Pergamon

Tetrahedron Letters 43 (2002) 5853–5857

TETRAHEDRON LETTERS

Stereoselective synthesis of 1,2- and 1,4-dihydropyridines by using cation–π interaction as a conformation-controlling tool

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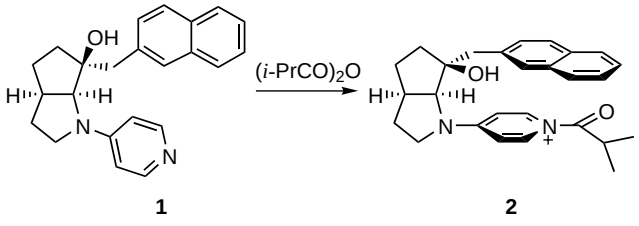
Received 1 May 2002; revised 10 June 2002; accepted 14 June 2002

Abstract—Selective shielding of one side of the pyridinium face by way of intramolecular cation–π complex formation enabled nucleophiles to attack the pyridinium ring from the non-shielded side. As a result, 1,2- and 1,4-dihydropyridines were formed in good stereoselectivities. ^{1}H NMR analysis and ab initio calculations at the RHF/3-21G* level supported the existence of cation–π interaction between the pyridinium and the aromatic ring of the chiral auxiliary.

Aromatic interactions have been utilized as a conformation-controlling tool in a variety of regio- and stereoselective syntheses.[1] However, although cation–π interactions have recently received considerable attention in various fields of chemistry and biochemistry,[2] little has been known about their synthetic applications except for recent reports of asymmetric acylation of *sec*-alcohols,[3,4] stereoselective β-galactosylation,[5] photooxidation of alkenes,[6] and photoisomerization of diphenylcyclopropane.[7]

Continuing our research on the synthesis of chiral 1,4-dihydropyridines,[8,9] we focused on catalysis **1** for the asymmetric acylation of racemic *sec*-alcohols developed by Kawabata and his colleagues,[3,4] where intermediary pyridinium salt **2** forms a closed conformation (Scheme 1). We considered that if pyridinium salt **3** possessing a similar chiral auxiliary has a closed conformation due to cation–π interaction, it can be applicable to the synthesis of chiral 1,2- and 1,4-dihydropyridines as shown in Fig. 1. Thus, the selective shielding of one side of the pyridinium face with the aromatic part would make nucleophiles possible to attack from the non-shielded side to give 1,2- or 1,4-dihydropyridines stereoselectively. We report here a new entry for the synthesis of chiral 1,2- or 1,4-dihydropyridines using a cation–π complex[10] as a key intermediate.

The chiral auxiliaries **5a**–**e** possessing various substituents were prepared from a ketone **4a**[3,11] or a chiral ketone **4b**[4] according to reported procedures. Acylation of **5a**–**e** with nicotinoyl chloride gave the nicotinic amides **6a**–**e** (Scheme 2). Similarly, the enantiomer of **6e** was prepared from **8** that is a diastereomer of **4b** (Scheme 3). After conversion of these amides into the corresponding pyridinium salts with methyl chloroformate in CH_2Cl_2, addition of a ketene silyl acetal, 1-methoxy-2-methyl-1-[(trimethylsilyl)oxy]-1-propene, at 0°C gave 1,4-adducts **9** as major products with a small amount of 1,6-adducts **10**.[12] The results are summarized in Table 1. Since most of the reported methods for the synthesis of chiral 1,4-dihydropyridines[13] are conducted



Scheme 1.

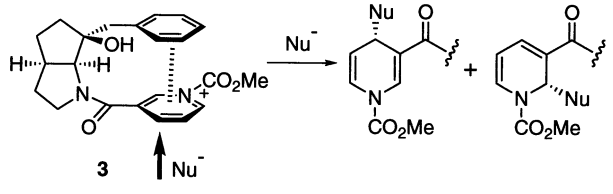


Figure 1. Strategy for the face-selective addition of nucleophiles to a pyridinium salt.

Keywords: pyridinium salts; cation–π interaction; stereocontrol; face-selective addition; 1,4-dihydropyridines; neighbouring group effects.

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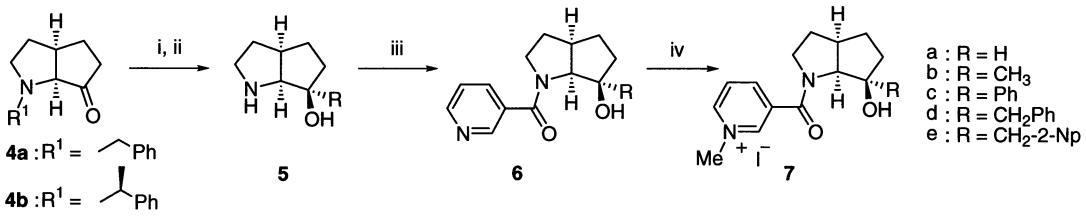
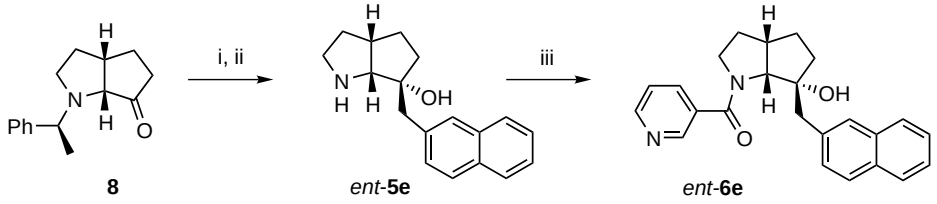
PII: S0040-4039(02)01166-8

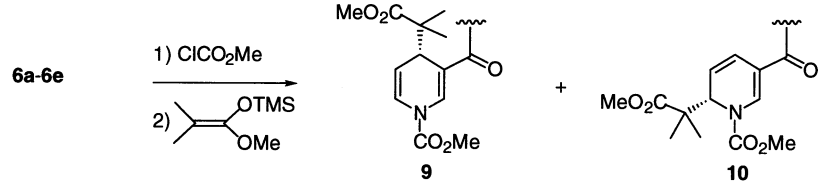


Scheme 2. *Reagents and conditions*: (i) RLi or RMgX, 73–92% yield; (ii) $Pd(OH)_2$, H_2, 82–88% yield; (iii) nicotinoyl chloride, Et_3N, 81–97% yield; (iv) MeI, 65–80% yield.



Scheme 3. *Reagents and conditions*: (i) BuLi, 2-methylnaphthalene, 52% yield; (ii) $Pd(OH)_2$, H_2, 86% yield; (iii) nicotinoyl chloride, Et_3N, 85% yield.

Table 1. Addition of a ketene silyl acetal to the pyridinium salt of **6**[a]



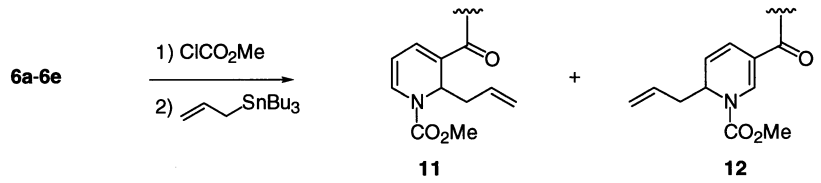
Entry	Substrate	Yield (%)	Ratio (**9**:**10**)[b]	de (%) of **9**[b]	de (%) of **10**[b]
1	**6a**	28	71:29	14	12
2	**6b**	40	88:12	56	18
3	**6c**	63	76:24	92	8
4	**6d**	57	95:5	99	32
5	**6e**	67	84:16	85	2

[a] CH_2Cl_2 was used as a solvent.
[b] Determined by ^1H NMR spectroscopy.

under coordination- or chelation-controlling conditions, ketene silyl acetals are rarely employed except for our previously reported method.[8a,9] Determination of the regio- and stereoselectivities was performed by ^1H NMR analysis based on the chemical shifts and their integration of the olefinic protons and the methine proton next to the nitrogen atom at the chiral auxiliary. The diastereomer ratio of **9** was significantly dependent on the substituents at the chiral auxiliary. Thus, when compound **6** possesses an aromatic moiety at the chiral auxiliary, higher selectivity was observed (entries 3–5). In particular, **6d** having a benzyl group was the most effective and resulted in excellent selectivity (entry 4). The substituent seems to affect not only the stereoselectivity but also the regioselectivity; addition to **6d** also gave the highest regioselectivities. Although the diastereoselectivity for the minor product **10** was much lower than that of the major adduct **9**, it is worthwhile noting that the stereoselectivity of 1,6-adduct **10d** was 32% de despite through 1,7-asymmetric induction process (entry 4).

When allyltributyltin was used as a nucleophile,[14] 1,2-adducts **11** were obtained as major products with 1,6-adducts **12** as minor products (Table 2). The stereoselectivity for **11** is also considerably dependent on the substituent at the chiral auxiliary similar to the reaction with the ketene silyl acetal as described above; when compound **6** has an aromatic substituent, higher selectivity was observed (entries 3, 4 and 6). The fact that whether the chiral auxiliary has an aromatic substituent or not is critical for the stereoselectivity strongly suggests the participation of the aromatic ring in the transition state of the addition reaction as shown in Fig. 1. The solvents employed also had a significant effect on the reaction rate and stereoselectivity; addition of 10 volume% of toluene to CH_2Cl_2 drastically slowed down the reaction rate and led to diminished

Table 2. Addition of allyltributyltin to the pyridinium salt of **6**[a]



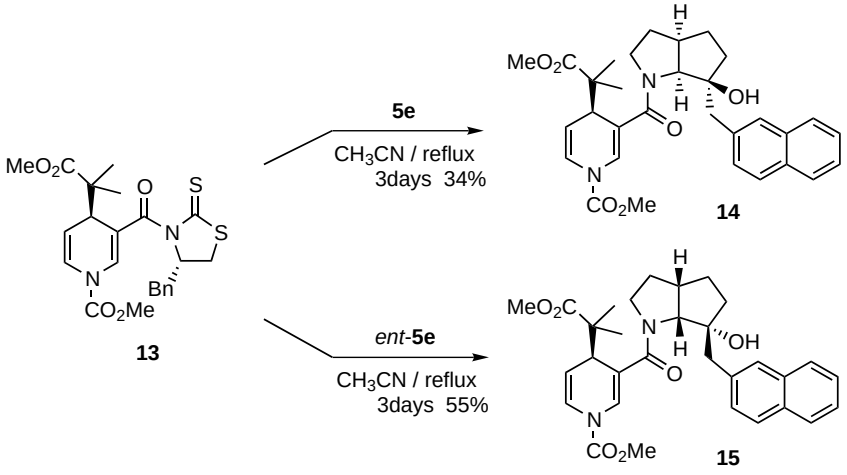
Entry	Substrate	Yield (%)[b]	Ratio (**11**:**12**)[c]	de (%) of **11**[c]
1	**6a**	65 (33)	82:18	14
2	**6b**	71 (40)	70:30	30
3	**6c**	84 (46)	73:27	84
4	**6d**	88 (56)	75:25	86
5	**6d**[d]	79 (24)	62:38	34
6	**6e**	79 (61)	78:22	60

[a] CH_2Cl_2 was used as a solvent unless otherwise noted.
[b] Conversion yield. Isolated yield is given in parentheses.
[c] Determined by ^1H NMR spectroscopy.
[d] A 10:1 mixture of CH_2Cl_2 and toluene was used as a solvent.

stereoselectivity (entry 5), and no reaction proceeded when toluene was used as a solvent. This unusual effect of toluene may be ascribed to the shielding of the pyridinium ring, which would prevent the nucleophiles from attacking the pyridinium face.

The absolute configuration of the stereogenic center at C4 of **9e** was determined by comparison with authentic samples **14** and **15**, which were prepared by the acyl transfer reaction of stereochemically known compound **13**[9] with chiral auxiliaries **5e** and *ent*-**5e**[4] (Scheme 4). Comparison of their ^1H NMR spectra and specific rotations[15] with those of **9e** and *ent*-**9e** clarified *ent*-**9e** to be identical with **15**; therefore, the newly produced chiral center of *ent*-**9e** is *R* and that of **9e** is *S*. The absolute configuration of the major product **11** would perhaps be *R* in analogy with the case of **9e**.

To elucidate the geometrical differences between the nicotinic amide **6** and the corresponding pyridinium salts, ^1H NMR analyses were carried out for **6b** and **6e**, and their *N*-methyl salts **7b** and **7e** as models of intermediate pyridinium salts. The differential NOE experiments for **6e** and **7e** led to evidence of their significant conformational differences. While no NOE was observed for **6e**, 5% NOE between the 5H of the pyridinium proton and the 1H or 4H of naphthyl group in **7e** was detected, suggesting the preferred conformation of **7e** to be a closed conformation. Table 3 shows $\Delta\delta$(**6e**–**b**) and $\Delta\delta$(**7e**–**b**) values at various temperatures. The very small values of $\Delta\delta$(**6e**–**b**) at 293 K imply that the pyridine and aromatic rings are apart from each other and there is no intramolecular π–π interaction in the neutral molecule **6e**. On the other hand, the $\Delta\delta$(**7e**–**b**) values were much larger than the $\Delta\delta$(**6e**–**b**) values and received substantial temperature effect; lowering the temperature decreased the $\Delta\delta$(**7e**–**b**) values, indicating that the pyridinium protons receive a shielding effect from the aromatic moiety. Since the shifts of the pyridinium protons to higher magnetic field are observed in various cation–π or π–π complexes,[16] the preferred conformation for **7e** is also suggested to be a closed conformation as described in Fig. 1.



Scheme 4.

Table 3. $\Delta\delta$(**6e–b**) and $\Delta\delta$(**7e–b**) values (ppm) for pyridine or pyridinium protons at various temperatures[a]

Temp (K)	$\Delta\delta$	H2	H4	H5	H6
293	$\Delta\delta$(**6e–b**)	+0.01	+0.01	0.00	0.00
293	$\Delta\delta$(**7e–b**)	+0.01	−0.06	−0.15	−0.06
223	$\Delta\delta$(**7e–b**)	−0.05	−0.15	−0.28	−0.22

[a] 270 MHz in $CDCl_3$.

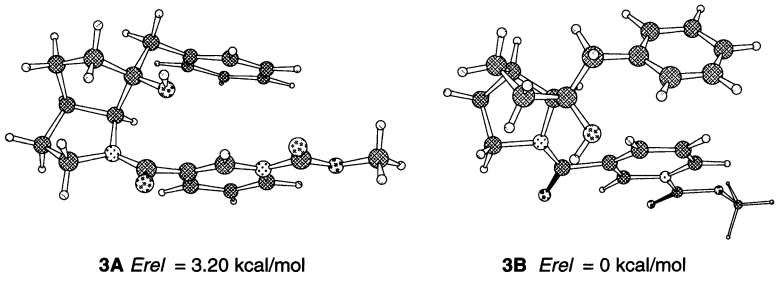


Figure 2. Conformers **A** and **B** obtained by ab initio calculations at the RHF/3-21G* level.

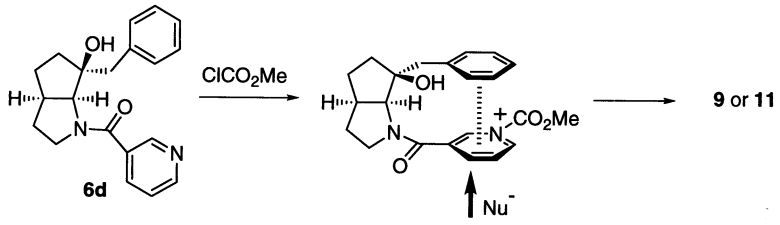


Figure 3. Working model for the nucleophilic addition.

Since all the pyridinium salts synthesized are unfortunately oily compounds, X-ray analysis could not be carried out to confirm their geometry. However, geometrical optimization for **3** by ab initio calculations at the RHF/3-21G* level provided supporting data for the predicted conformation in Fig. 1.[17] Thus, comparison of the energies between two stable closed conformers **3A** and **3B** suggests that **3B** is more stable than **3A** by 3.20 kcal/mol, which would be sufficient energy to give high face-selectivity in the addition reactions (Fig. 2).

All of the foregoing data provide the following working model for the face-selective addition to the pyridinium as shown in Fig. 3: (a) conversion of a pyridine moiety into a pyridinium salt forms a cation–π complex, where the one side of the pyridinium face is selectively shielded; (b) a nucleophile attacks this complex from the non-shielded side to give a dihydropyridine stereoselectively.

In summary, we have demonstrated that cation–π interaction is a potentially useful conformation-controlling tool in face-selective addition reactions. The selective shielding of one side of the pyridinium face enabled nucleophiles to attack the pyridinium from the non-shielded side, as a result, 1,2- and 1,4-dihydropyridines were formed in good stereoselectivities. Further studies on this series are now in progress and will be reported in due course.

Acknowledgements

We wish to express our gratitude to Professor T. Kawabata in Kyoto University for his helpful instruction and suggestions on the synthesis of the chiral auxiliaries. This work was financially supported by Japan Society for the Promotion of Science (13650901).

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