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Synthesis of optically active (+)-2-benzyl-, (+)-2-octyl-, and (+)-2-tetradec-5′-enylcyclobutanones via metallated chiral imines or hydrazones

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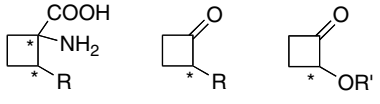
Abstract—A practical asymmetric synthesis of (*R*)-2-benzyl-, (*S*)-2-octyl-, and (*S*)-2-tetradec-5′-enylcyclobutanones was investigated using enantiopure (*S*)-α-methylbenzylamine, (*R*)-methoxymethylbenzylamine, or hydrazine (RAMP). These amines were treated with cyclobutanone to afford the corresponding imines or hydrazones, respectively. Metallation of these imine derivatives followed by alkylation with *n*-octylbromide, benzylbromide, or tetradec-5-enylbromide gave, after hydrolysis, (*S*)-2-octylcyclobutanone and for the first time optically active (*R*)-2-benzylcyclobutanone and (*S*)-2-tetradec-5′-enylcyclobutanone (TECB) with 67–87% ee. The absolute configuration was also established.

1. Introduction

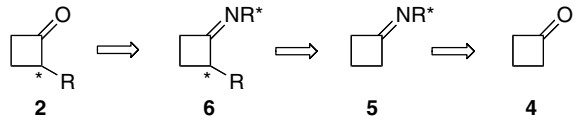
The synthesis of optically active α-substituted cyclobutanones via asymmetric reactions has not received much attention. Only a few methods occurring through a ring enlargement of hydroxycyclopropylcarbinol[1] or spiropentane derivatives[2a,b] or with chirality transfer.[2c] Poor to good enantiomeric excesses were generally obtained.

Over the course of our work on the asymmetric synthesis of cyclic analogues of naturally occurring α-amino acids,[3] we have previously published the aminocyclobutanecarboxylic acids **1**[4] prepared from readily available racemic α-substituted cyclobutanones **2**.[4,5] We had already prepared enantiopure α-alkoxycyclobutanones **3** by an enzyme-catalyzed transesterification.[6]



1 **2** **3**

In connection with our ongoing program, we report herein the asymmetric alkylation of *N*-cyclobutylidene amines or hydrazone derivatives **5**, an easy to perform and efficient route to enantiomerically enriched 2-alkylcyclobutanones **2** via the corresponding imines **6** (Scheme 1). Only very recently a synthesis of racemic 2-alkylated cyclobutanones was published,[7] and used as markers for irradiated foodstuffs.[8]



2 **6** **5** **4**

Scheme 1.

2. Results and discussion

Commercially available cyclobutanone **4** was converted into *N*-(cyclobutylidene)-amine or hydrazone **5** by reaction with (*S*)-α-methylbenzylamine **7A** (1 equiv) or (*R*)-**7B** (Scheme 2) in diethyl ether in the presence of triethylamine (2.5 equiv) and stoichiometric amounts of titanium(IV) chloride, while with RAMP-**7C**,[9] simple heating was enough to give the hydrazone **5C**. Without purification, the cyclobutanone imine derivatives **5**[10]

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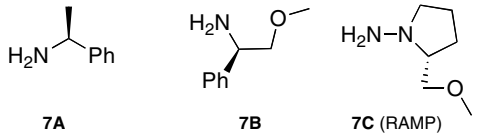


Scheme 2.

were deprotonated with LDA (or NaHMDS) in THF at −78 °C and the resulting 1-azaallylic anion intermediates were reacted with various alkylbromides to afford the corresponding *N*-2-alkyl-1-cyclobutylidene amines **6**. The later crude imines **6** were hydrolyzed with aqueous oxalic acid from −78 °C to room temperature giving enantiomerically enriched 2-alkylcyclobutanones **2** in good yields and high enantiomeric excesses (Table 1).

First, the asymmetric alkylation[11] of imine **5A** (prepared from cyclobutanone **4** and amine **7A**) conducted with LDA at −78 °C for 1 h, then addition of benzylbromide at −78 °C to room temperature, gave 2-benzylcyclobutanone **2a** with moderate yield and poor enantiomeric excess (Table 1, entry 1). Improved results were achieved by using amines **7B** and **7C**, which gave **2a** with 44% and 76% ee, respectively (Table 1, entries 2 and 3). Furthermore, increasing the reaction time of LDA at −78 °C (4 h instead of 1 h) before adding benzylbromide, enhanced both the yield and the enantioselectivity of the resulting 2-benzylcyclobutanone (*R*)-**2a** {$[\alpha]_D$ = +124 (*c* 1, $CHCl_3$), 79% ee} (entry 4). However, using NaHMDS as base does not give a better result (entry 5). On the other hand, upon treatment with octylbromide or tetradec-5-enylbromide,[7c] hydrazone **5C** gave under the same conditions 2-octylcyclobutanone (*S*)-**2b** or 2-tetradec-5′-enylcyclobutanone (*S*)-(+)-**2c**, respectively, with good yields and high enantiomeric excesses {$[\alpha]_D$ = +42.7 (*c* 1, $CHCl_3$), 88% ee} (Table 1, entries 6 and 7), and {$[\alpha]_D$ = +22.7 (*c* 0.4, $CHCl_3$), 67% ee} (Table 1, entry 8).

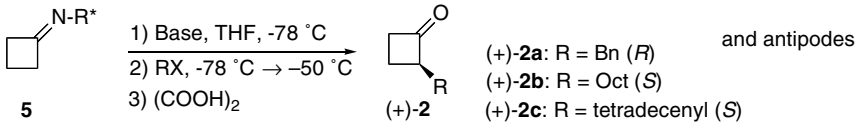
The (*S*) absolute configuration of (+)-**2b** was assigned by comparison of its specific rotation with that of literature (*R*)-(−)-**2b**.[1d,e] However, the (*R*) absolute configuration of (+)-**2a** (benzyl group), unknown in enantiomerically enriched form, was assigned by analogy to the alkylation product (+)-(*S*)-**2b** (octyl group), which must have, under the same conditions, the same geometry but reverse absolute configuration (compare in Table 1, entries 4 and 7). Likewise, the absolute configuration of (+)-**2c** must be (*S*).

We therefore observed that the (*R*)-benzylcyclobutanone **2a**[7b,12] underwent a slow epimerization on standing at 20 °C for 3 days (from 80% to 15% ee). However it was stable under acidic conditions (oxalic acid, 20 °C, 3 days).

It is noteworthy that the alkylation of **5A** at −78 °C with LDA, and BnBr followed by treatment in situ of the resulting **6A.a** with LDA (1 equiv), then hydrolysis with guaiacol[13] or oxalic acid does not give the expected (*R*)-**2a**, but benzylcyclobutanone (*S*)-**2a** (with 24% ee), thus, indicating that no deprotonation of **6A.a** occurred under these conditions (Scheme 3).

A plausible mechanism can be explained for this asymmetric alkylation. As shown in Figure 1, deprotonation of RAMP-hydrazone **5C** with lithium diisopropylamide results in azaenolate **8C**, a conformationally rigid and chelated E_{CC},Z_{CN} structure.[11c] Electrophilic attack on this rigid intermediate proceeding under high diastereofacial differentiation, leads to alkylcyclobutanone (*R*)- or (*S*)-**2** in high enantiomeric purity. These results are in agreement with those given by Enders and Eichenauer.[11d] While from enamine **5B**, the rigid intermediate **8B** providing favorable *re* face approach of the electrophile, gives the antipode (*S*)- or (*R*)-(−)-**2** but in a moderate enantioselectivity.

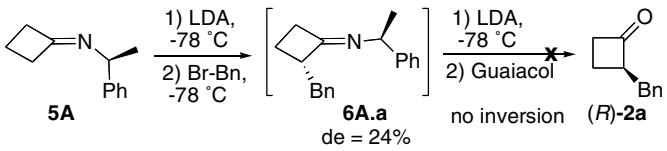
Table 1. Asymmetric alkylation of imines **5** under various conditions



5

Entry	H_2NR^*	Base	RX	2-Alkylcyclobutanones				
				2	Yield (%)	$[\alpha]_D$	Abs. conf.	Ee[a] (%)
1	(*S*)-**7A**	LDA	$PhCH_2$–Br	**2a**	42	−37.7	(*S*)	24
2	(*R*)-**7B**	LDA	$PhCH_2$–Br	**2a**	41	−69	(*S*)	44
3	(*R*)-**7C**	LDA	$PhCH_2$–Br	**2a**	25	+119	(*R*)	76
4	(*R*)-**7C**	LDA[b]	$PhCH_2$–Br	**2a**	64	+124	(*R*)	79
5	(*R*)-**7C**	NaHMDS	$PhCH_2$–Br	**2a**	24	ND[d]	(*R*)	66
6	(*R*)-**7C**	LDA	C_8H_{15}–Br	**2b**	50	+42.7	(*S*)[c]	87
7	(*R*)-**7C**	LDA[b]	C_8H_{15}–Br	**2b**	65	+39.1	(*S*)[c]	79.6
8	(*R*)-**7C**	LDA[b]	$C_{14}H_{27}$–Br[e]	**2c**	35	+22.7	(*S*)	67

[a] Enantiomeric excesses were measured by GC analysis using chiral column (β-cyclodextrine DM).
[b] LDA was reacted with imine of cyclobutanone at −78 °C for 4 h before adding alkylbromide.
[c] The absolute configuration was assigned by comparison to the known product **2b** (Ref. 1d,e).
[d] ND: not determined.
[e] *Z*-Tetradec-5-enylbromide.



Scheme 3. Attempt to improve enantiomeric excess by double LDA treatment.

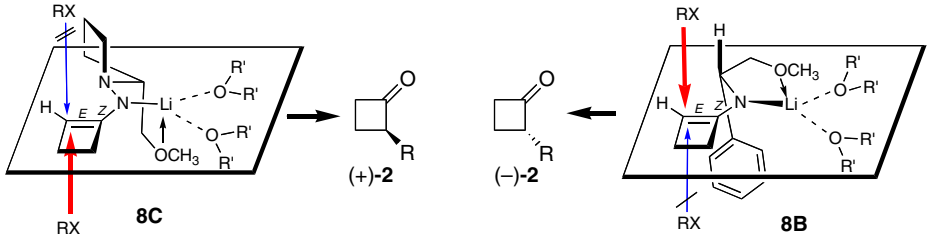


Figure 1. Proposed mechanism of enamine cyclobutanone alkylation.

3. Conclusion

We have developed a practical asymmetric alkylation for the synthesis of (*R*)-benzyl-, (*S*)-octyl-, and (*S*)-tetradec-5′-enylcyclobutanones or antipodes with reasonably good yields and high enantiomeric excesses up to 87%, thus providing the first preparation of optically active 2-benzyl- and 2-tetradec-5′-enylcyclobutanones.[14] This approach should constitute a complementary method to our enzymatic reaction[6] for preparing several optically active cyclobutanones used in the synthesis of enantiopure aminocyclobutanecarboxylic acids,[4] which is currently in progress in our laboratory.

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10. (a) Data for crude **5A**: ^{1}H NMR ($CDCl_3$): δ 1.47 (d, J = 6.5 Hz, 3H), 1.80–2.10 (m, 2H), 2.75–3.15 (m, 4H), 4.42 (q, J = 6.5 Hz, 1H), 7.13–7.46 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 13.1 (C_3), 24.3 (CH_3), 34.6 (C_4), 37.9 (C_2), 60.2 ($C_{1'}$), [6 arom. C: 126.6 (2C), 126.7 (1C), 128.3 (2C), 145.2 (1C)], 170.9 (C=N).
(b) Data for crude **5B**: ^{1}H NMR ($CDCl_3$): δ 1.82–2.08 (m, 2H), 2.66–2.86 (m, 1H), 2.86–3.20 (m, 3H), 3.37 (s, 3H), 3.60 (dd, J = 4.5, 9.3 Hz, 1H), 3.70 (dd, J = 8.3, 9.3 Hz, 1H), 4.465 (dd, J = 4.5, 8.3 Hz, 1H), 7.20–7.45 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 13.0 (C_3), 35.2 (C_4), 38.0 (C_2), 59.0 (CH_3), 65.0 (*C*H–N), 78.0 (*C*H_2–O), [6 arom. C: 127.1 (1C), 127.3 (2C), 128.3 (2C), 140.9 (1C)], 173.9 (C=N).
(c) Data for crude **5C**: ^{1}H NMR ($CDCl_3$): δ 1.55–1.74 (m, 1H), 1.74–2.10 (m, 5H), 2.42–2.74 (m, 1H), 2.80–3.21 (m, 4H), 3.22–3.40 (m, 3H), 3.38 (s, 3H, CH_3), 3.54 (dd, J = 3.7, 9.3 Hz, 1H, CH_2O); ^{13}C NMR ($CDCl_3$): δ 14.0 (C_3), 22.3 (t), 25.9 (t), 35.1 (C_4), 36.0 (C_2), 53.4 (t), 59.1 (q), 65.7 (d), 75.1 (t), 154.9 (C_1).
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14. *General asymmetric alkylation procedure*: To a cooled solution (−78 °C) of crude imine or hydrazone **5** [1 mmol, prepared from cyclobutanone **4** (1.2 mmol) and amines or hydrazine **7** (1 mmol)] in THF (3 mL), was added dropwise a solution of LDA (2.2 mmol). The mixture was stirred at −78 °C for 4 h, then alkylbromide (2 mmol) was added at −78 °C, stirred at −78 °C (3 h), warmed up to −50 °C (3 h), and recooled at −78 °C (14 h). The cold resulting mixture (−78 °C) was hydrolyzed with an aqueous saturated solution of oxalic acid (3 mL) and ether (3 mL), with stirring at −78 °C (5 min) then at room temperature for 24 h. The mixture was extracted with ether (3 × 30 mL), and the organic layer was dried ($MgSO_4$), filtered, and then concentrated under partial vacuum (30 °C, $P > 200$ mmHg). The residue was purified by chromatography on silica gel column (eluent, ether–pentane, 5/95 → 1/9) to give pure 2-alkylcyclobutanone **2** (as noted in Table 1).

(a) Data for (*R*)-(+)-2-benzylcyclobutanone (*R*)-**2a**: $[\alpha]_D$ = +119 (*c* 0.6, $CHCl_3$) (76% ee), R_f = 0.50 (ether–pentane, 2/8), $t_R(R)$ = 38.48 min; $t_R(S)$ = 37.66 min (cyclodextrine DM, 145 °C, 0.5 bar); ^{1}H NMR ($CDCl_3$): δ 1.50–1.95 (m, 1H), 2.09–2.30 (m, 1H), 2.54–3.18 (m, 2H), 2.84 (A part of ABC system, J_{AB} = 14.5 Hz, J_{AC} = 9.1 Hz, $1H_{benzyl}$), 3.06 (B part of ABC system, J_{AB} = 14.5 Hz, J_{BC} = 5.5 Hz, $1H_{benzyl}$), 3.50–3.71 (m, 1H), 7.10–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 16.6 (C_3), 35.1 ($C_{1'}$), 44.5 (C_4), 61.2 (C_2), [6 arom. C: 126.3 (1C), 128.5 (2C), 128.7 (2C), 138.8 (1C)], 211.5 (C_1); IR (neat): ν 3086 cm^{-1}, 3028, 2923, 1778 (C=O), 1603, 1496, 1454; MS (EI) *m/z*: 160 (M^+, 39), 131 (30), 118 (60), *117* (100), 104 (27), 91 (36).

(b) Data for (*S*)-(+)-2-octylcyclobutanone (*S*)-**2b**: $[\alpha]_D$ = +39.1 (*c* 1, $CHCl_3$) (79.6% ee) {lit. for (*R*)-**2b**: $[\alpha]_D$ = −32 (*c* 0.56, $CHCl_3$) 64% ee},[1e] R_f = 0.57 (ether–pentane,1/9), $t_R(S)$ = 72.11 min; $t_R(R)$ = 71.02 min (cyclodextrine DM, 125 °C, 0.5 bar); ^{1}H NMR ($CDCl_3$): δ 0.87 (t, J = 6.6 Hz, 3H), 1.10–1.55 (m, 14H), 1.55–1.80 (m, 1H–C_3), 2.05–2.29 (m, 1H–C_3), 2.79–3.15 (m, 2H–C_4), 3.15–3.88 (m, 1H–C_2); ^{13}C NMR ($CDCl_3$): δ 14.1 (CH_3), 16.9 (C_3), 22.6, 27.0, 29.2, 29.4, 29.45, 29.5, 31.8, 44.4 (C_4), 60.6 (C_2), 212.6 (C_1); IR (neat): ν 2926 cm^{-1}, 1782 (C=O), 1466; MS (EI) *m/z*: 182 (M^+, 1), 164 (3), 112 (20), 98 (100), 84 (31), 83 (27).

(c) Data for (*S*)-(+)-2-(tetradec-5-enyl)-cyclobutanone (*S*)-**2c**: $[\alpha]_D$ = +22.7 (*c* 0.4, $CHCl_3$) (67% ee) R_f = 0.58 (ether–pentane, 2/8), $t_R(S)$ = 267.54 min; $t_R(R)$ = 264.39 min (cyclodextrine DM, 145 °C, 1 bar); ^{1}H NMR ($CDCl_3$): δ 0.88 (t, J = 6.6 Hz, 3H), 1.16–1.56 (m, 17H), 1.56–1.84 (m, 2H), 1.84–2.09 (m, 4H), 2.09–2.30 (m, 1H–C_3), 2.77–3.13 (m, 2H–C_4), 3.15–3.88 (m, 1H–C_2), 5.20–5.36 (m, $2H_{olefin}$); ^{13}C NMR ($CDCl_3$): δ 14.1 (CH_3), 16.9 (C_3), 22.7, 26.7, 27.0, 27.2, 29.3 (2C), 29.4, 29.5 (2C), 29.7, 31.9, 44.4 (C_4), 60.6 (C_2), 129.3 (C=C), 130.2 (C=C), 212.2 (C_1); IR (neat): ν 2926 cm^{-1}, 1782 (C=O), 1645 (C=C), 1463.