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Tetrahedron Letters 45 (2004) 3565–3568
Tetrahedron Letters

Stereoselective synthesis of activated cyclopropanes with an α-pyridinium acetamide bearing an 8-phenylmenthyl group as the chiral auxiliary

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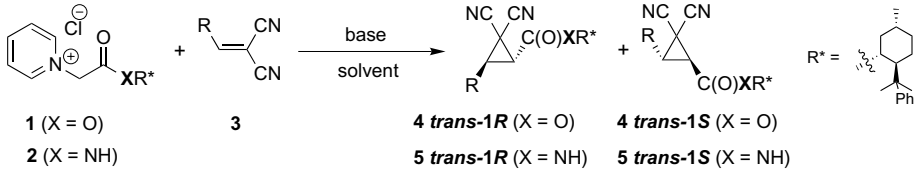
Received 14 February 2004; revised 4 March 2004; accepted 10 March 2004

Abstract—The reaction between an α-pyridinium acetamide bearing an 8-phenylmenthyl group as the chiral auxiliary and β-substituted methylidenemalononitriles gave rise to *trans*-cyclopropanes with diastereomeric ratios of up to 98:2. For most of the reactions, the absolute stereochemistry of the major product was found to be opposite of that of the major products of the reaction of the corresponding ester series, which also utilized the 8-phenylmenthyl group.

The high reactivity of cyclopropanes[1] has been attributed to their strained nature, and due to this character, certain cyclopropanes have been found to show bioactivity[2] and some others have been utilized as building blocks en route to complex structures.[3] Thus, the asymmetric synthesis of cyclopropanes has been a well examined subject.[4] Although high levels of asymmetric induction has been reported for catalytic reactions involving metal-carbenoid reactions,[4b,5] so far, satisfactory results have been limited to cyclopropanes that are not highly substituted. For cyclopropanes with multiple numbers of electron-withdrawing groups that are viable of further functionalization, not many examples are known. For such type of cyclopropanes, the ylide method, which usually utilizes ylides prepared from sulfonium salts or chloromethylcarbonyl compounds, is more commonly used.[4b,6] Pyridinium ylides have also been found to be applicable for cyclopropanation[7] and we have recently described the first asymmetric variant[8] using an α-pyridinium acetate **1** bearing an 8-phenylmenthyl group[9,10] as the chiral auxiliary (Scheme 1). Using **1**, moderate diastereoselectivities were observed in **4**. We assumed that the first C–C bond formation involved the Michael addition of the pyridinium ylide to the substituted methylidenemalononitrile substrate. Since the ylide from the α-pyridinium acetate is highly



1 (X = O)
2 (X = NH)

3

4 ***trans*-1*R*** (X = O) **4** ***trans*-1*S*** (X = O)
5 ***trans*-1*R*** (X = NH) **5** ***trans*-1*S*** (X = NH)

Scheme 1.

Keywords: Diastereoselective; Activated cyclopropane; 8-Phenylmenthylamine; Pyridinium ylide; Methylidenemalononitrile.

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0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.03.044

stabilized we reasoned that the observed moderate selectivity was due to facile retro-Michael addition that could intervene. In order to minimize this reverse reaction, we envisioned that the use of amides in the place of esters would be the solution. To this end, we prepared the amide analog **2** and found that for certain substrates, the selectivity could be raised, and also that the stereochemistry of the major product became opposite of that of the ester analog determined by X-ray structural analysis. Herein we describe our results.

Although the amine analog of highly utilized 8-phenylmenthol would seemingly be useful as a chiral auxiliary, only a single report on its use was seen in the literature when we commenced on this project and that with no details on its preparation.[11] Thus, we initiated our studies by examining methods of preparing **7** (Scheme 2). In analogy with the preparation of menthylamine from natural menthone via dissolving metal reduction of the oxime of menthone,[12] 8-phenylmenthone[13] was converted to its methoxyimine **6**.[14] Refluxing mixtures of **6** and sodium in absolute ethanol gave rise to diastereomeric mixtures of the required amine **7** with ratios up to 89:11. Ratios were typically over 80:20 and yields in the range of 68–97%.[15] The use of methanol in the place of ethanol lead to substantially reduced yield, and the use of Na with *i*-PrOH in toluene as in the synthesis of the corresponding alcohol from menthone gave rise to product in the ratio of only 67:33.[13] The oxime of 8-phenylmenthone was also useful, giving amine **7** in 61% with 83:17 selectivity. Although the diastereomers of **7** could be separated by slow and careful chromatography, the mixture was typically used as is and converted to chloroacetamide **8**, which could be purified by recrystallization.[16] The NMR of **8** clearly indicated that the amino group was oriented equatorial, and this was confirmed by X-ray structural analysis of the minor diastereomer **8**-ax (axial N).[17] The pyridinium salt **2** was obtained upon treating **8** with pyridine neat.[18]

In the case of the ester series, the diastereoselectivity for the phenyl substituted substrate (**3a**) had been found to vary in the range of 64:36–83:17 depending upon solvent although practically no difference in selectivity was observed with change of the base. Thus, these two conditions were first examined. Using **3a** with four different bases (Table 1), it was found that Et_3N and LiH functioned best for high yield, giving only the *trans* substituted cyclopropane as in the case of the ester series. However, the diastereoselectivity was found to be low in comparison with the ester series, contrary to expectations. The reaction itself was found to be somewhat sluggish and generally required room temperature whereas 0 °C was sufficient for the ester series. To establish the stereochemistry of the products, X-ray structural analysis of the minor product, which formed better-shaped crystals, was carried out. The absolute stereochemistry was found to be *trans*-1*S*,[17] the opposite to that of the major 4-pyridyl substituted cyclopropane diastereomer of the ester series (*trans*-1*R*), thus it followed that the major phenyl substituted product (**5a**) had the same stereochemistry as that in the ester series.

Table 1. Cyclopropanation using **3a** (R = Ph)

Entry	Base	Solvent	Temperature	Yield (%)	Dr[a]
1	Et_3N	CH_2Cl_2	Rt	86	62:38
2	LiH	CH_2Cl_2	Rt	97	64:36
3	DBU	CH_3CN	Rt	0	—
4	*t*-BuOK	CH_3CN	0 °C	20	54:46

[a] Determined by ^1H NMR of the crude product.

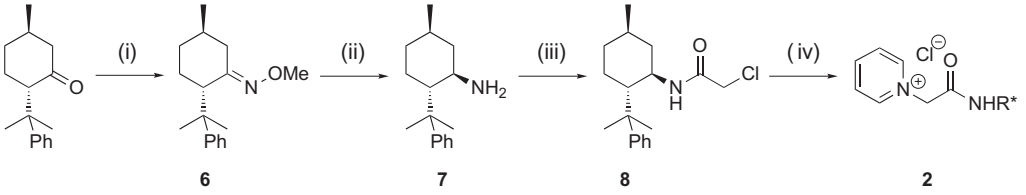
Since the selectivity was disappointing for **3a**, we decided to examine the effect of solvent using the *t*-butyl substituted methylidenemalononitrile (**3b**) as the substrate with Et_3N as base.[19] As a result, high selectivities (up to 2:98) were achieved with little dependence on the nature of the solvent (Table 2). Although EtOH was favorably used in previously reported examinations,[7,8] it was not effective here. Interestingly, the X-ray structural analysis of the major product revealed that the major product had stereochemistry opposite (*trans*-1*S*) to that of the major Ph diastereomer of **5a**, indicating that the stereochemical course of the reaction had changed.[17]

As for substrates with aliphatic substituents, practically no selectivity was observed for the one with the unbranched *n*-butyl group (**3d**), whereas a ratio of 12:88, which exceeds the best ratio (86:14) in the ester series, was observed for that with a more sterically demanding *i*-propyl group (**3c**) (Table 3). 1-Adamantyl substituted

Table 2. Cyclopropanation using **3b** (R = *t*-Bu)

Entry	Base	Solvent	Temperature	Yield (%)	Dr[a]
1	Et_3N	CH_2Cl_2	Rt	62	7:93
2	LiH	CH_2Cl_2	Rt	84	5:95
3	Et_3N	CH_3CN	Rt	59	2:98
4	Et_3N	THF	Rt	83	5:95
5	Et_3N	Toluene	Rt	61	6:94
6	Et_3N	DMF	Rt	69	4:96
7	Et_3N	EtOH	Rt	0	—

[a] Determined by ^1H NMR of the crude product.



Scheme 2. Reagents and conditions: (i) NH_3OMeCl, pyridine, EtOH, 95%; (ii) Na, EtOH, reflux, 68–97%, up to 89:11; (iii) $ClCH_2COCl$, $C_6H_5NMe_2$, ether, 87%, diastereomerically pure; (iv) pyridine, reflux, 97%.

Table 3. Cyclopropanation reaction with various substrates (RCH = CXCN)

Entry	Substrate	R	X	Base	Solvent	Temperature	Product	Yield (%)	Dr[a]
1	**3a**	Ph	CN	LiH	CH_2Cl_2	Rt	**5a**	97	64:36
2	**3b**	*t*-Bu	CN	Et_3N	CH_3CN	Rt	**5b**	59	2:98
3	**3c**	*i*-Pr	CN	LiH	CH_2Cl_2	Rt	**5c**	45	12:88
4	**3c**	*i*-Pr	CN	Et_3N	CH_3CN	0 °C	**5c**	13	Nd
5	**3d**	*n*-Bu	CN	Et_3N	CH_2Cl_2	0 °C	**5d**	70	43:57
6	**3d**	*n*-Bu	CN	LiH	CH_2Cl_2	Rt	**5d**	81	45:55
7	**3e**	1-Adamantyl	CN	Et_3N	CH_2Cl_2	Reflux	**5e**	100	8:92
8	**3e**	1-Adamantyl	CN	Et_3N	CH_3CN	Reflux	**5e**	88	7:93
9	**3f**	*t*-Bu	CO_2Me	Et_3N	CH_2Cl_2	Reflux	**5f**	83	8:92
10	**3f**	*t*-Bu	CO_2Me	LiH	CH_2Cl_2	Reflux	**5f**	62	5:95
11	**3f**	*t*-Bu	CO_2Me	Et_3N	CH_3CN	Reflux	**5f**	78	7:93
12	**3g**	4-Py	CN	Et_3N	CH_2Cl_2	Rt	**5g**	52	47:53
13	**3h**	1-Naphthyl	CN	Et_3N	CH_2Cl_2	Rt	**5h**	94	37:63
14	**3h**	1-Naphthyl	CN	Et_3N	CH_3CN	Rt	**5h**	99	15:85
15	**3i**	2-ClC_6H_4	CN	Et_3N	CH_2Cl_2	Rt	**5i**	100	36:64
16	**3i**	2-ClC_6H_4	CN	Et_3N	CH_3CN	Rt	**5i**	96	13:87
17	**3j**	2,6-$Cl_2C_6H_3$	CN	Et_3N	CH_2Cl_2	Reflux	**5j**	100	16:84
18	**3j**	2,6-$Cl_2C_6H_3$	CN	Et_3N	CH_3CN	Rt	**5j**	50	12:88

[a] Determined by ^1H NMR of the crude product.

3e and *t*-butyl substituted α-cyanoacrylate **3f** were also found to give high selectivity, even though higher reaction temperatures were required. As for substrates with aromatic groups, the one with the electronegative 4-pyridyl group (**3g**) turned out slightly to favor the diastereomer bearing stereochemistry opposite to that of the major diastereomer of **5a**. Substrates with hindered aromatic substituents also gave rise to the *trans*-1*S* diastereomer with moderate diastereoselectivity (15:85–12:88). Here, MeCN was clearly the better solvent. The minor diastereomer of the 2-chlorophenyl product was found to be *trans*-1*R*, thus implying that the major product for substrates with bulky aromatic substituents were all *trans*-1*S*.[17]

In summary, we have utilized the 8-phenylmenthylamine chiral auxiliary for the cyclopropanation reactions of pyridinium ylides to give products bearing three electron-withdrawing groups. High diastereoselectivity was observed especially for bulky Michael acceptor reactants, and the stereochemical course of the reaction turned out to be opposite of that of the ester series. Detailed studies of this reaction are currently in progress.

Acknowledgements

This work was supported in part by a Grant-in-Aid for Scientific Research (No 14540497) from the Japan Society for the Promotion of Science. We also acknowledge the Natural Science Center for Basic Research and Development of Hiroshima University for machine time on analytical instruments.

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14. A mixture of 8-phenylmenthone[13] (1.41 g, 6.11 mmol), *O*-methylhydroxylamine hydrochloride (0.87 g, 10.5 mmol), and pyridine (1.00 mL, 12.4 mmol) in EtOH (18 mL) was heated at reflux for 3 h. After the solvents were removed in vacuo, water and ethyl acetate were added to the residue. The aqueous layer was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried (Na_2SO_4), and removed in vacuo. The residue was purified by silica gel column chromatography (hexane/EtOAc = 30:1) to give **6** as a colorless oil (1.50 g, 95%): $R_f = 0.73$ (hexane/EtOAc = 5:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38–7.34 (m, 2H), 7.30–7.24 (m, 2H), 7.17–7.12 (m, 1H), 3.74 (s, 3H), 3.00 (ddd, $J = 13.1$, 4.3, 1.8 Hz, 1H), 2.42 (dd, $J = 11.3$, 4.3 Hz, 1H), 1.71–1.54 (m, 3H), 1.52 (s, 3H), 1.44 (s, 3H), 1.40 (dd, $J = 13.1$, 11.3 Hz, 1H), 1.33 (dtd, $J = 13.1$, 11.3, 3.4 Hz, 1H), 0.96 (dtd, $J = 13.1$, 11.3, 3.4 Hz, 1H), 0.91 (d, $J = 6.4$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.3, 150.5, 127.6, 126.1, 125.2, 61.0, 52.8, 40.1, 34.5, 33.9, 33.1, 28.6, 26.8, 24.9, 22.2; IR (neat) 1639, 1601, 1446, 1049, 872, 848, 775, 760, 702 cm^{-1}; $[\alpha]_D^{22}$ −27.9 (*c* 1.04, $CHCl_3$); HRMS (EI$^+$) *m*/*z* calcd for $C_{17}H_{25}NO$ 259.1936, found 259.1936; Anal. Calcd for $C_{17}H_{25}NO$: C, 78.72; H, 9.71; N, 5.40. Found: C, 79.00; H, 9.79; N, 5.43.
15. A solution of **6** (1.16 g, 4.48 mmol) in EtOH (5.80 mL) was heated to reflux. Then Na (1.45 g, 63.1 mmol) and EtOH (6.50 mL) were added. The reaction mixture was heated for 15 h, poured into ice and extracted with ether. The combined organic extracts were washed with brine, dried (Na_2SO_4), and removed in vacuo. The crude product was purified by silica gel column chromatography (CH_2Cl_2/MeOH/Et_3N = 40:2:1) to give **7** as a pale yellow oil (0.94 g, 91%, diastereomeric mixture 89:11). Further careful chromatography (CH_2Cl_2/MeOH/Et_3N = 60:2:1) gave pure **7** as the slower eluting component: $R_f = 0.43$ (CH_2Cl_2/MeOH = 10:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40–7.36 (m, 2H), 7.33–7.27 (m, 2H), 7.18–7.13 (m, 1H), 2.64 (ddd, $J = 11.3$, 10.1, 3.4 Hz, 1H), 1.82 (dq, $J = 13.1$, 3.4 Hz, 1H), 1.74–1.67 (m, 2H), 1.65 (ddd, $J = 12.2$, 10.1, 3.4 Hz, 1H), 1.46–1.35 (m, 1H), 1.38 (s, 3H), 1.22 (s, 3H), 1.11 (dtd, $J = 13.1$, 12.2, 3.4 Hz, 1H), 0.90 (dtd, $J = 13.1$, 12.2, 3.4 Hz, 1H), 0.89–0.84 (m, 2H), 0.87 (d, $J = 6.4$ Hz, 3H), 0.78 (ddd, $J = 12.8$, 12.2, 11.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.9, 128.3, 125.4, 125.4, 54.2, 53.2, 46.6, 39.9, 35.3, 32.0, 30.6, 27.0, 22.7, 22.2; IR (neat) 3394, 1601, 1030, 833, 764, 702 cm^{-1}; $[\alpha]_D^{22}$ −33.6 (*c* 1.02, $CHCl_3$); HRMS (EI$^+$) *m*/*z* calcd for $C_{16}H_{25}N$ 231.1987, found 231.1981. Anal. Calcd for $C_{16}H_{25}N$: C, 83.06; H, 10.89; N, 6.05. Found: C, 82.89; H, 10.87; N, 6.09.
16. To a solution of diastereomerically pure **7** (1.11 g, 4.78 mmol) and *N*,*N*-dimethylaniline (0.85 mL, 6.7 mmol) in ether (30 mL) was added chloroacetyl chloride (0.50 mL, 6.3 mmol). The reaction mixture was heated at reflux for 4 h, quenched with H_2O and extracted with ether. The combined organic extracts were washed with aq $NaHCO_3$ and brine, dried (Na_2SO_4), and removed in vacuo. The crude product was purified by silica gel column chromatography (hexane/EtOAc = 5:1) and recrystallization (EtOH) to give **8** as needles (1.27 g, 87%): $R_f = 0.23$ (hexane/EtOAc = 5:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36–7.27 (m, 4H), 7.20–7.14 (m, 1H), 5.40 (d, $J = 9.1$ Hz, 1H), 3.89 (ddd, $J = 11.3$, 10.7, 3.4 Hz, 1H), 3.58 (d, $J = 14.6$ Hz, 1H), 3.38 (d, $J = 14.6$ Hz, 1H), 2.01 (dq, $J = 13.1$, 3.4 Hz, 1H), 1.92 (ddd, $J = 11.9$, 10.7, 3.4 Hz, 1H), 1.83–1.75 (m, 2H), 1.57–1.45 (m, 1H), 1.32 (s, 3H), 1.26 (dtd, $J = 13.1$, 11.9, 3.4 Hz, 1H), 1.16 (s, 3H), 0.96 (dtd, $J = 13.1$, 11.9, 3.4 Hz, 1H), 0.87 (d, $J = 6.7$ Hz, 3H), 0.82 (ddd, $J = 13.1$, 12.2, 11.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.8, 152.5, 128.5, 125.7, 124.8, 50.7, 43.8, 42.6, 39.6, 34.8, 31.7, 31.3, 26.9, 21.8, 21.1; IR (Nujol) 3313, 1655, 1543, 1219, 775, 709, 613 cm^{-1}; $[\alpha]_D^{22}$ +61.3 (*c* 1.07, $CHCl_3$); HRMS (EI$^+$) *m*/*z* calcd for $C_{18}H_{26}ClNO$ 307.1703, found 307.1692; Anal. Calcd for $C_{18}H_{26}ClNO$: C, 70.22; H, 8.51; N, 4.55. Found: C, 70.31; H, 8.74; N, 4.45; mp 126–131 °C.
17. Crystallographic data for X-ray structures have been deposited with the Cambridge Crystallographic Data Centre as CCDC-231391 (**8**-ax), 231392 (**5a**-minor), 231393 (**5b**-major), and 231394 (**5i**-minor). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB12 1EZ, UK (fax: +44-(0)1223-336033 or email: deposit@ccdc.cam.ac.uk).
18. A mixture of **8** (300.2 mg, 0.98 mmol) and pyridine (1.00 mL, 12.4 mmol) was heated at 100 °C for 2 h. Then the mixture was cooled to room temperature and ether was added. The liberated solid was washed with ether, filtered, and dried in vacuo to give **2** as a hygroscopic pale brown solid (366.4 mg, 97%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.18 (d, $J = 5.5$ Hz, 2H), 8.53 (d, $J = 9.8$ Hz, 1H), 8.46 (t, $J = 7.9$ Hz, 1H), 8.03 (t, $J = 7.0$ Hz, 2H), 7.41 (d, $J = 7.3$ Hz, 2H), 7.34 (t, $J = 7.6$ Hz, 2H), 7.14 (t, $J = 7.3$ Hz, 1H), 5.64 (d, $J = 14.3$ Hz, 1H), 4.66 (d, $J = 14.3$ Hz, 1H), 3.79 (ddd, $J = 11.3$, 10.7, 3.4 Hz, 1H), 2.12 (ddd, $J = 12.2$, 10.7, 3.4 Hz, 1H), 1.73 (dq, $J = 13.1$, 3.4 Hz, 1H), 1.70–1.65 (m, 1H), 1.65–1.58 (m, 1H), 1.41–1.32 (m, 1H), 1.36 (s, 3H), 1.27 (ddd, $J = 13.1$, 12.2, 11.3 Hz, 1H), 1.18 (s, 3H), 1.12 (dtd, $J = 13.1$, 12.2, 3.4 Hz, 1H), 0.91 (dtd, $J = 13.1$, 12.2, 3.4 Hz, 1H), 0.82 (d, $J = 6.4$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.4, 151.9, 145.7, 145.1, 128.1, 127.5, 125.6, 125.0, 61.7, 50.9, 49.5, 42.8, 40.1, 34.2, 31.9, 28.7, 27.0, 24.1, 21.7; IR (Nujol) 3375, 3182, 1674, 1632, 1562, 1292, 702, 675 cm^{-1}; $[\alpha]_D^{22}$ −2.93 (*c* 2.24, $CHCl_3$); HRMS (EI$^+$) *m*/*z* calcd for $C_{23}H_{31}ClN_2O$ 386.2125, found 386.2144; Anal. Calcd for $C_{23}H_{31}ClN_2O{\cdot}H_2O$: C, 68.21; H, 8.21; N, 6.92. Found: C, 68.46; H, 8.17; N, 6.81; mp 219–222 °C.
19. *Typical procedure* (**5b**): To a solution of **2** (53.2 mg, 0.14 mmol) in CH_3CN (1.5 mL) was added Et_3N (0.03 mL, 0.22 mmol), followed by a solution of **3b** (14.4 mg, 0.11 mmol) in CH_3CN (1.5 mL) at 0 °C. The mixture was stirred for 17 h, during which time the mixture was allowed to warm to room temperature. Usual workup and chromatography [silica gel, hexane/EtOAc = 7:1, $R_f = 0.43$ (hexane/EtOAc = 3:1)] gave a mixture of **5b** (25.5 mg, 59%, dr = 2:98).