Enantioselective Michael reactions promoted by recoverable dimeric anthryl-derived *Cinchona* phase-transfer catalysts

Rafael Chinchilla, Patricia Mazón, Carmen Nájera,* Francisco J. Ortega, and Miguel Yus

Departamento de Química Orgánica and Instituto de Síntesis Orgánica (ISO), Universidad de Alicante, Apartado 99, 03080 Alicante, Spain
E-mail: cnajera@ua.es

Dedicated to Professor E. Juaristi on occasion of his 55th birthday
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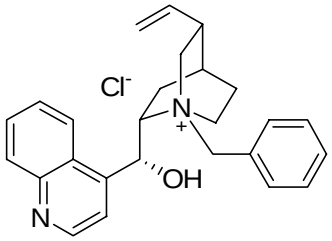
Abstract
Dimeric cinchonidine and cinchonine-derived ammonium salts have been used as phase transfer catalysts in the Michael addition reaction of *N*-(diphenylmethylene)glycine *tert*-butyl ester to electron-poor olefins. The enantioselectivity of the reaction (up to 97% *ee*) was dependent of the counter-anion present in the ammonium salt, and the catalysts could be recovered by precipitation.

Keywords: Asymmetric synthesis, ammonium salts, phase-transfer catalysis, Michael addition, amino acids

Introduction

The synthesis of optically active α-amino acids still remains as an important synthetic challenge which has boosted the development of many methodologies.[1] Amongst all of them, the easily scalable phase-transfer catalysis (PTC),[2] has been applied profusely, especially for the asymmetric alkylation of glycine and alanine Schiff bases.[1n,o,2g-i] Thus, the pioneering works of O'Donnell[3] on the use of quaternized *Cinchona* alkaloids,[4] such as the cinchonidine-derived ammonium salt **1**, as chiral PTC catalysts for the enantioselective alkylation of benzophenone imine glycinates, were improved independently by Lygo (**2a**)[5] and Corey (**2b**),[6] achieving high degrees of enantioselection using a very simple procedure. In addition, dimeric,[7] trimeric,[8] dendrimeric[9] *Cinchona* alkaloid-derived catalysts, and even polymer-supported,[10] have been employed for this type of PTC alkylations.[10] Other non-*Cinchona*-derived catalysts such as spiro ammonium[11] and phosphonium salts,[12] TADDOL[13a,b] and other tartaric derivatives,[13c,d]

guanidinium salts,[13e] binaphthyl-derived amines[13b,14] and salen-metal complexes[15] have also been used.



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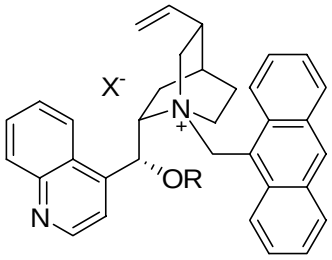
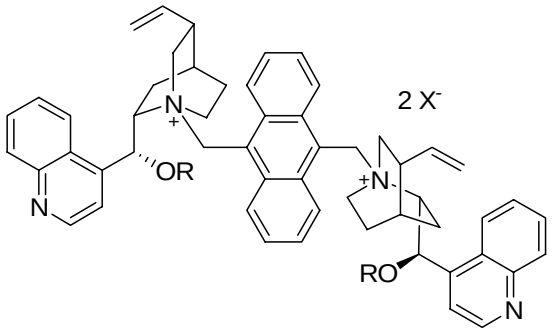


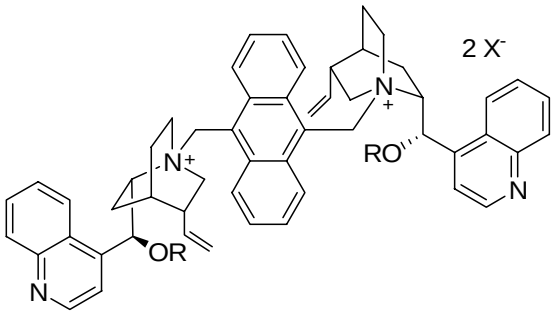
2a, R = H, X = Cl
2b, R = Allyl, X = Br

On the contrary of all the extensive work devoted to the PTC-promoted asymmetric synthesis of α-amino acids through alkylation reactions, only some efforts have been devoted to the use of the asymmetric PTC preparation of amino acid derivatives through such an important process as the Michael addition reaction. Thus, Corey's cinchonidine-derived ammonium salt **2b** has been used in the conjugate addition reaction of benzophenone imine *tert*-butyl glycinate to different Michael acceptors achieving high enantioselectivities,[16] the same catalyst being employed in the asymmetric synthesis of (*S*)-ornithine,[17] (ε-^{13}C,ε-^{15}N)-enriched lysine[18] and solid-phase bounded glycinates.[19] In addition, asymmetric PTC Michael addition reactions have been performed using other chiral ammonium salts derived from L-tartrate[20] and (S)-BINOL,[21] both achieving moderate enantioselectivities. Moreover, chiral guanidines from (*R*)-1-phenylethanamine have also been used although achieving low *ee*'s,[22] much better results being achieved using guanidines from C_2-symmetric 1,2-diphenylethane-1,2-diamines[23] or even a chiral crown ether from *chiro*-inositol.[24]

We have recently prepared dimeric ammonium salts derived from cinchonidine or cinchonine and a bridging (anthracen-9,10-yl)dimethyl moiety, **3a**,**d** and **4a**,**d** respectively, which have shown good enantioselection as catalysts in the PTC alkylation of benzophenone imine glycinates.[7c] These ammonium salts present a unique effect of the accompanying counter-anion in the enantioselectivity of the alkylation reaction.[25] Thus, the tetrafluoroborate or hexafluorophosphate anions in cinchonidine-derived salts **3b**,**e** and **3c**,**f** and in cinchonine-derived salts **4b**,**e** and **4c**,**f** gave generally place to higher *ee*'s compared to the chloride or bromide anions in **3a**,**d** or **4a**,**d** The more noticeable differences and higher *ee*'s were generally observed when the *O*-allylated dimeric catalysts **3d**,**e**,**f** and **4d**,**e**,**f** were employed. With these antecedents we decide to continue the study of the behavior of these dimeric *O*-allylated *Cinchona*-derived dimeric ammonium salts as PTC catalysts. Here we describe the enantioselective Michael addition reaction of benzophenone imine-derived *tert*-butyl glycinate with electron poor olefins.



3a, R = H, X = Cl
3b, R = H, X = BF_4
3c, R = H, X = PF_6
3d, R = Allyl, X = Br
3e, R = Allyl, X = BF_4
3f, R = Allyl, X = PF_6

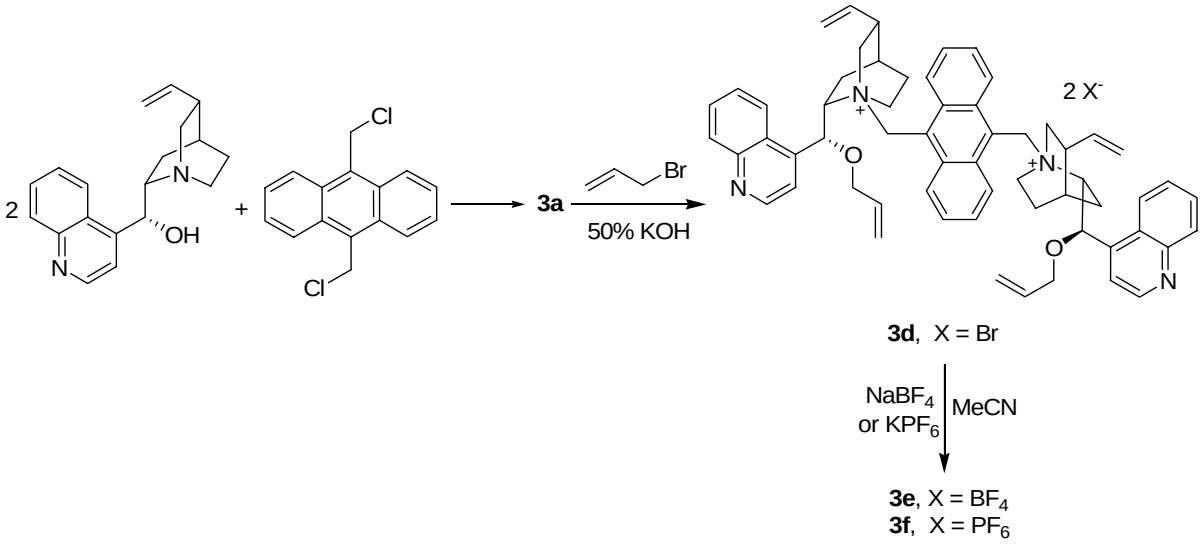


4a, R = H, X = Cl
4b, R = H, X = BF_4
4c, R = H, X = PF_6
4d, R = Allyl, X = Br
4e, R = Allyl, X = BF_4
4f, R = Allyl, X = PF_6

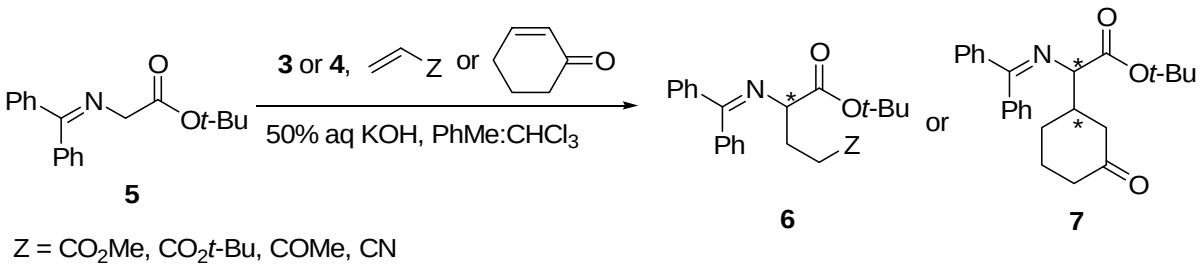
Results and Discussion

The chiral PTC cinchonidinium-derived catalysts were prepared starting from dimeric chloride salt **3a**, which was obtained by reaction of 9,10-di(chloromethyl)anthracene with cinchonidine as described (Scheme 1).[7c] *O*-Allylation of ammonium salt **3a** gave place to the dimeric cinchonidinium salt **3d**, and further exchange of the bromide anions by the tetrafluoroborate and the hexafluorophosphate anions after reaction with sodium tetrafluoroborate or potassium hexafluorophosphate afforded salts **3e** and **3f**, respectively.[25] Similarly, we prepared their *O*-allylated cinchoninium counterparts **4d**, **4e** and **4f**, which can be considered as *pseudoenantiomers* of the formers, therefore driving to an opposite enantioselection.[4f]

All this array of dimeric ammonium salts bearing different counter-anions were employed as chiral PTC catalysts (5 mol%) in the Michael addition reaction of *tert*-butyl *N*-(diphenylmethylene)glycinate (**5**) to different electron-deficient olefins (Scheme 2, Table 1). The aqueous base selected for these PTC reaction was 50% KOH whereas the solvent employed was a mixture of toluene/chloroform (7/3 v/v), these reaction conditions being the previously found as more appropriate when working with these dimeric PTC catalysts.[7c,25] The reactions were monitored by GLC, an their enantioselectivity was measured by chiral GLC analysis[26] of the corresponding *N*-trifluoroacetamide esters from **6** or **7**,[27] whereas the absolute configuration was determined by comparison of the retention times obtained by chiral HPLC analysis of the final products with those of the literature.[23] The catalysts could be recovered by precipitation with ether when the reaction was finished and reused,[25] affording similar chemical yields and enantioselectivities.



Scheme 1. Synthesis of *O*-allylated cinchonidine-derived ammonium salts.

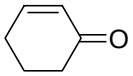


Scheme 2. Asymmetric Michael addition reactions under PTC conditions.

The Michael addition reaction of glycinate **5** with methyl acrylate under the above mentioned conditions and employing the dimeric bromide **3d** as PTC catalysts gave a 26% *ee* of the corresponding adduct (*S*)-**6a** when the reaction was carried out at -55 ºC, a value which experienced no increment when the temperature was lowered to -78 ºC (Table 1, entries 1 and 2). The anion-interchanged tetrafluoroborate and hexafluorophosphate dimeric salts **3e** and **3f** gave even lower *ee*'s working at -55 ºC, the reaction time being increased considerably, especially in the case of using the hexafluorophosphate **3f** as catalyst, which also gave the lowest enantioselectivity (Table 1, entries 3 and 4). We expected that increasing the steric bulkiness of the Michael acceptor would drive to higher enantioselectivities, therefore we employed *tert*-butyl acrylate as electron-deficient olefin for the conjugate addition. Disappointingly, when cinchonidine-derived bromide **3d** was used as PTC catalyst, the corresponding adduct (*S*)-**6b** was obtained in only 20% *ee*, which is a lower value than when using methyl acrylate (Table 1, entry 5). The use of the tetrafluoroborate dimeric salt **3e** improved slightly the enantioselection up to 30% but with low yield, whereas the hexafluorophosphate **3f** again performed poorly, with very long reaction times, low yield and only 16% *ee* of (*S*)-**6b** (Table 1, entries 6 and 7). Other

Michael acceptor such as methyl vinyl ketone also gave very low *ee*'s of the corresponding adduct (*S*)-**6c** with all the cinchonidine-derived catalysts (Table 1, entries 8-10), catalyst **3f** affording higher *ee*.

Table 1. Asymmetric Michael addition reactions under PTC reaction conditions

Ent.	Cat.		Olefin	T (ºC)	t (h)	Product		
	No.	X				No.[a]	Yield (%)[b]	*ee* (%)[c,d]
1	**3d**	Br	CH_2=$CHCO_2Me$	-55	5	(*S*)-**6a**	78	26
2	**3d**	Br		-78	6	(*S*)-**6a**	73	24
3	**3e**	BF_4		-55	19	(*S*)-**6a**	68	20
4	**3f**	PF_6		-55	48	(*S*)-**6a**	24	12
5	**3d**	Br	CH_2=$CHCO_2$*t*-Bu	-55	7	(*S*)-**6b**	74	20
6	**3e**	BF_4		-55	48	(*S*)-**6b**	12	30
7	**3f**	PF_6		-55	72	(*S*)-**6b**	13	16
8	**3d**	Br	CH_2=$CHCOCH_3$	-55	7	(*S*)-**6c**	93	11
9	**3e**	BF_4		-55	24	(*S*)-**6c**	94	12
10	**3f**	PF_6		-55	48	(*S*)-**6c**	64	24
11	**3d**	Br	CH_2=$CHCN$	0	2	(*S*)-**6d**	89	41
12	**3d**	Br		-35	3	(*S*)-**6d**	82	72
13	**3e**	BF_4		-35	3	(*S*)-**6d**	85	80
14	**3f**	PF_6		-35	4	(*S*)-**6d**	72	88
15	**3f**	PF_6		-55	96	(*S*)-**6d**	14	80
16	**4d**	Br		-35	6	(*R*)-**6d**	72	60
17	**4e**	BF_4		-35	24	(*R*)-**6d**	59	6
18	**4f**	PF_6		-35	48	(*R*)-**6d**	70	79
19	**3d**	Br		-35	4	(2*S*,3*S*)-**7**	83	92[e]/50[f] (70)
20	**3e**	BF_4		-35	7	(2*S*,3*S*)-**7**	57	76[e]/32[f] (71)
21	**3f**	PF_6		-35	48	(2*S*,3*S*)-**7**	32	97[e]/68[f] (86)
22	**4d**	Br		-35	6	(2*R*,3*R*)-**7**	92	90[e]/47[f] (92)
23	**4e**	BF_4		-35	26	(2*R*,3*R*)-**7**	73	81[e]/46[f] (80)
24	**4f**	PF_6		-35	6	(2*R*,3*R*)-**7**	91	91[e]/50[f] (76)

[a] Configuration of the major isomer (HPLC, Chiralcel OD).

[b] Crude yield determined by ^{1}H NMR (300 MHz).

[c] Determined by chiral GLC from the corresponding trifluoroacetamides (see text).

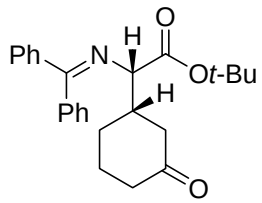
[d] In parenthesis, diastereomeric excess.

[e] *Ee* of the major diastereomer.

[f] *Ee* of the minor diastereomer.

However, when a low sterically demanding olefin such as acrylonitrile was employed in the conjugate addition, a 41% *ee* of the adduct (*S*)-**6d** was obtained using bromide **3d** as PTC catalysts and working at 0 ºC, this enantioselectivity being increased up to 72% *ee* when the temperature was lowered to -35 ºC (Table 1, entries 11 and 12). When the ammonium tetrafluoroborate salt **3e** was used as catalyst, the enantioselection for (*S*)-**6d** rose to 80% *ee* (Table 1, entry 13), whereas now the hexafluorophosphate **3f** performed the best as catalyst, allowing the enantioselectivity to reach to 88% *ee* (Table 1, entry 14). Lowering the temperature to -55 ºC did not give a higher *ee*, but a low yield and extremely long reaction time (Table 1, entry 15). As expected, when the cinchonine derived bromide **4d** was used as PTC catalyst, the enantioselectivity for the Michael adduct was the opposite, and a 60% *ee* of (*R*)-**6d** was obtained (Table 1, entry 16), whereas hexafluorophosphate **4f** gave a higher *ee* and tetrafluoroborate **4e** a very low enantioselection (Table 1, entries 17 and 18).

When we employed as Michael acceptor a cyclic electron-deficient olefin such as 2-cyclohexenone, performing the reaction with the dimeric bromide **3d** as PTC catalyst at -35 ºC, the adducts **7** were obtained in a 70% *de*, the major diastereomer (2*S*,3*S*)-**7** being obtained in 92% *ee* and being assigned according to the literature,[16] whereas the minor diastereomer was obtained in 50% *ee* (Table 1, entry 19). The use of the cinchonidinium-derived tetrafluoroborate **3e** gave place to a similar *de* of **7**, although to lower *ee*'s for both diastereomers (Table 1, entry 20). As in the case of using acrylonitrile as Michael acceptor, the hexafluorophosphate salt **3f** gave rise, not only to the higher distereoselection (86% *de*) for **7**, but also to the higher enantioselection for (2*S*,3*S*)-**7** (97% *ee*), although in a long reaction time (Table 1, entry 21). In addition, in the cinchonine-derived series **4**, the major diastereomer was the same than in the cinchonidine series **3** but the enantioselectivity was opposite as expected, bromide **4d** giving place to almost identical enantioselection than its *pseudoenantiomer* **3d**, allowing to obtain (2*R*,*R*)-**7** in a 90% *ee* (Table 1, entry 22). The hexafluorophosphate **4f** gave similar results than **3f**, whereas the cinchonine-derived tetrafluoroborate **4e** gave better results than its counterpart **3e** (table 1, entries 23 and 24).



(2*S*,3*S*)-**7**

We can conclude that dimeric cinchonidinium and cinchoninium-derived ammonium salts bearing different counter-anions can be employed as chiral phase-transfer catalysts in the asymmetric Michael addition reaction of a benzophenone imine-derived glycinate with electron-poor olefins. The best enantioselectivity in open chain Michael acceptors was achieved for

acrylonitrile using hexafluorophosphate-containing ammonium salts as catalysts, cinchonidinium and cinchoninium giving place to products with opposite configuration. The enantioselection was higher when cyclohexenone was used as Michael acceptor, *ee*'s up to 97% being achieved. The dimeric catalysts could be separated from the reaction medium by precipitation and reused.

Experimental Section

General Procedures. All the reagents and solvents employed were of the best grade available and were used without further purification. IR data were collected on a Nicolet Impact 400D-FT spectrometer and only diagnostic bands are given. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC-300 at 300 MHz and 75 MHz, respectively, using $CDCl_3$ as solvent and TMS as internal standard and the coupling constants are given in Hz. The enantiomeric excesses of products **6** and **7** were determined by GLC analyses (Crownpack Chirasil-L-Val column, 25 m x 0.25 mm i.d. Conditions: P = 85 kPa, 1 min 85ºC, 2ºC/min to 180ºC) of their corresponding *N*-trifluoroacetamide esters, obtained after 15% aq citric acid hydrolysis of the imines **6** or **7** and further reaction with trifluoroacetic anhydride.[26] GLC reference racemic samples were prepared from the corresponding racemic **6** and **7**, which were obtained using *n*-tetrabutylammonium bromide as phase-transfer catalyst. HPLC determinations were performed using a Chiralcel OD column (Conditions: *n*-hexane/isopropanol 100:1, flow rate: 1.0 mL min^{-1}, detection: 254 nm).

Asymmetric Michael addition reactions under PTC conditions. General procedure
A mixture of **5** (74 mg, 0.25 mmol), the corresponding olefin (1.25 mmol) and the catalyst **3d**,**e**,**f** or **4d**,**e**,**f** (0.013 mmol) in toluene/$CHCl_3$ (7/3 v/v, 1.5 mL) was cooled (see Table 1) and aqueous 50% solution of KOH (0.37 mL) was added. The mixture was vigorously stirred and monitored by GLC. When the reaction was finished, ether (2 mL) was added and the mixture was filtered for recovering the solid calalysts. Water (10 mL) was added to the filtrate and the mixture was extracted with EtOAc (3 x 10 mL). The organics were dried (Na_2SO_4) and evaporated *in vacuo*, affording crude products, which were analyzed by ^{1}H NMR.
1-*tert*-Butyl 5-methyl 2-(diphenylmethyleneamino)pentanedioate (6a).[19a] IR ($CHCl_3$) υ 1736, 1624, 1150 cm^{-1}. ^{1}H NMR δ_H 1.44 (9H, s), 2.20 (2H, m), 2.35 (2H, m), 3.59 (3H, s), 3.96 (1H, t, *J* = 6.2), 7.18 (2H, m), 7.30-7.45 (6H, m), 7.64 (2H, m). ^{13}C NMR δ_C 28.0, 28.6, 30.5, 51.5, 64.8, 81.2, 127.8, 128.0, 128.2, 128.5, 128.8, 130.2, 136.3, 139.3, 170.7, 173.6. Trifluoroacetamide: t_r (*R*) 27.75 min, t_r (*S*) 28.96 min.
Di-*tert*-butyl 2-(Diphenylmethyleneamino)pentanedioate (6b).[22] IR ($CHCl_3$) υ 1733, 1148 cm^{-1}. ^{1}H NMR δ_H 1.38 (9H, s), 1.45 (9H, s), 2.17 (2H, m), 2.26 (2H, m), 3.94 (1H, m), 7.18 (1H, m), 7.30-7.49 (6H, m), 7.59 (2H, m), 7.80 (1H, m). ^{13}C NMR δ_C 28.0, 28.9, 32.0, 68.0, 80.1, 81.1, 127.8, 128.0, 128.3, 128.5, 128.8, 130.2, 136.5, 139.6, 170.6, 172.5. Trifluoroacetamide: t_r (*R*) 33.59 min, t_r (*S*) 34.71 min.

***tert*-Butyl 2-(Diphenylmethyleneamino)-5-oxohexanoate (6c).**[19a] IR ($CHCl_3$) υ 1738, 1722, 1624 cm^{-1}. ^1H NMR δ_H 1.44 (9H, s), 2.09-2.23 (5H, m), 2.41 (2H, m), 4.05 (1H, m), 7.17 (1H, m), 7.31-7.51 (5H, m), 7.61 (2H, m), 7.80 (2H, m). ^{13}C NMR δ_C 27.8, 28.0, 29.9, 39.9, 64.7, 81.1, 127.7, 128.0, 128.5, 128.6, 128.8, 130.3, 136.5, 139.5, 170.5, 171.0, 208.2. Trifluoroacetamide: t_r (*R*) 26.93 min, t_r (*S*) 28.02 min.

***tert*-Butyl 4-Cyano-2-(diphenylmethyleneamino)butanoate (6d).**[19a] IR ($CHCl_3$) υ 2250, 1730, 1619, 1147 cm^{-1}. ^1H NMR δ_H 1.43 (9H, s), 2.25 (2H, m), 2.51 (2H, m), 4.05 (1H, dd, *J* 7.6, 4.5), 7.19 (2H, m), 7.31-7.49 (6H, m), 7.65 (2H, m). ^{13}C NMR δ_C 13.8, 28.7, 29.4, 63.7, 81.9, 119.4, 127.7, 128.1, 128.6, 128.8, 130.7, 136.1, 139.1, 169.9, 172.1. Trifluoroacetamide: t_r (*R*) 39.64 min, t_r (*S*) 40.52 min.

***tert*-Butyl 2-(Diphenylmethyleneamino)-2-(3-oxocyclohexyl)acetate (7).**[16] IR ($CHCl_3$) υ 1738, 1629. ^1H NMR (Major diast.) δ_H 1.43 (9H, s), 1.45 (1H, m), 1.63 (2H, m), 1.82-2.41 (6H, m), 3.91 (1H, m), 7.13 (2H, m), 7.29-7.51 (5H, m), 7.62 (1H, m), 7.67 (1H, m), 7.81 (1H, m). ^{13}C NMR (Major diast.) δ_C 25.7, 28.1, 28.5, 41.3, 42.1, 46.3, 69.3, 81.5, 127.7, 128.1, 128.5, 128.6, 128.8, 130.5, 136.6, 137.8, 170.0, 171.1, 211.6. (Minor diast.) δ_H 1.41 (9H, s), 1.45 (1H, m), 1.61 (2H, m), 1.82-2.41 (6H, m), 3.90 (1H, m), 7.13 (2H, m), 7.29-7.51 (5H, m), 7.62 (1H, m), 7.67 (1H, m), 7.81 (1H, m). Trifluoroacetamide: major diast.: t_r (2*R*,3*R*) 42.56 min, t_r (2*S*,3*S*) 43.59 min. minor diast.: t_r (2*S*,3*R*) 42.24 min, t_r (2*R*,3*S*) 43.30 min.

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