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The asymmetric Michael-type alkylation of chiral β-enamino esters: critical role of a benzyl ester group in the racemization of adducts

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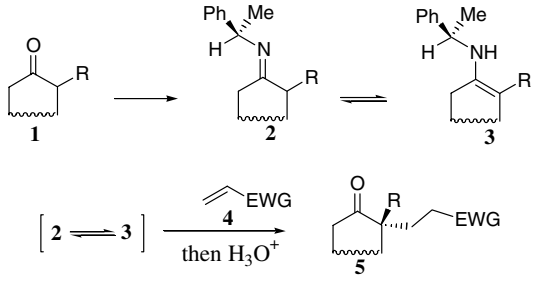
Abstract—In contrast with keto diester (*R*)-**10a** bearing a methyl ester group at the quaternary carbon center, the benzyl ester analogue (*R*)-**10a** partially racemized during workup, thereby revealing that the nature of the ester group at the quaternary carbon center has a critical role in the rate of racemization of such Michael adducts.

1. Introduction

Owing to the widespread presence of quaternary carbon centers (QCC_s) in natural products (e.g., terpenes, steroids, alkaloids), their stereocontrolled elaboration remains a central challenge of contemporary organic synthesis. In this respect, the asymmetric Michael reaction involving chiral imines under neutral conditions, which we disclosed in 1985, has emerged as a simple and efficient tool for the stereoselective construction of QCC_s.[1] Basically, condensation of chiral imines **2**, derived from *racemic* 2-substituted ketones **1** and enantiopure 1-phenylethylamine, to electron-deficient alkenes **4** furnished after hydrolytic workup 2,2-ketones **5** in fair yields and with high degrees of regio- and stereoselectivity. It has been established that the nucleophilic partners involved in this reaction are, in fact the more substituted secondary enamines **3**, in tautomeric equilibrium with imines **2** (Scheme 1).[2]



Scheme 1.

A great variety of substrates have been successfully used in this Michael reaction, without alteration of its remarkable features. The utilization of β-keto ester **1** ($R = CO_2R'$) is of peculiar interest, giving facile access to highly functionalized chiral synthons, exemplified by **6** (note that with such substrates, the imine/enamine tautomeric equilibrium is completely displaced toward the enamino ester form **3**, $R = CO_2R'$).[3] However, because of the significant acidity of the β-keto ester moiety (pK_a ca. 11), subsequent racemization of the adducts, involving a transient retro-Michael process may now occur. For instance, after careful distillation under a reduced pressure, the ee of adduct **6** (originally $\geqslant 95\%$) was significantly lowered, reflecting a partial

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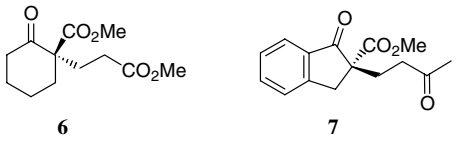
thermal racemization. The presence of a conjugate aromatic nucleus in the starting β-keto ester notably enhances its acidity, the interfering retro-Michael process is now highly favored: adduct **7** of 87% ee completely racemized within a few weeks, when kept in the solid state at room temperature (Scheme 2).[4]



Scheme 2.

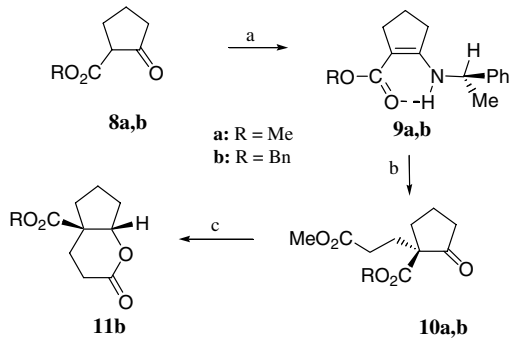
Herein, we report that in contrast with adduct (*R*)-**10a**, the benzyl ester analogue (*R*)-**10b** partially racemized during workup, thereby revealing that the nature of the ester group at the quaternary carbon center has also a critical role in the rate of racemization of Michael adducts.

2. Results and discussion

Although keto diesters of type **6** constitute particularly attractive chiral building blocks for the synthesis of a variety of complex molecules, the critical problem of discriminating the two ester groups should be resolved. A conventional solution to this problem would be the utilization of a benzyl ester group, selectively cleavable by hydrogenolysis. In this respect, we recently envisioned that Michael adduct (*R*)-**10b** to be a key chiral intermediate in the synthesis of (−)-cephalotaxine.[5] However, although the addition of benzyl enamino ester (*R*)-**9b** to methyl acrylate furnished the desired adduct (*R*)-**10b** with a satisfactory chemical yield of 70%, its ee, determined by chiral HPLC, was only 55%.

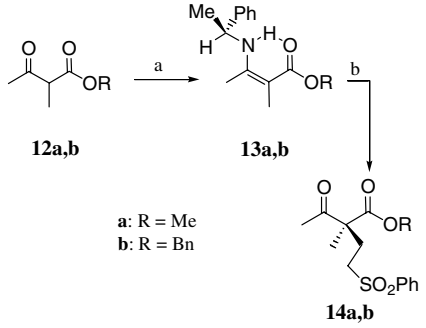
The assumption that partial racemization of **10b** might take place during HPLC analysis[4] was discarded by converting **10b** into 'non-racemizable' bicyclic lactone **11b** of pure *cis* ring junction by stereoselective reduction of the keto group followed by lactonization of the resulting hydroxy-diester. The ee of **11b** established by chiral HPLC was 60%, a value very close to that of progenitor **10b**. Since the ee of Michael adduct (*R*)-**10a**, the methyl analogue of (*R*)-**10b**, was found to be $\geqslant$95%,[5] it is manifested that the decrease of enantioselectivity observed in the case of adduct (*R*)-**10b** is due to the presence of the benzyl ester group at the quaternary carbon center (Scheme 3).

However, considering that the addition of acyclic methyl enamino ester (*S*)-**13a** and benzyl analogue (*S*)-**13b** (both of pure *Z* geometry, secured by the intramolecular hydrogen bonding) to phenyl vinyl sulfone has furnished the corresponding adducts (*S*)-**14a** and (*S*)-**14b** with similar ees (98% and 94%, respectively, both determined by chiral HPLC), it is clear that in conjunction with the presence of the benzyl ester group at the quaternary carbon center, other structural factors (particularly the nature of the electron-withdrawing group harbored by the starting Michael acceptor) are responsible for



Scheme 3. Reagents and conditions: (a) (*R*)-1-phenylethylamine, mixture of basic Al_2O_3, SiO_2, and 5 Å molecular sieves (2:1:9), cyclohexane, 20 °C, 3 days; (b) methyl acrylate, $MgBr_2$, Et_2O–THF, 24 h, 20 °C, then 20% aqueous AcOH, 70%; (c) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, −78 °C, then CSA, refluxing toluene, 75%.

the erosion of selectivity observed with adduct (*R*)-**10b** (Scheme 4).



Scheme 4. Reagents and conditions: (a) (*S*)-1-phenylethylamine, mixture of basic Al_2O_3, SiO_2, and 5 Å molecular sieves (2:1:9), cyclohexane, 20 °C, 3 days; (b) phenyl vinyl sulfone, refluxing THF, 5 days, then 20% aqueous AcOH, 63% (**15a**), 80% (**15b**).

The argument that the decrease in enantioselectivity observed in the case of adduct (*R*)-**10b** does not reflect a kinetic control, but very likely a subsequent partial racemization during workup, was strengthened by calculating the enthalpies of formation of transition states corresponding to the *Re*- and *Si*-approaches in the addition of enamino ester **9b** with methyl acrylate.

All the RHF AM1[6] transition structures were located using the procedures implemented in MOPAC (Version 5.0).[7] All variables were optimized by minimizing the sum of the squared scalar gradients (NLLSQ and SIGMA).[8,9] Force calculations were carried out to ensure that the transition structures located had one imaginary frequency. Final values of the gradient norms were $<$1 kcal/Å and each transition structure had one negative eigenvalue in the Hessian matrix as required. The (*S*)-*cis* configuration of the methyl acrylate was chosen for the calculations, since it was energetically favored over the (*S*)-*trans* one.[2b]

In analogy with computational studies performed earlier with a related enaminone and methyl acrylate,[2c] these calculations revealed a *syn*-approach of the reactants, with the *endo*-arrangement of the ester part of the

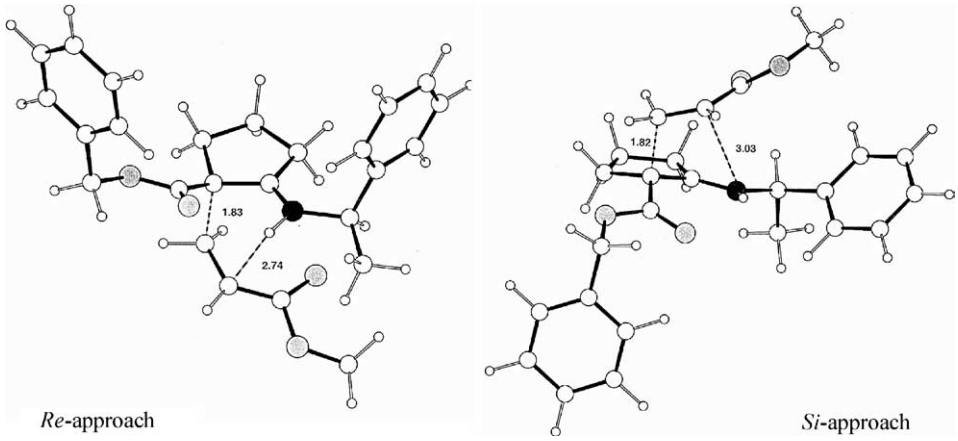


Figure 1. AM1 optimized transition state geometries for diastereomeric approaches of **9** + methyl acrylate; forming C–C and C–H bonds which are symbolized by dotted lines (distances in Å).

Table 1. Enthalpies of formation of transition states for addition of **9** + methyl acrylate (kcal/mol)

Benzyl dihedral angle	*Re*-approach	*Si*-approach
90°	−79.6[a]	−77.0
180°	−79.1	−76.8
−90°	−79.3	−77.3[a]

[a] Lowest energy transition states selected in the present study.

acrylate partner (the carbomethoxy group facing the nitrogen atom of enamino ester **9b**), a transition state structure geometry, which suggests the implication of a six-membered 'aza-ene-synthesis-like' pericyclic process, in which the NH proton of the enamino ester is transferred to the α-vinylic center of methyl acrylate, in a nearly concerted fashion with the creation of the C–C bond.[2a] When methyl acrylate approaches the *Re* π-face, the chiral auxiliary moiety adopts a conformation where the phenyl dihedral angle is about 75°. Conversely, when methyl acrylate approaches the *Si* π-face, in order to minimize the steric effects the phenyl group is pushed away from its most stable position (ca. 75°, a dihedral angle value encountered in the *Re*-approach and in the crystal structure of a related enamino ester),[10] resulting in a dihedral angle of 165°. Triads of sub-conformers corresponding to the rotation of the benzyl group around CH_2–O bond (dihedral angles: 90°, 180°, and −90°) were also generated. The AM1 optimized transition state geometries are shown in Figure 1; the enthalpies of formation of all the possible transition states are given in Table 1. The energy difference between the two more stable competing *Re* and *Si* transition states ($\Delta\Delta H = 2.3$ kcal/mol) predicts a π-facial discrimination in favor of the *Re*-approach with a selectivity of ca. 40:1 (95% ee), a value which is in excellent agreement with the experimental selectivities obtained by using a variety of β-enamino esters as nucleophilic partners in the present asymmetric Michael reaction.[1,2]

3. Conclusion

In conclusion, we have demonstrated that adduct (*R*)-**10b**, resulting from the asymmetric Michael addition between enamino ester (*R*)-**9b** and methyl acrylate, suffered from a notable decrease of enantioselectivity (55%), compared to the typical values obtained in this series (⩾95%). This erosion of selectivity, which involves an interfering retro-Michael process taking place during workup, was attributed to the presence in this adduct of the benzyl ester group at the quaternary carbon center, an assumption strengthened by calculating the enthalpies of formation of the corresponding diastereomeric transition states. However, since adduct (*S*)-**14a** and benzyl analogue (*S*)-**14b** exhibited similar ees (98% and 94%, respectively), additional structural factors should be evoked to rationalize the unusually facile racemization of (*R*)-**10b**.

4. Experimental

4.1. General

Diethyl ether and tetrahydrofuran (THF) were distilled over Na-benzophenone ketyl. Crude products were purified by column chromatography on silica gel of 60–120 mesh. IR were recorded on a Bruker VECTOR 22 spectrometer. The ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ solution on a Bruker AC 200 or Bruker Avance 300 spectrometer (200 and 50 MHz, or 300 and 75 MHz, for ^{1}H and ^{13}C, respectively). Optical rotations were measured at 589 nm in a 1 dm-cell on a Optical Activity Limited AA-10R. For unambiguous assignment of enantiomers in chiral HPLC, comparisons were made in all cases with the corresponding racemates. Elemental analyses were performed by the Service de Microanalyse, Centre d'Etudes Pharmaceutiques, Chatenay-Malabry, France, with a Perkin–Elmer 2400 analyzer.

4.2. General procedure for the preparation of enamino esters 9, 13a, and 13b

To a mixture of 2 g of basic aluminum oxide, 1 g of silica gel (230–400 mesh) and 9 g of powdered 5 Å molecular sieves was added a solution of 30 mmol of keto ester and 35 mmol of enantiopure 1-phenylethylamine in 20 mL of cyclohexane. The resulting slurry was stirred

at 20 °C under nitrogen for 3 days and filtered through a pad of Celite. The organic layers were concentrated in vacuo and the excess chiral amine removed by distillation (0.05 Torr, oil bath 50 °C). The residual enamino ester was engaged in the next stage without further purification.

4.2.1. (*R*)-3-(1-Carbobenzyloxy-2-oxocyclopentyl)-propanoic acid methyl ester 10. To a stirred solution of magnesium bromide in Et_2O [prepared by dropwise addition of 28.5 mmol of 1,2-dibromoethane to 27 mmol of magnesium in Et_2O (40 mL)] were added enamino ester **9** (26 mmol) in Et_2O (50 mL) and methyl acrylate (34 mmol) in THF (10 mL). The resulting mixture was stirred for 1 day at 20 °C, after which 100 mL of 20% aqueous acetic acid was added. The mixture was stirred for an additional 1 day at 20 °C. The solvents were removed under reduced pressure and 1 M hydrochloric acid (20 mL) then added. The mixture was extracted with Et_2O (4 × 100 mL) and the combined organic layers washed with brine, dried over $MgSO_4$, and concentrated. Chromatography of the residue over silica gel (ethyl acetate–cyclohexane 1:4) afforded keto ester **10** as an oil; yield 70%; $[\alpha]_D = -1.4$ (*c* 2.82, AcOEt);[11] IR (neat, cm^{-1}): 1729; ^1H NMR ($CDCl_3$, 200 MHz) δ: 7.4–7.3 (m, 5H), 5.17 (d, $J = 12.4$ Hz, 1H), 5.13 (d, $J = 12.4$ Hz, 1H), 3.66 (s, 3H), 2.54–1.86 (m, 10H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 214.0 (C), 173.3 (C), 170.8 (C), 135.4 (C), 128.6 (2CH), 128.3 (CH), 127.9 (2CH), 67.0 (CH_2), 59.3 (C), 51.6 (CH_3), 37.8 (CH_2), 33.6 (CH_2), 29.5 (CH_2), 28.4 (CH_2), 19.5 (CH_2). Anal. Calcd for $C_{17}H_{20}O_5$: C, 67.09; H, 6.62. Found: C, 67.01; H, 6.61. HPLC analysis (Daicel Chiralcel OD, eluent: 20% AcOEt in cyclohexane): two peaks in the 3.4:1 ratio, major isomer t_R 9.9 min, minor isomer t_R 11.8 min.

4.2.2. (1a*S*,4a*R*)-2-Oxo-hexahydro-cyclopenta(*b*)pyran-4a-carboxylic acid benzyl ester 11. To a solution of 4.9 mmol of keto ester **10** in 30 mL of methanol was added 7.9 mmol of cerium chloride heptahydrate. The mixture was stirred for 1 h at 20 °C and then cooled to −78 °C. Sodium borohydride (4.9 mmol) was added over a period of 45 min. The mixture was poured into 1 M hydrochloric acid (10 mL) and extracted with ethyl acetate (50 mL). The organic layers were washed with a satured aqueous solution of sodium hydrogencarbonate (10 mL), dried over $MgSO_4$, and concentrated. A solution of camphorsulfonic acid (150 mg) in 90 mL of toluene was added, the resulting mixture refluxed for 15 h, and the solvent removed under vacuo. Chromatography of the residue over silica gel (ethyl acetate–cyclohexane 1:2) afforded lactone ester **11** as an oil; yield 75%; IR (neat, cm^{-1}): 1723; ^1H NMR ($CDCl_3$, 200 MHz) δ: 7.41–7.30 (m, 5H), 5.47 (m, 2H), 5.33 (dd, $J = 5.9$, 3.4 Hz, 1H), 2.53–1.64 (m, 10H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 174.2 (C), 171.9 (C), 135.1 (C), 128.3 (2CH), 127.9 (CH), 127.6 (2CH), 84.1 (CH), 66.7 (CH_2), 51.3 (C), 36.2 (CH_2), 33.3 (CH_2), 28.0 (CH_2), 27.9 (CH_2), 22.3 (CH_2). HPLC analysis (Daicel Chiralcel OD, eluent: 20% AcOEt in cyclohexane): two peaks in the 4:1 ratio, minor isomer t_R 11.9 min, major isomer t_R 13.0 min.

4.2.3. (*S*)-2-(2-Benzenesulfonylethyl)-3-methyl-3-oxo-butyric acid methyl ester 14a. A stirred solution of enamine **13a** (10 mmol) and phenyl vinyl sulfone (14 mmol) in 50 mL of THF was refluxed under nitrogen for 5 days. The same workup procedure used to prepare **10** (Section 4.2.1) was applied. Chromatography over silica gel (ethyl acetate –cyclohexane 1:2) gave **14a** as an oil; yield 63%; $[\alpha]_D = -26.0$ (*c* 0.88, $CHCl_3$); IR (neat, cm^{-1}): 1735, 1715; ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.91 (m, 2H), 7.64 (m, 3H), 3.71 (s, 3H), 3.10 (m, 2H), 2.16 (m, 2H), 2.11 (s, 3H), 1.34 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 204.0 (C); 172.0 (C), 138.4 (C), 133.8 (CH), 129.2 (2CH), 127.9 (2CH), 58.0 (C), 52.7 (CH_3), 51.7 (CH_2), 27.6 (CH_2), 25.9 (CH_3), 19.2 (CH_3). Anal. Calcd for $C_{14}H_{18}O_5S$: C, 56.36; H, 6.08. Found: C, 56.66; H, 6.19. HPLC analysis (Daicel Chiralcel AD, eluent: 4% isopropanol in hexane): two peaks in the *ca* 100:1 ratio, minor isomer t_R 54.2 min, major isomer t_R 56.3 min.

4.2.4. (*S*)-2-(2-Benzenesulfonylethyl)-3-methyl-3-oxo-butyric acid benzyl ester 14b. The same procedure used to prepared **14a** (Section 4.2.3) was applied. **14b**: oil; yield 80%; $[\alpha]_D = -16.4$ (*c* 1.64, $CHCl_3$), IR (neat, cm^{-1}): 1738; 1717; ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.84 (m, 2H), 7.64 (s, 1H), 7.53 (m, 2H), 7.32 (m, 5H), 5.13 (s, 2H), 3.03 (m, 2H), 2.17 (m, 2H), 2.02 (s, 3H), 1.32 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 203.9 (C), 171.3 (C), 138.5 (C), 134.7 (C), 133.8 (CH), 129.3 (2CH), 128.6 (2CH), 128.6 (CH), 128.4 (2CH), 127.9 (2CH), 67.4 (CH_2), 58.1 (C), 51.7 (CH_2), 27.6 (CH_2), 25.9 (CH_3), 19.3 (CH_3). Anal. Calcd for $C_{20}H_{22}O_5S$: C, 64.15; H, 5.92. Found: C, 64.22; H, 6.02. HPLC analysis (Daicel Chiralcel AD, eluent: 4% isopropanol in hexane): two peaks in the 32:1 ratio, minor isomer t_R 39.9 min, major isomer t_R 44.1 min.

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11. Due to the facile racemization of this adduct, the absolute value was considered to be insignificant.