Amino Acids (1998) 14:311–318

Amino
Acids
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Printed in Austria

Asymmetric imine-ene reactions: Diastereofacial selective reactions with chiral glyoxylate-derived α-imino esters and asymmetric catalysis of enantiofacial selective reactions with prochiral α-imino esters

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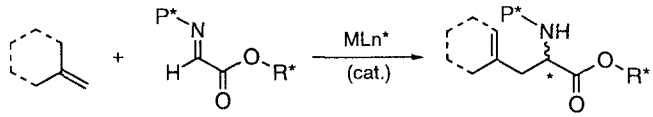
Accepted September 10, 1997

Summary. The diastereofacial selective "imine-ene" reactions with α-imino esters, prepared from (−)-8-phenylmenthyl glyoxylate, are shown to provide an efficient entry to the asymmetric synthesis of α-amino acids. The feasibility study of the asymmetric catalysis is also reported on the enantiofacial selective ene reactions with prochiral α-imino esters.

Keywords: Amino acids – Ene reaction – Diastereofacial selectivity – Enantiofacial selectivity – Binaphthol titanium complex

Introduction

The asymmetric synthesis of not only proteinogenic but also nonproteinogenic α-amino acids has become an area of great interest because of the advent of peptide-derived chemotherapeutics (Barrett, 1985; Greenstein et al., 1984; Spatola, 1983; Wagner et al., 1983; Altenbach, 1991; Williams, 1989). The asymmetric ene reaction (Mikami, 1995, 1992; Snider, 1991) with α-imino ester as a glycine equivalent should constitute a direct and versatile entry to the asymmetric synthesis of α-amino acids, if the C-C bond formation takes place regioselectively at the imino carbon. Indeed, in some intramolecular cases, the "imine-ene" reactions take an alternative course with formation of C-N bonds (Koch et al., 1983, 1986). Furthermore, intermolecular imine-ene reactions have been so far restricted to *achiral* cases (Tschaen, 1984, 1982; Achmatowicz, 1981; Hayashi, 1990). We now wish to report the first example of the asymmetric intermolecular imine-ene reactions with chiral α-imino esters and the feasibility study of the asymmetric catalysis of imine-ene reactions with prochiral α-imino esters (Scheme 1).



Scheme 1

Material and methods

^{1}H and ^{13}C NMR were measured on a Varian Gemini 300 (300 MHz) spectrometer. Chemical shifts of ^{1}H NMR were expressed in parts per million downfield from tetramethylsilane as an internal standard ($\delta = 0$) in $CDCl_3$. Significant ^{1}H NMR data were tabulated in the following order: multiplicity (s: singlet; d: doublet; t: triplet; q: quartet; bs: broad singlet; m: multiplet). Chemical shifts of ^{13}C NMR were expressed in parts per million in $CDCl_3$ as an internal standard ($\delta = 77.1$).

The lewis acid-promoted imine-ene reaction

To a solution of the α-imino ester (1 mmol) in 5 ml of dichloromethane at -78°C was added a 1 *M* dichloromethane solution of Lewis acid (1 ml) and stirred for 30 min at room temperature. To this mixture at -78°C was added olefin (3 mmol). The mixture was quenched with sat. sodium bicarbonate. The aqueous layer was extracted with ethyl acetate and the combined organic layer was dried over anhydrous magnesium sulfate. Removal of the organic solvent in vacuo gave the crude product. Purification by silica gel chromatography gave the ene product.

1a (2*R*): ^{1}H NMR ($CDCl_3$, TMS) δ 1.33 (d, J = 6.6 Hz, 3H), 1.72 (s, 3H), 2.35 (d, J = 7.2 Hz, 2H), 3.48 (t, J = 7.2 Hz, 1H), 3.49 (s, 3H), 3.76 (q, J = 6.6 Hz, 1H), 4.47 (s, 1H), 4.79 (s, 1H), 7.15~7.33 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 22.3, 23.2, 42.2, 54.5, 57.2, 58.5, 114.0, 127.3, 127.5, 128.6, 141.9, 145.7, 175.8.

1b (2*R*): ^{1}H NMR ($CDCl_3$, TMS) δ 1.50 (d, J = 6.6 Hz, 3H), 1.69 (s, 3H), 1.95 (bs, 1H), 2.38 (d, J = 7.1 Hz, 2H), 3.59 (s, 3H), 3.61 (t, J = 7.1 Hz, 1H), 4.66 (q, J = 6.6 Hz, 1H), 4.75 (s, 1H), 4.80 (s, 1H), 7.45~7.54 (m, 3H), 7.64, (d, J = 7.1 Hz, 1H), 7.74 (d, J = 8.0 Hz, 1H), 7.85 (d, J = 8.4 Hz, 1H), 8.20 (d, J = 8.0 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 22.0, 22.2, 41.9, 51.5, 57.8, 113.6, 123.0, 123.3, 125.3, 125.6, 125.8, 127.5, 128.9, 131.0, 133.9, 140.8, 141.5, 175.3.

1c (2*S*): ^{1}H NMR ($CDCl_3$, TMS) δ 0.89, (d, J = 6.8 Hz, 6H), 1.70 (s, 3H), 1.78~2.01 (m, 2H), 2.28 (dd, J = 8.7, 13.7 Hz, 1H), 2.38 (dd, 5.9, 13.7 Hz, 1H), 3.04 (d, J = 5.8 Hz, 1H), 3.33 (dd, J = 5.9, 8.7 Hz, 1H), 3.66 (s, 6H), 4.78 (s, 1H), 4.83 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 18.4, 19.0, 21.5, 31.7, 41.8, 51.6, 51.9, 57.8, 65.3, 114.6, 141.4, 174.9, 175.4.

1d (2*S*): ^{1}H NMR ($CDCl_3$, TMS) δ 1.57 (s, 3H), 2.35~2.40 (m, 2H), 3.20 (dd, J = 6.2, 8.2 Hz, 1H), 3.67 (s, 3H), 3.71, (s, 3H), 4.44 (s, 1H), 4.78 (s, 1H), 4.84 (s, 1H), 7.29~7.36 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 21.8, 41.7, 51.8, 52.4, 56.1, 63.2, 114.2, 127.9, 128.5, 128.6, 137.4, 141.0, 172.4, 174.6.

1e (2*S*): ^{1}H NMR ($CDCl_3$, TMS) δ 0.90 (d, J = 6.6 Hz, 3H), 1.20 (s, 3H), 1.31 (s, 3H), 1.65 (s, 3H), 0.81~2.17 (m, 10H), 2.41 (brs, 1H), 3.28 (dd, J = 3.6, 8.2 Hz, 1H), 4.68 (s, 1H), 4.79 (s, 1H), 4.88 (dt, J = 4.3, 10.7 Hz, 1H), 7.10~7.35 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 21.7, 22.2, 22.8, 26.2, 29.6, 31.2, 34.4, 39.3, 41.5, 42.2, 50.2, 68.2, 75.6, 113.4, 125.1, 127.9, 141.0, 151.7, 174.1.

1f (2*S*): ^{1}H NMR ($CDCl_3$, TMS): δ 0.73~2.31 (m, 8H), 0.82 (d, *J* = 6.6 Hz, 3H), 1.08 (s, 6H), 1.52~2.22 (m, 10H), 2.41 (s, 3H), 3.50 (dt, *J* = 5.3, 8.7 Hz, 1H), 4.47 (d, *J* = 8.7 Hz, 1H), 4.56 (ddm, *J* = 4.1, 10.7 Hz 1H), 5.32 (s, 1H), 7.15~7.30 (m, 5H), 7.28 (d, 2H), 7.71 (d, *J* = 8.4 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 21.6, 21.8, 22.1, 22.7, 23.9, 25.3, 26.5, 27.9, 28.7, 31.2, 34.6, 39.4, 40.9, 42.0, 50.0, 54.2, 76.9, 125.2, 126.1, 127.3, 128.3, 129.6, 132.4, 137.7, 143.3, 151.0, 157.6, 170.1.

1f (2*R*): ^{1}H NMR ($CDCl_3$, TMS): δ 0.73~2.30 (m, 8H), 0.81 (d, J = 6.5 Hz, 3H), 1.16 (s, 3H), 1.24 (s, 3H), 1.50~2.21 (m, 10H), 2.41 (s, 3H), 3.66 (dt, J = 4.6, 9.1 Hz, 1H), 4.61 (d, J = 8.2 Hz, 1H), 4.64 (ddm, J = 5.6, 10.7 Hz, 1H), 5.40 (s, 1H), 7.10~7.32 (m, 5H), 7.29 (d, 2H), 7.69 (d, J = 8.4 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 21.8, 22.1, 22.6, 22.7, 25.3, 26.5, 27.0, 27.4, 27.7, 31.3, 34.5, 40.0, 40.6, 41.1, 49.7, 54.3, 77.4, 125.5, 126.6, 127.4, 128.2, 129.6, 131.9, 137.5, 143.0, 151.1, 157.6, 171.1.

The imine-ene reaction catalyzed by (R)-BINOL-derived titanium complex

To a suspension of molecular sieves (MS 4A, activated powder) (250 mg) in dichloromethane (1.5 mL) was added (*R*)-BINOL-derived titanium complex (21.5 mg, 0.05 mmol) at room temperature. After stirring for 5 min, a solution of iminoacetate (0.5 mmol) in dichloromethane (0.5 mL) and then olefin (0.75 mmol) was added to the mixture at the indicated temperature. After stirring for 10 h at that temperature, ether (2 mL) and sat. sodium bicarbonate (2 mL) was added to the mixture. MS 4A was filtered off through a pad of Celite and the filtrate was extracted with ethyl acetate three times. The combined organic layer was washed with brine, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure. Chromatographic separation by silica gel gave the product.

5a: ^{1}H NMR ($CDCl_3$, TMS): δ 1.49 (m, 4H), 1.75 (bs, 2H), 1.94 (bs, 2H), 2.28 (d, J = 6.8 Hz, 2H), 2.42 (s, 3H), 3.50 (s, 3H), 3.99 (dt, J = 8.2, 6.2 Hz, 1H), 5.03 (d, J = 8.2 Hz, 1H), 5.43 (s, 1H), 7.29 (d, J = 9.09 Hz, 2H), 7.72 (d, J = 8.0 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 21.6, 22.1, 22.7, 25.4, 27.9, 42.0, 52.3, 54.4, 126.7, 127.3, 129.5, 131.7, 136.7, 143.5, 172,1.

5b: ^{1}H NMR ($CDCl_3$, TMS): δ 1.12 (t, J = 7.2 Hz, 3H), 1.50 (m, 4H), 1.80 (m, 2H), 1.93 (bs, 2H), 2.29 (m, 2H), 2.41 (s, 3H), 3.92 (q, 2H), 3.97 (m, 1H), 5.10 (d, J = 5.9 Hz, 1H), 5.43 (s, 1H), 7.27 (d, J = 8.4 Hz, 2H), 7.72 (d, J = 8.4 Hz, 2H).^{13}C NMR ($CDCl_3$): δ 13.9, 21.5, 22.0, 22.6, 25.3, 27.8, 42.1, 54.4, 61.4, 126.5, 127.3, 129.5, 131.9, 136.9, 143.5, 171.7.

5c: ^{1}H NMR ($CDCl_3$, TMS): δ 1.62 (m, 4H), 1.90 (m, 2H), 2.04 (m, 2H), 2.43 (m, 2H), 3.79 (s, 3H), 4.32 (m, 1H), 5.55 (bs, 1H), 5.66 (d, J = 28.6 Hz, 1H).

5d: ^{1}H NMR ($CDCl_3$, TMS): δ 1.27 (t, J = 7.1 Hz, 3H), 1.59 (m, 4H), 1.82 (m, 2H), 1.92 (m, 2H), 2.40 (m, 1H), 4.16 (q, J = 7.1 Hz, 2H), 4.18 (m, 1H), 5.47 (bs, 1H), 5.58 (d, J = 8.5 Hz, 1H).

Results and discussion

Diastereofacial selective reactions with chiral glyoxylate-derived α-imino esters

First of all, attempted reactions of isobutene with α-imino esters, prepared in situ in the presence of molecular sieves (MS 4A) from achiral glyoxylates and (*R*)-arylethylamine, were found to give indeed the imine-ene products with formation of C-C bonds, using an appropriate Lewis acid such as $SnCl_4$ or $TiCl_4$. All the ene reactions preferentially afforded *D*(*R*)-α-amino esters (entries 1~4) (Mikami et al., 1993), except with $EtAlCl_2$ to provide *N*-ethyl product. Of interest is (*R*)-naphthylethylimine to provide higher *D*(*R*)-selectivity (Yamamoto et al., 1986) but lower chemical yield (entry 5).

The reactions with imines derived from (*S*)-α-amino esters afforded higher but still insufficient level of diastereofacial selectivity along with better chemical yield (entries 6~8). α-Trifluoromethanesulfonyloxy esters have been used in the reaction with amines to give the chiral α-amino acids without serious racemization (Effenberger et al., 1983). Thus, the *L*(*S*)-

stereochemistry of the major diastereomer was determined after hydrogenation through comparison with an authentic $L(S)$-leucine derivative obtained with $2S$-α-trifluoromethanesulfonyloxy isovalerate. The sense of asymmetric induction thus determined is exactly the same as reported for the reaction of allylic metals (Tanaka, 1990; Bocoum, 1991) where the S-amino esters produce the $L(S)$-chiralities.

Significantly, (−)-8-phenylmenthol (Whitesell, 1992, 1982; Corey, 1975; Oppolzer, 1981; Yamamoto, 1988; Mikami, 1991) derived α-imino esters were

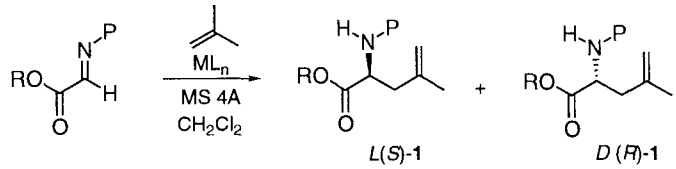
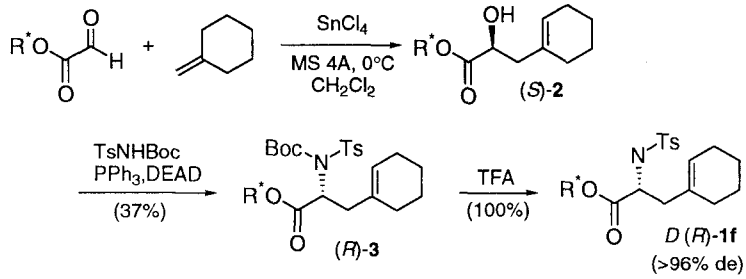


Fig. 1



Scheme 2

Table 1. Asymmetric imine-ene reaction with glyoxylate-delived α-imino esters[a]

Entry	R	P	MLn	Temp (°C)	% Yield	L (2S) : D (2R)
1a	Me	$CH(Ph)CH_3$	$MeAlCl_2$	20	22	45 : 55
2a			$MeAl(OTf)_2$	20	33	35 : 65
3a			$SnCl_4$	20	61	30 : 70
4a			$TiCl_4$	−78	21	20 : 80
5b		$CH(Np)CH_3$			13	15 : 85
6c		$CH(Pr^i)CO_2Me$		−30	76	80 : 20
7c				−78	40	85 : 15
8d		$CH(Ph)CO_2Me$		−30	82	72 : 28
9e[b]	Ph	Bn	$TiCl_4$	20	21	88 : 12
10e[b]			$SnCl_4$	20	32	90 : 10
11e[c]				20	76	97 : 3
12f[d]		Ts		0	60	>99 : <1

[a] Unless otherwise marked, the ene reaction was carried out using the isolated imine and an excess (ca. 2 eq) of isobutene. [b] Via the in situ preparation of imine. [c] Via the in situ preparation of imine in the presence of $SnCl_4$ (1 eq). [d] Methylenecyclohexane was used instead of isobutene. For the preparation of imine see: Hamley et al., 1991.

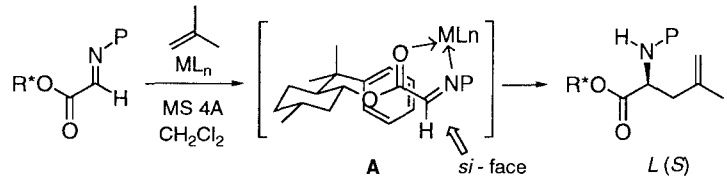


Fig. 2

found to exhibit remarkably high diastereofacial selectivity along with high chemical yield (entries 11~12). The *L*(*S*)-stereochemistry of the major diastereomer was determined through comparison with an authentic *D*(*R*)-diastereomer obtained from (−)-8-phenylmenthyl (*S*)-trifyloxyester, which was obtained via the "carbonyl-ene" reaction (−)-8-phenylmenthol-derived glyoxlate (Scheme 2).

Induction of *L*(*S*)-chirality in the imine-ene reactions of (−)-8-phenylmenthol-derived α-imino esters indicates that the *syn*-chelation (**A**) is also favorable with α-imino esters. Thus, olefins presumably attack the imine carbon from the *si*-face, since the phenyl group blocks the attack from the *re*-face (**A**).

Asymmetric catalysis of enantiofacial selective reactions with prochiral α-imino esters

Next, we examined the asymmetric catalysis of imine-ene reactions with prochiral α-imino esters by using chiral binaphthol-derived titanium (BINOL-Ti) complex. Glyoxylate-imines having sulfonyl groups as the *N*-substituent were investigated as α-imino esters since those were considered to show high ene-reactivity (Table 2).

The reaction was carried out by adding an olefin and freshly prepared imine to the solution of the chiral BINOL-Ti complex at room remperature. Though the yield was very low, the imine-ene product was obtained along with the glyoxylate-ene product presumably because of decomposition of imines to glyoxlate. The enantiomeric excess of imine-ene product were extremely low, in spite of the high enantiomeric excess of the glyoxylate-ene product.

We then examined the imine-ene reaction under both thermal (Braxmeier et al., 1985) and Lewis acid catalysis conditions. However, we couldn't observe any significant acceleration effect by the Lewis acid catalysis.

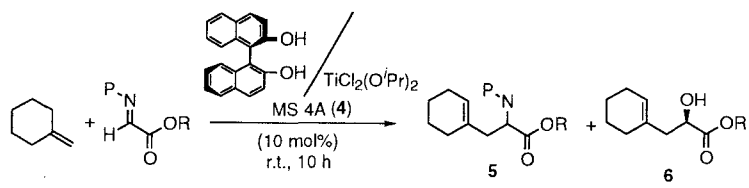
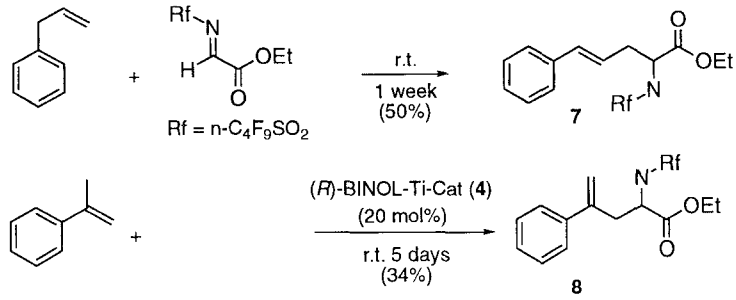


Fig. 3

Table 2. Asymmetric catalytic imine-ene reaction[a]

Entry	P=	R=	5% yield	:	6% yield
1a	p-$CH_3C_6H_4SO_4$	Me	7 (0% ee)	:	15 (95% ee)
2b		Et	7 (0% ee)	:	15 (95% ee)
3b[b]			7 (0% ee)	:	–
4c	$C_4F_9SO_4$	Me	7 (0% ee)	:	15 (95% ee)
5d	CF_3SO_4	Me	7 (0% ee)	:	15 (95% ee)

[a] % ee was determined by ^1H NMR analysis of (S)- and (R)-MTPA ester derivatives after $LiAlH_4$ reduction and esterification. [b] $SnCl_4$ was used as an equimolar amount of Lewis acid.



Scheme 3

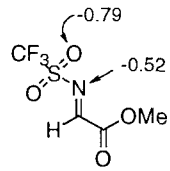


Fig. 4

Semiempirical molecular orbital calculation (PM3 (Stewart, 1989)) of sulfonyl-imine was then performed to show that the partial charge of sulfonyl oxygen (−0.79) is larger than that of nitrogen (−0.52). Therefore, the Lewis acids are considered to be more easily coordinated with sulfonyl oxygen rather than the nitrogen. The coordination of chiral catalyst with sulfonyl oxygen might be the reason for the very little acceleration and extremely low enantiomeric excess attained by the chiral Lewis acid catalyst. Unfortunately, benzylimines are so unreactive under the Lewis acid catalysis to give no imine-ene product.

In summary, we have reported diastereofacial selective "imine-ene" reactions with chiral glyoxylate-derived α-imino esters and feasibility studies on the asymmetric catalysis of enantiofacial selective reactions with prochiral α-imino esters. Further studies along these lines are now under way in our laboratory.

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Received May 6, 1997