, using *N*-benzylquininium chloride **3a** as the catalyst (10 mol %), and excess aq 50% K_3PO_4 at −20 °C (Table 1, entry 1). The Mannich addition proceeded smoothly over 48 h, and to our delight it was possible to generate the targeted aza-MBH adduct **4a** simply by adding formalin to the mixture and stirring the reaction for 4 h. Enantioselectivity was unfortunately not satisfactory, even after extensive variation of the catalyst, solvent, base, and reaction temperature. The influence of the phosphonate Mannich donor **1** was thus inspected, and we found that by using a weaker base such as aq K_2CO_3 the keto derivative **1c** gave better enantioselection as compared to the ester **1a** and cyano derivative **1b** (Table 1, entries 2, 3). As the enantioselectivity was still not satisfactory, even with the keto derivative **1c**, we considered a different directing group with an acidifying effect similar to that of a phosphonate:[9a] diphenylphosphine oxide. Donors **1d**−**f**, prepared by simple and scalable Arbuzov-type alkylations,[11] were tested in the reaction with **2a**. Whereas the ester derivative **1d** did not react in the Mannich step, even when using aq 50% K_3PO_4 (Table 1, entry 4), both cyano and keto compounds **1e** and **1f** afforded the corresponding Mannich bases smoothly. However, as expected, these Mannich intermediates were found to undergo the olefination process (Horner olefination)[12] more reluctantly as compared to the corresponding phosphonates. As a further efficiency, the aza-MBH adducts **4** could be obtained with a one-pot protocol simply by running the olefination with addition of a large excess of base (50% K_3PO_4, 20 equiv) and heating the mixture to 45 °C. With this procedure, **4b** and **4c** were isolated, and the keto derivative **4c** displayed the best and, for the first time, satisfactory enantiomeric excess, in line with the results obtained with phosphonates **1a**−**c** (Table 1, entries 5, 6). Catalysts **3b**−**e**, bearing ortho-substituted benzyl groups at the quinuclidine nitrogen, were then tested in the reaction with **1f** (Table 1, entries 7−10). We have already employed these types of catalysts, originally developed for PTC alkylations of benzophenone imines derived from glycine,[13] in several asymmetric Mannich-type PTC reactions.[5,7c,9b,14] We believe that the positive influence exerted by these ortho substituents on the enantioselectivity of the reaction is not due to electronic effects[15] but rather to their assistance in rigidifying catalyst structure, possibly through hydrogen-bond interactions between one of their lone pairs, the protons of a molecule of water, and a lone pair of the 9-hydroxy group of quinine, as observed by X-ray on a similar derivative.[16] A more rigid ionic couple may render more efficient the transfer of the chiral information from catalyst to substrates.[5] In particular, catalyst **3e**, possessing a methoxy moiety, proved to be the most efficient and was thus employed for the final optimization efforts devoted to improve the conversion of the Mannich step. Whereas doubling the concentration of the mixture slightly improved the conversion without influencing the ee of **4c** (Table 1, entry 11), using other inorganic bases such as solid Cs_2CO_3

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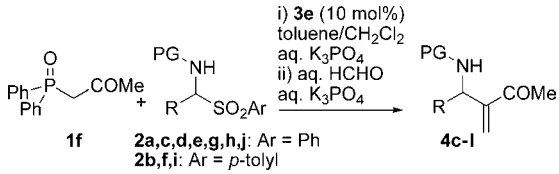
Table 2. **One-pot protocol for the preparation of aza-MBH adducts 4: reaction scope**[a]



entry	2	R	Pg	4	yield[b] (%)	ee[c] (%)
1	**2a**	$Ph(CH_2)_2$	Boc	**4c**	67	94
2	**2b**	*n*-hexyl	Boc	**4d**	75	94
3	**2c**	Me	Boc	**4e**	63	83
4[d]	**2d**	$PhCH_2$	Boc	**4f**	42	80
5	**2e**	Ph	Boc	**4g**	67	92
6	**2f**	*p*-$MeOC_6H_4$	Boc	**4h**	69	98
7	**2g**	*p*-ClC_6H_4	Boc	**4i**	77	86
8	**2h**	2-thienyl	Boc	**4j**	88	93
9	**2i**	$Ph(CH_2)_2$	Cbz	**4k**	89	84
10	**2j**	Ph	Cbz	**4l**	58	84

[a] Conditions: **2a**−**j** (0.20 mmol), **1f** (0.22 mmol), **3e** (0.020 mmol, 10 mol %), in toluene/CH_2Cl_2 7:3 (1.0 mL), aq 50% K_3PO_4 (1.0 mmol), −20 °C, 60 h; then aq 37% HCHO (1.0 mmol), aq 50% K_3PO_4 (4.0 mmol), 45 °C 4 h for **4c, d, f**−**i**, **l,** rt 60 h for **4e**, **j**, **k**. [b] Isolated yield after chromatography on silica gel. [c] Determined by chiral stationary phase HPLC. [d] 1.5 equiv of **1f** was used.

or aq 50% K_3PO_4 in excess (with catalyst **3a**) lowered the enantioselectivity of the reaction (Table 1, entries 12, 13). However, we found after further experimentation that the same latter base could be successfully used with the optimum catalyst **3e**, in a toluene/CH_2Cl_2 (7:3) mixture with a lower excess (1.1 equiv) of the Mannich donor **1f** (Table 1, entry 14).

Before exploring the scope of the reaction, a preparation of catalyst **3e** relying on its isolation by precipitation was developed (see Experimental Section), thus avoiding the cumbersome chromatographic purification step of our previous synthetic protocol.[7c] The optimized conditions were then applied to a few α-amidosulfones **2a**−**j** (Table 2). We eventually found that slightly better yields could be obtained in some cases by running the Horner olefination step at ambient temperature (Table 2, entries 3, 8, 9) for prolonged reaction time, instead of at 45 °C. Employing the appropriate conditions, *N*-Boc protected aza-MBH adducts **4c**−**j** could be prepared in moderate to good yields (over two steps), and with generally good enantioselectivities, starting from *N*-Boc α-amidosulfones **2a**−**h** derived from both aliphatic and aromatic aldehydes (entries 1−8). A Cbz protecting group could also be used in the reaction, as exemplified for products **4k**, **l** (entries 9, 10). The diminished enantioselectivities observed in some cases may not be ascribed to a racemic background reaction, as control experiments performed either with α-amidosulfone **2c** or with the preformed *N*-Boc benzylidene imine derived from **2e** did not show the formation of Mannich adduct in the absence of catalyst **3e**.

Conclusions

We have described a new Mannich-olefination sequence for the obtainment of enantioenriched *N*-Boc and *N*-Cbz protected aza-MBH adducts that relies on a quinine-based phase-transfer catalyst. The preparation via more classical approaches of these enantioenriched compounds, bearing synthetically useful *N*-Boc and *N*-Cbz protecting groups at nitrogen, is not trivial. This new protocol enables the one-pot obtainment of these versatile synthetic intermediates from stable, easy to prepare and cheap starting materials and catalysts. We expect these conditions to be amenable to the preparation of important compounds at preparative scale.

Experimental Section

^1H, ^{13}C, ^{31}P NMR spectra were recorded on a Varian AS 400 or 600 spectrometer. Chemical shifts (δ) are reported in ppm relative to residual solvent signals for ^1H and ^{13}C NMR,[17] and to an external reference for ^{31}P NMR (85% H_3PO_4, 0.0 ppm). ^{13}C and ^{31}P NMR spectra were acquired with ^1H broad band decoupled mode. Mass spectra were recorded on a micromass LCT spectrometer using electrospray (ES) ionisation techniques. Chromatographic purifications were performed using 70−230 mesh silica. α-Amidosulfones **2a**−**j** were prepared following literature procedures.[18] Racemic samples were prepared using tetrabutylammonium bromide as a catalyst at r.t. overnight.

1-(Diphenylphosphoryl)propan-2-one (1f).[11] Chloroacetone (8.17 mL, 103 mmol, 1.25 equiv) was added to crude ethoxydiphenylphosphine[19] (19.09 g, 83.0 mmol). The resulting liquid was heated at 100 °C for 1.5 h. After cooling to r.t., the crude product solidified and was collected by filtration, and washed with toluene. Spectroscopically pure **1f** was then obtained as a white solid (11.20 g, 52% yield) by crystallization from *i*-Pr_2O/THF. ^1H NMR (400 MHz, $CDCl_3$): δ 7.83−7.68 (m, 4H), 7.55−7.49 (m, 2H), 7.48−7.42 (m, 4H), 3.58 (d, J = 15.0 Hz, 2H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.8 (d, J = 6 Hz), 132.2 (d, J = 3 Hz), 131.8 (d, J = 102 Hz), 130.8 (d, J = 10 Hz), 128.7 (d, J = 12 Hz), 47.9 (d, J = 57 Hz), 32.6; ^{31}P NMR (162 MHz, $CDCl_3$): δ 26.9.

N-(2-Methoxybenzyl)quininium Chloride (3e). 2-Methoxybenzyl chloride (1.81 mL, 13 mmol, 1.3 equiv) was added to a stirred suspension of quinine (3.24 g, 10 mmol) in a toluene/THF 1:1 mixture (30 mL). The resulting suspension was heated to 70 °C with stirring for 24 h. After cooling to r.t., MeOH was added to the mixture with stirring, until all the gummy purple solid turned into a fine particle suspension (ca. 10 mL). Stirring was stopped, toluene (8 mL) was added, followed by Et_2O (30 mL), then the mixture was allowed to stand at r.t. for 1 h. Spectroscopically pure **3e** was obtained as a pale red solid (3.03 g, 63% yield) by filtration, followed by several washings with Et_2O. Spectral data were in accordance to our previous report.[7c]

General Procedure for the One-Pot Preparation of aza-MBH Adducts 4c−**l.** α-Amidosulfone **2a**−**j** (0.20 mmol), diphenylphosphorylketone **1f** (56.8 mg, 0.22 mmol, 1.1 equiv), and catalyst **3e** (9.6 mg, 0.020 mmol) were weighed in a vial equipped with a magnetic stirring bar. The solids were suspended/dissolved in a toluene/CH_2Cl_2 (7:3) mixture (1.0 mL), the vial was capped and cooled to −20 °C. Aqueous K_3PO_4 (50% $^w/_w$, 270 μL, 1.0 mmol, 5.0 equiv) was then added in one

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portion. After the resulting biphasic mixture had been vigorously stirred at the same temperature for 60 h, aq formaldehyde (37% $^{w}/_{w}$, 74.5 μL, 1.0 mmol, 5.0 equiv) was added, followed by another portion of aq K_3PO_4 (50% $^{w}/_{w}$, 1.08 mL, 4.0 mmol, 20.0 equiv). The mixture was then heated to 45 °C with stirring for 4 h for compounds **4c**, **d**, **f**−**i**, **l** or stirred at rt for 60 h, for compounds **4e**, **j**, **k**. The organic layer was then charged directly on a silica gel chromatographic column, the aqueous phase was extracted with toluene (2 × 0.5 mL), and the extracts were charged as well. The aza-MBH adducts **4c**−**l** were obtained, eluting with petroleum ether/Et_2O mixtures.

(+)-*tert*-Butyl 4-Methylene-5-oxo-1-phenylhexan-3-ylcarbamate (4c). Following the general procedure, the title compound was obtained as white solid in 67% yield, after chromatography on silica gel (petroleum ether/Et_2O, 7:3). The ee of the product was determined by HPLC (Chiralcel OJ-H, *n*-hexane/*i*-PrOH 95:5, 0.75 mL/min, λ = 215 nm: τ_{maj} = 16.1 min, τ_{min} = 14.3 min, 94% ee). $[\alpha]^{22}_D$ = +10 (*c* 0.84, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29−7.23 (m, 2H), 7.19−7.13 (m, 3H), 6.05 (s, 1H), 5.92 (br s, 1H), 5.30 (br d, *J* = 8.8 Hz, 1H), 4.39 (br q, *J* = 7.9 Hz, 1H), 2.73−2.51 (m, 2H), 2.31 (s, 3H), 2.02−1.85 (m, 2H), 1.42 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.8, 155.2, 147.9, 141.3, 128.3, 127.2, 125.9, 79.2, 53.9, 36.3, 32.9, 28.4, 26.6; ESI-MS: 326 [M + Na^+].

(+)-*tert*-Butyl 3-Methylene-2-oxodecan-4-ylcarbamate (4d). Following the general procedure, the title compound was obtained as a colorless oil in 75% yield, after chromatography on silica gel (petroleum ether/Et_2O, 8:2). The ee of the product was determined by HPLC (Chiralpak AD-H, *n*-hexane/*i*-PrOH 95:5, 0.75 mL/min, λ = 215 nm: τ_{maj} = 6.6 min, τ_{min} = 7.2 min, 94% ee). $[\alpha]^{22}_D$ = +12 (*c* 0.75, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.01 (br s, 1H), 5.82 (br s, 1H), 5.19 (br d, *J* = 8.9 Hz, 1H), 4.29 (br q, *J* = 7.6 Hz, 1H), 2.30 (s, 3H), 1.61−1.49 (m, 2H), 1.39 (s, 9H), 1.30−1.13 (m, 8H), 0.83 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 199.8, 155.2, 148.3, 126.7, 79.1, 53.9, 34.7, 31.7, 28.8, 28.4, 26.6, 26.5, 22.5, 14.0; ESI-MS: 306 [M + Na^+].

(+)-*tert*-Butyl 3-Methylene-4-oxopentan-2-ylcarbamate (4e). Following the general procedure, the title compound was obtained as white solid in 63% yield, after chromatography on silica gel (petroleum ether/Et_2O, 7:3). The ee of the product was determined by HPLC (Chiralcel OJ-H, *n*-hexane/*i*-PrOH 95:5, 0.75 mL/min, λ = 215 nm: τ_{maj} = 8.8 min, τ_{min} = 7.9 min, 83% ee). $[\alpha]^{22}_D$ = +12 (*c* 0.53, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.01 (s, 1H), 5.92 (s, 1H), 5.13 (br s, 1H), 4.51 (br q, *J* = 8.0 Hz, 1H), 2.32 (s, 3H), 1.41 (s, 9H), 1.26 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.5, 154.9, 149.6, 125.5, 79.2, 48.7, 28.3, 26.6, 21.2; ESI-MS: 236 [M + Na^+].

(-)-*tert*-Butyl 3-Methylene-4-oxo-1-phenylpentan-2-ylcarbamate (4f). Following the general procedure but using 1.5 equiv of **1f**, the title compound was obtained as white solid in 42% yield, after chromatography on silica gel (petroleum ether/Et_2O, 7:3). The ee of the product was determined by HPLC (Chiralpak AD-H, *n*-hexane/*i*-PrOH 95:5, 0.75 mL/min, λ = 215 nm: τ_{maj} = 12.3 min, τ_{min} = 13.0 min, 80% ee). $[\alpha]^{22}_D$ = −7 (*c* 0.42, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28−7.22 (m, 2H), 7.21−7.15 (m, 1H), 7.13−7.08 (m, 2H), 5.94 (br s, 1H), 5.68 (br s, 1H), 5.35 (br d, *J* = 8.2 Hz, 1H), 4.63 (br q, *J* = 7.8 Hz, 1H), 2.94 (br d, *J* = 7.3 Hz, 2H), 2.31 (br s, 3H), 1.37 (br s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.4, 155.0, 146.8, 129.2, 128.3, 127.9, 126.4, 79.3, 55.1, 40.8, 28.3, 26.6; ESI-MS: 312 [M + Na^+].

(-)-*tert*-Butyl 2-Methylene-3-oxo-1-phenylbutylcarbamate (4g). Following the general procedure, the title compound was obtained as white solid in 67% yield, after chromatography on silica gel (petroleum ether/Et_2O, 7:3). The ee of the product was determined by HPLC (Chiralpak AD-H, *n*-hexane/*i*-PrOH 95:5, 0.75 mL/min, λ = 215 nm: τ_{maj} = 18.6 min, τ_{min} = 15.2 min, 92% ee). $[\alpha]^{22}_D$ = −19 (*c* 0.59, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.30−7.18 (m, 5H), 6.20 (s, 1H), 6.10 (s, 1H), 5.63 (d, *J* = 8.2 Hz, 1H), 5.51 (br s, 1H), 2.28 (s, 3H), 1.43 (br s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 199.1, 155.2, 148.1, 140.4, 128.7, 127.6, 127.0, 126.7, 79.9, 56.4, 28.6, 26.8; ESI-MS: 298 [M + Na^+].

(-)-*tert*-Butyl 1-(4-methoxyphenyl)-2-methylene-3-oxobutylcarbamate (4h). Following the general procedure, the title compound was obtained as a thick oil in 69% yield, after chromatography on silica gel (petroleum ether/Et_2O, 65:35). The ee of the product was determined by HPLC (Chiralpak AD-H, *n*-hexane/*i*-PrOH 90:10, 0.75 mL/min, λ = 215 nm: τ_{maj} = 16.1 min, τ_{min} = 14.5 min, 98% ee). $[\alpha]^{22}_D$ = −47 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.16 (br d, *J* = 8.5 Hz, 2H), 6.82−6.79 (m, 2H), 6.17 (s, 1H), 6.06 (br s, 1H), 5.58 (br d, *J* = 8.1 Hz, 1H), 5.41 (br s, 1H), 3.75 (s, 3H), 2.28 (s, 3H), 1.42 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 199.1, 159.1, 155.1, 148.3, 132.6, 128.0, 126.3, 114.1, 79.9, 55.8, 55.5, 28.6, 26.9; ESI-MS: 328 [M + Na^+].

(-)-*tert*-Butyl 1-(4-Chlorophenyl)-2-methylene-3-oxobutylcarbamate (4i). Following the general procedure, the title compound was obtained as a white solid in 77% yield, after chromatography on silica gel (petroleum ether/Et_2O, 65:35). The ee of the product was determined by HPLC (Chiralpak AD-H, *n*-hexane/*i*-PrOH 90:10, 0.75 mL/min, λ = 215 nm: τ_{maj} = 11.8 min, τ_{min} = 10.5 min, 86% ee). $[\alpha]^{22}_D$ = −1 (*c* 1.2, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.26−7.23 (m, 2H), 7.19−7.16 (m, 2H), 6.21 (s, 1H), 6.11 (br s, 1H), 5.58 (br d, *J* = 8.6 Hz, 1H), 5.54 (br s, 1H), 2.29 (s, 3H), 1.42 (br s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 199.1, 155.2, 147.7, 139.1, 133.3, 128.8, 128.0, 127.7, 80.1, 56.1, 28.6, 26.8; ESI-MS: 332 [M + Na^+].

(-)-*tert*-Butyl 2-Methylene-3-oxo-1-(thiophen-2-yl)butylcarbamate (4j). Following the general procedure, the title compound was obtained as white solid in 88% yield, after chromatography on silica gel (petroleum ether/Et_2O, 7:3). The ee of the product was determined by HPLC (Chiralpak AD-H, *n*-hexane/*i*-PrOH 95:5, 0.75 mL/min, λ = 215 nm: τ_{maj} = 16.9 min, τ_{min} = 14.7 min, 93% ee). $[\alpha]^{22}_D$ = −17 (*c* 0.71, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.16 (dd, *J* = 5.3, 1.2 Hz, 1H), 6.90 (dd, *J* = 5.1, 3.5 Hz, 1H), 6.85 (dt, J_d = 3.4 Hz, J_t = 1.1 Hz, 1H), 6.20 (s, 1H), 6.13 (br s, 1H), 5.84 (br d, *J* = 9.0 Hz, 1H), 5.71 (br s, 1H), 2.34 (s, 3H), 1.44 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.7, 154.7, 147.3, 144.5, 127.0, 126.9, 124.6, 124.5, 79.8, 52.6, 28.3, 26.5; ESI-MS: 304 [M + Na^+].

(+)-Benzyl 4-Methylene-5-oxo-1-phenylhexan-3-ylcarbamate (4k). Following the general procedure, the title compound was obtained as white solid in 89% yield, after

chromatography on silica gel (petroleum ether/Et_2O, 6:4). The ee of the product was determined by HPLC (Chiralpak AD-H, *n*-hexane/*i*-PrOH 95:5, 0.75 mL/min, $\lambda = 215$ nm: $\tau_{maj} = 34.2$ min, $\tau_{min} = 37.3$ min, 84% ee). $[\alpha]^{22}_D = +8$ (*c* 1.18, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40−7.29 (m, 4H), 7.28−7.22 (m, 3H), 7.21−7.10 (m, 3H), 6.06 (br s, 1H), 5.95 (br s, 1H), 5.59 (br d, $J = 9.3$ Hz, 1H), 5.12 (d, $J = 12.0$ Hz, 1H), 5.05 (d, $J = 12.0$ Hz, 1H), 4.46 (br q, $J = 8.0$ Hz, 1H), 2.71−2.52 (m, 2H), 2.31 (s, 3H), 2.08−1.88 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.7, 155.7, 147.5, 141.1, 136.4, 128.4, 128.3, 128.2, 128.0, 127.5, 125.9, 66.6, 54.4, 36.0, 32.8, 26.5; ESI-MS: 360 [M + Na^+].

(-)-Benzyl 2-Methylene-3-oxo-1-phenylbutylcarbamate (4l). Following the general procedure, the title compound was obtained as a white solid in 58% yield, after chromatography on silica gel (petroleum ether/Et_2O, 65:35). The ee of the product was determined by HPLC (Chiralpak AD-H, *n*-hexane/*i*-PrOH 80:20, 0.75 mL/min, $\lambda = 215$ nm: $\tau_{maj} = 26.2$ min, $\tau_{min} = 17.5$ min, 84% ee). $[\alpha]^{22}_D = -9$ (*c* 0.83, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.38−7.17 (m, 10H), 6.21 (br s, 1H), 6.12 (br s, 1H), 5.83 (br s, 1H), 5.71 (br d, $J = 8.8$ Hz, 1H), 5.11 (br s, 2H), 2.29 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 199.1, 155.8, 147.8, 140.1, 136.6, 128.8, 128.7, 128.4, 127.7, 127.5, 126.6, 67.2, 57.0, 26.8; ESI-MS: 332 [M + Na^+].

Acknowledgment

We acknowledge financial support from "Stereoselezione in Sintesi Organica Metodologie e Applicazioni" 2007.

Supporting Information Available

Copies of the NMR spectra for compounds **1f**, **3e**, **4c**−**l**. This material is available free of charge via the Internet at http://pubs.acs.org or from the authors.

Received for review February 1, 2010.

OP1000308