Pergamon

Tetrahedron Letters 42 (2001) 3621–3624

TETRAHEDRON LETTERS

Dynamic kinetic resolution of hemiaminals with axially chiral twisted amides

Shinji Yamada* and Emiko Noguchi

Department of Chemistry, Faculty of Science, Ochanomizu University, Bunkyo-ku, Tokyo 112-8610, Japan

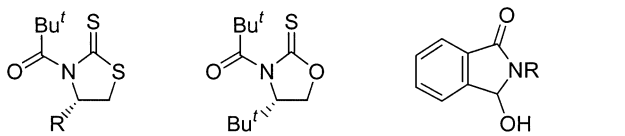
Received 9 February 2001; revised 21 March 2001; accepted 23 March 2001

Abstract—Dynamic kinetic resolution of *N*-acylhemiaminals was performed by enantioselective acylation of the hydroxy groups with chiral twisted amides. The stereoselectivity was reversed in the presence of 4-DMAP. The absolute configuration of the products was determined based on the sign of CD Cotton effects. © 2001 Elsevier Science Ltd. All rights reserved.

The significant importance of dynamic kinetic resolution in asymmetric synthesis has been recognized because chiral compounds are obtained from racemic ones in more than 50% yields.[1] Various substrates, the (*R*)- and (*S*)-isomers of which are capable of interconversion due to tautomerism, have often been employed for this purpose. Recently, asymmetric acylation of hemiaminals via dynamic kinetic resolution has been performed by enzymatic acyl-transfer reactions[2,3] and the products are utilized as chiral building blocks for various organic syntheses.[4]

Continuing our research on the enantioselective acylation of *sec*-alcohols using axially chiral twisted amides,[5] we focused on the asymmetric acylation of hemiaminals for the following reasons: (1) little has been known of the non-enzymatic dynamic kinetic resolution of hemiaminals and (2) acylation with the twisted amides having moderate reactivity will satisfy the prerequisite of the dynamic kinetic resolution, namely, that the rate of the acylation step must be much slower than that of interconversion between the (*R*)- and (*S*)-isomers. We report here that acylation of *N*-acylhemiaminals with chiral twisted amides successfully provided chiral esters via dynamic kinetic resolution, and surprisingly, the selectivity was reversed in the presence of a catalytic amount of 4-DMAP.

We employed chiral twisted amides, (*S*)-4-alkyl-3-pivaloyl-1,3-thiazolidine-2-thiones **1**–**3** and (*S*)-4-*tert*-butyl-3-pivaloyl-1,3-oxazolidine-2-thione (**4**),[6] as acylating reagents and *N*-methylhemiaminal **5**[7] and newly prepared *N*-acylhemiaminals **6**–**9**[8,9] as substrates. Acylation of hemiaminals **5**–**9** with amides **1**–**4** was conducted in toluene at 80°C for 2–10 days under neutral conditions. The enantiomer ratio was determined by HPLC analysis using a chiral stationary phase. The results are shown in Table 1.[10] While no selectivity was obtained for the acylation of *N*-methylhemiaminal **5**, the acylation of *N*-acylhemiaminals **6**–**9** proceeded with good stereoselectivity to give the corresponding (*R*)-pivalates **10**, the absolute configuration of which was determined by CD spectra as described later. The fact that good selectivities were obtained for *N*-acylhemiaminals means that the acylation obviously proceeded via dynamic kinetic resolution under these reaction conditions (Scheme 1). The significant difference in the selectivities between *N*-methyl- and *N*-acylhemiaminals would be ascribed to the difference in their inversion rates. Thus, the k_{inv} of *N*-acylhemiaminals will be larger and that of *N*-methylhemiaminal **5** is smaller than the k_R and k_S of acylation with the amides (Scheme 1). Dynamic HPLC analysis supported this consideration; *N*-acylhemiaminals were easily isomerized in Chiralpak AS at rt, whereas *N*-methylhemiami-



1 : R = Bn
2 : R = *i*-Pr
3 : R = *t*-Bu

4

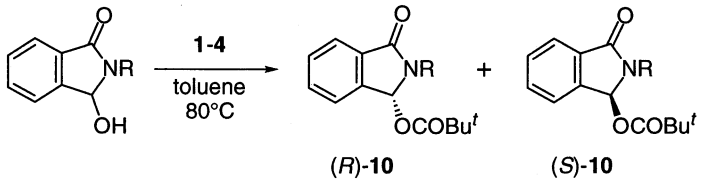
5 : R = CH_3
6 : R = $COCH_3$
7 : R = COC_2H_5
8 : R = $COCH(CH_3)_2$
9 : R = $COC(CH_3)_3$

Keywords: dynamic kinetic resolution; acylation; twisted amide; hemiaminal.

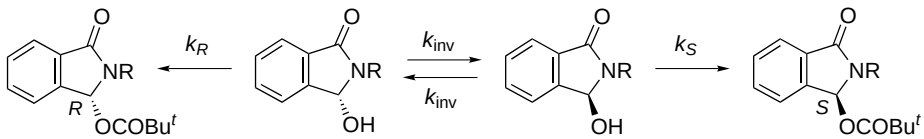
* Corresponding author. Tel.: +81-3-5978-5349; fax: +81-3-5978-5715; e-mail: yamada@cc.ocha.ac.jp

0040-4039/01/$ - see front matter © 2001 Elsevier Science Ltd. All rights reserved.
PII: S0040-4039(01)00521-4

Table 1. Dynamic kinetic resolution of hemiaminals **5–9** with amides **1–4** under neutral conditions



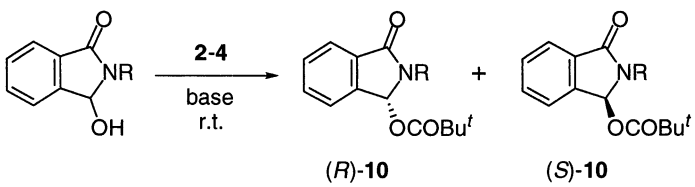
Entry	Aminal	Amide (equiv.)	Time (days)	Yield (%)	e.r. (*R*:*S*)
1	**5**	**4** (1.4)	2	65	50:50
2	**6**	**4** (1.2)	3	62	81:19
3	**7**	**4** (1.8)	7	70	81:19
4	**8**	**4** (1.5)	7	74	83:17
5	**9**	**4** (2.0)	7	76	84:16
6	**9**	**3** (1.8)	3	94	82:18
7	**9**	**2** (1.6)	9	91	75:25
8	**9**	**1** (1.3)	10	19	68:32



Scheme 1.

nal **5** was scarcely inverted even at 75°C for 3 hours in the column. The kinetic resolution of **5** with 0.5 equiv. of amide **4** also suggested its very slow inversion rate; the ee was decreased with decrease of **5**.[11] The substituent at C4 in the amides significantly affected the enantiomer ratio; the acylation with amides **3** and **4** having the bulkiest substituent at the 4-position gave the highest selectivity (entries 5–8). This is in agreement with the reported substituent effect in the kinetic resolution of racemic *sec*-alcohols with chiral twisted amides,[5] suggesting that this stereoselectivity can be explained by the previously reported mechanism where axial chirality of the twisted amides is critical for the selectivity. On the other hand, the *N*-substituents of *N*-acylhemiaminals had little effect on the selectivity (entries 2–5). However, possessing an acyl group at the N atom seems to contribute to the good stereoselectivity because the kinetic resolution of *N*-methylhemiaminal **5** resulted in very low selectivity.[11] The very low yield in the acylation with amide **1** is due to the generation of a by-product formed by the addition of **9** to the thiocarbonyl of **1** (entry 8).

Table 2. Dynamic kinetic resolution of hemiaminals **8** and **9** with **2–4** in the presence of bases



Entry	Aminal	Amide (equiv.)	Base (equiv.)	Solvent	Time (days)	Yield (%)	e.r. (*R*:*S*)
1	**9**	**3** (1.1)	NaH (1.1)	Toluene	0.3	54	47:53
2	**9**	**3** (1.6)	DBU (0.5)	Toluene	3	74	50:50
3	**9**	**3** (1.8)	Et_3N (2.0)	Toluene	18	40	85:15
4	**9**	**3** (1.5)	2,6-Lutidine (2.0)	Toluene	7	47	80:20
5	**9**	**3** (1.5)	2-DMAP (2.0)	Toluene	10	18	84:16
6	**9**	**3** (1.8)	4-DMAP (0.5)	Toluene	1	99	15:85
7	**9**	**3** (1.6)	4-DMAP (0.5)	CH_2Cl_2	2	94	13:87
8	**9**	**3** (2.0)	4-DMAP (0.5)	THF	2	94	19:81
9	**9**	**3** (2.0)	4-DMAP (0.5)	*t*-BuOH	2	96	20:80
10	**9**	**3** (1.3)	4-DMAP (0.1)	Toluene	1	80	18:82
11	**8**	**3** (1.5)	4-DMAP (0.5)	Toluene	1	99	14:86
12	**9**	**4** (1.8)	4-DMAP (0.5)	Toluene	2	95	16:84
13	**9**	**2** (1.5)	4-DMAP (0.5)	Toluene	1	99	16:84

Since prolonged time is required to complete the acylation reaction under the neutral conditions, we employed bases to accelerate the reaction rate (Table 2). In the presence of a strong base such as sodium hydride and DBU, the reaction proceeded at rt; however, no selectivity was obtained (entries 1 and 2). Triethylamine, 2,6-lutidine, and 2-DMAP were also effective to accelerate the reaction rate and the acylation proceeded at rt with good selectivities (entries 3–5). It is remarkable that addition of 4-DMAP reversed the stereoselectivity to give (*S*)-isomers as major products with good selectivities (entries 6–13), though the other pyridine bases did not exhibit such effects.[12] Various solvents such as tetrahydrofuran, dichloromethane and even *tert*-butanol were available in this reaction (entries 7–9). Reducing the amount of 4-DMAP to 10 mol% still attained good selectivity (entry 10). The acylation with the other amides **2** and **4** also gave good stereoselectivity (entries 12 and 13).

The absolute configuration of the product pivalates was determined by CD spectra according to an empirical rule proposed by Feringa and co-workers, where both signs of Cotton effects for n–π* and π–π* absorption bands are important to determine the absolute configuration.[13] Fig. 1 shows the CD spectra for both products **10A**, obtained under neutral conditions (Table 1, entry 5), and **10B**, obtained in the presence of 4-DMAP (Table 2, entry 6). The π–π* and n–π* Cotton effects are observed at 207 and 244 nm, respectively. From the opposite Cotton effects, it is apparent that they have opposite configuration to each other. The signs of their Cotton effects suggested that the absolute configuration of the major enantiomer obtained under neutral conditions is *R*, whereas that obtained in the presence of 4-DMAP is *S*.

In order to gain insight into the unusual effect of 4-DMAP on the reversal of the stereoselectivity, ^{1}H NMR measurements of hemiaminal **9** in the presence of bases were carried out (Table 3). Among the bases employed, 4-DMAP caused significant downfield shifts of the methine and hydroxy protons, and an increase in the amount of 4-DMAP resulted in further downfield shifts of the methine proton. These observations indicate that the hydrogen bond of 4-DMAP with the hydroxy group of **9** is much stronger than that of the others. On the other hand, the ^{1}H NMR spectrum of the chiral amide **3** was scarcely changed whether in the presence of 4-DMAP or in the absence of it. Although the details of the reaction mechanism are still not clear, the effect of 4-DMAP may be due to its strong coordination to the hydroxy group. Thus, this strong coordination would render the complex to behave as if like one compound as well as enhancing the nucleophilicity of the hydroxy group, and therefore, the selectivity may reverse only in the presence of 4-DMAP.

In conclusion, dynamic kinetic resolution of hemiaminals was performed by the acyl-transfer reaction using chiral twisted amides as acylating reagents. The success of the resolution would be due to the following two characteristic features of the twisted amides: (1) the moderate reactivity arising from the amide bond twisting toward the hydroxy groups, (2) the axial chirality in the amide linkage induced by the adjacent chiral center. Thus, the moderate reactivity satisfied the prerequisite of the dynamic kinetic resolution, namely, that the rate

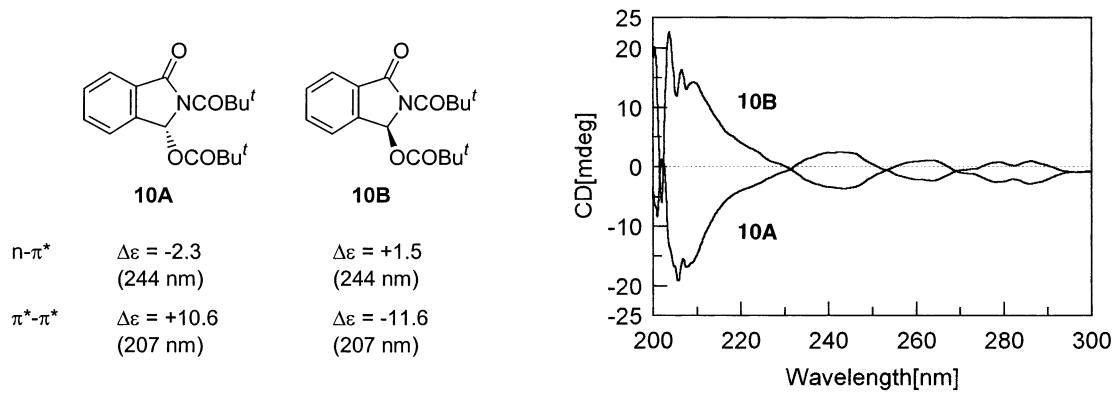


Figure 1. CD spectra for **10A** and **10B** and their $\Delta\varepsilon$ values.

Table 3. δCH and δOH (ppm)[a] of hemiaminal **9** in the presence of bases

Base (equiv.)	4-DMAP		2-DMAP		2,6-Lutidine	
	δCH	δOH	δCH	δOH	δCH	δOH
0	6.10 (d)	4.48 (d)	6.10 (d)	4.48 (d)	6.10 (d)	4.48 (d)
0.5	6.23 (s)	5.28 (br s)	6.11 (s)	4.48 (br s)	6.14 (s)	4.69 (br s)
1.0	6.32 (s)	–[b]	6.12 (s)	–[b]	6.17 (s)	4.88 (br s)
2.0	6.40 (s)	–[b]	6.13 (s)	–[b]	6.21 (s)	5.16 (br s)

[a] 270 MHz.
[b] Not observed.

of acylation step must be much slower than that of interconversion between the (*R*)- and (*S*)-isomers, and the induced axial chirality enabled discrimination of the two enantiomeric hydroxy groups.

References

1. For reviews, see: (a) Noyori, R.; Tokunaga, M.; Kitamura, M. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 36; (b) Ward, R. S. *Tetrahedron: Asymmetry* **1995**, *6*, 1475; (c) Caddick, C.; Jenkins, K. *Chem. Soc. Rev.* **1996**, 447.
2. van der Deen, H.; Cuiper, A. D.; Hof, R. P.; van Oeveren, A.; Feringa, B. L.; Kellogg, R. M. *J. Am. Chem. Soc.* **1996**, *118*, 3801.
3. Cuiper, A. D.; Kouwijzer, M. L. C. E.; Grootenhuis, P. D. J.; Kellogg, R. M.; Feringa, B. L. *J. Org. Chem.* **1999**, *64*, 9529.
4. For recent examples, see: (a) Dijkink, J.; Cintrat, J.-C.; Speckamp, W. N.; Hiemstra, H. *Tetrahedron Lett.* **1999**, *40*, 5919; (b) Cuiper, A. D.; Kellogg, R. M.; Feringa, B. L. *Chem. Commun.* **1998**, 655.
5. (a) Yamada, S.; Katsumata, H. *J. Org. Chem.* **1999**, *64*, 9365; (b) Yamada, S.; Ohe, T. *Tetrahedron Lett.* **1996**, *37*, 6777.
6. Yamada, S.; Sugaki, T.; Matsuzaki, K. *J. Org. Chem.* **1996**, *61*, 5932.
7. Flitsch, W. *Chem. Ber.* **1970**, *103*, 3025.
8. Hemiaminals **6**–**9** were prepared from 3-hydroxy-2,3-dyhydroisoindol-1-one in good yields via the following successive reactions: protection of the hydroxy group with ethyl vinyl ether, *N*-acylation with acid chloride after *N*-lithiation, and deprotection with PPTS in *t*-butanol.
9. All new compounds were fully characterized by ^{1}H NMR, ^{13}C NMR, IR, MS and HRMS.
10. Representative experiment under neutral conditions: A mixture of hemiaminal **9** (50 mg, 0.21 mmol) and amide **4** (78.8 mg, 0.32 mmol) in dry toluene (5 ml) was stirred at 80°C for 4 days. Then amide **4** (26.2 mg, 0.1 mmol) was again added to the solution and stirred at 80°C for a further 3 days. The reaction mixture was concentrated and separated by preparative TLC using a 3:1:1 mixture of hexane, ethyl acetate and CH_2Cl_2 as an eluent solvent to afford pivalate **10** in 76% yield. HPLC analysis of the enantiomer ratio using a Chiralpak AD column with a 4:1 mixture of hexane and *i*-PrOH as an eluent solvent showed that the ratio is 84:16.
11. The yields and the ee are as follows: 2%, 5.1% ee; 34%, 4.3% ee; 40%, 3.0% ee.
12. Representative experiment in the presence of 4-DMAP: To a solution of hemiaminal **9** (50 mg, 0.21 mmol) and amide **3** (100 mg, 0.42 mmol) in dry toluene (5 ml) was added 4-DMAP (13 mg, 0.11 mmol) at room temperature under a nitrogen atmosphere, and the solution was stirred for 23 h. The reaction mixture was concentrated and separated by preparative TLC using a 4:1 mixture of hexane and ethyl acetate as an eluent solvent to afford pure pivalate **10** in 99.8% yield. HPLC analysis of the enantiomer ratio using a Chiralpak AD column with a 4:1 mixture of hexane and *i*-PrOH as an eluent solvent showed that the ratio is 15:85.
13. Cuiper, A. D.; Brzostowska, M.; Gawronski, J. K.; Smeets, W. J. J.; Spek, A. L.; Hiemstra, H.; Kellogg, R. M.; Feringa, B. L. *J. Org. Chem.* **1999**, *64*, 2567.