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Tetrahedron
Tetrahedron 63 (2007) 7816–7822

On the scope of diastereoselective allylation of various chiral glyoxylic oxime ethers with allyltributylstannane in the presence of a Lewis acid and triallylaluminum

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Received 20 April 2007; revised 23 May 2007; accepted 24 May 2007
Available online 27 May 2007

Abstract—The nucleophilic allylation of various chiral auxiliaries derived glyoxylic oxime ethers was studied. The use of allyltributylstannane in the presence of a Lewis acid and triallylaluminum provided the corresponding homoallylic amines in high chemical yields (up to 89%) and excellent stereoselectivities (up to >99%). The stereochemical bias of the allylation is proposed.

1. Introduction

The nucleophilic addition of organometals to a carbonyl/imine group represented one of the most straightforward methods for the construction of C–C bonds. The allylation of an α-imino carbonyl group provides the corresponding allylglycine derivatives, which are attractive targets as building blocks for synthesis of peptides,[1] lactams,[2] and a number of biologically active compounds.[3] Numerous allylic reagents have been developed over the last several decades for the allylation of carbonyl/imine functionalities.[4] These include allyllithium,[5] allylsilane,[6] allylstannane,[7] and other allylmetals.[8] The Barbier-type allylation using allyl halides with different metal sources has been reported.[9] On the other hand, applications of organoaluminum reagents in organic synthesis have received less attention, compared to other organometallic reagents.[10]

Considerable progress has been achieved in stereoselective nucleophilic allylation of imines[11] and hydrazones[12] in recent years. The allylation of the less reactive imine functionality usually requires the presence of a Lewis acid. Very recently we reported on the diastereoselective allylation of glyoxylic oxime ethers derived from camphorsultam, *N*-phenyl and *N*-tosyl camphorpyrazolidinone using allyltributylstannane in the presence of $Sn(OTf)_2$.[13] The desired homoallylic amine derivatives were obtained in excellent diastereoselectivity and high material yields. This offers a new route for the preparation of α-amino acids. In this report, the scope and generality of the diastereoselective allylation of various chiral glyoxylic oxime ethers are described. In addition to the more commonly employed allyltributylstannane in the presence of a Lewis acid, a more reactive triallylaluminum reagent was also studied. High to excellent material yields and stereoselectivity were obtained for some of the chiral glyoxylic oxime ethers. The stereochemical course of the reactions is proposed.

2. Results and discussion

The starting α-glyoxylic oxime ethers bearing various auxiliaries are readily prepared. Treatment of *O*-benzyloxyamine hydrochloride with glyoxylic acid in H_2O affords the corresponding oxime ether **2** in 90% yield. The α-oxime ether glyoxylic acid chloride was then prepared ($SOCl_2$) followed by the treatment of the chiral auxiliaries (**a**–**h**) with NaH in THF at 0 °C for 2 h. A wide structural variety of chiral auxiliaries were examined, including camphorsultam, *N*-phenyl camphorpyrazolidinone, *N*-tosyl camphorpyrazolidinone, (*S*)-(+)-4-phenyl-oxazolidin-2-one, 10,10-diphenyl-2,10-camphandiol, (−)-menthol, (−)-borneol, and (−)-pinanediol. The desired chiral glyoxylic oxime ethers (**3a**–**h**) were obtained in good to high material yields (76–90%).[14] With the chiral glyoxylic oxime ethers in hand, we then turned our attention to the allylation reaction. The camphorsultam derived glyoxylic oxime ether **3a** was chosen as the probe substrate. The palladium–indium iodide-mediated allylation/alkylation reaction of camphorsultam derived glyoxylic oxime ether in aqueous media has been reported.[15] However, these reports were limited to camphorsultam

Keywords: Allylation; Glyoxylic oxime ether; Chiral auxiliary; Triallylaluminum.
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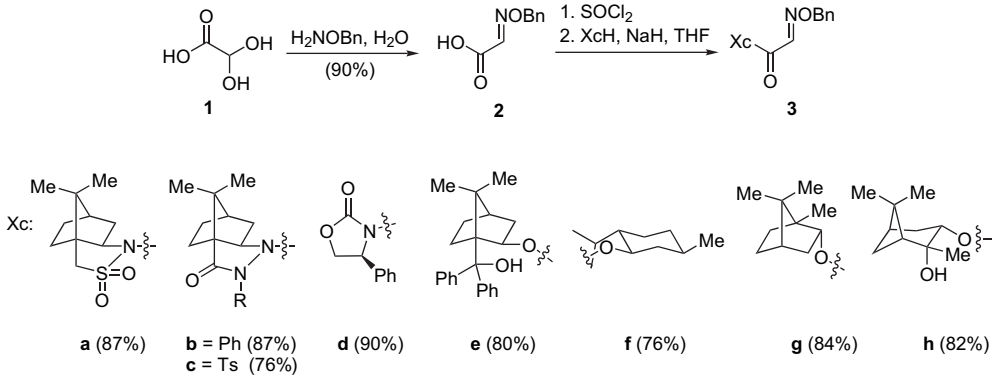
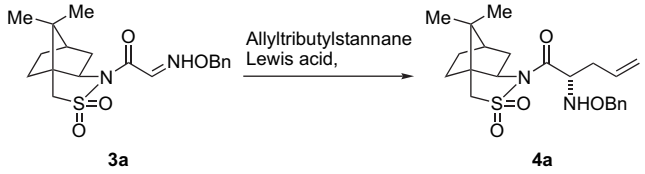
doi:10.1016/j.tet.2007.05.091



derived substrates. Various metal triflates were then screened. No reaction occurred when **3a** was treated with allyltributylstannane in the presence of various Lewis acids ($Sc(OTf)_3$, $Yb(OTf)_3$, $Eu(OTf)_3$, $Sm(OTf)_3$, $La(OTf)_3$, and $PdCl_2$) in CH_3CN (Table 1, entries 1–6). Both the stereoselectivity and the rate of the reaction were improved when $Zn(OTf)_2$ was used at ambient temperature (Table 1, entry 7). A slight improvement in diastereoselectivity was observed when the reaction was carried out at 0 °C (Table 1, entry 8). The diastereoselectivity of the reaction was determined based on ^1H NMR and HPLC analysis. The absolute stereochemistry of the newly generated stereogenic center of the major diastereomer was assigned as an *S* configuration by single crystal X-ray analysis. No further improvement was observed when various solvents (THF, ether, CH_2Cl_2, and toluene) were used under the same reaction conditions (data not shown). The reaction proceeded to completion in 6 h when AgOTf was used and was complete after 30 min when $Sn(OTf)_2$ was used at ambient temperature (entries 9 and 10). Stereoselectivity was slightly improved when the reaction was carried out at 0 and −25 °C and further improved at −40 °C for a reaction in the presence of $Sn(OTf)_2$ (entries 11–13). This is comparable to the best results obtained for the allylation of the camphorsultam derived glyoxylic oxime ether. This also turned out to be the optimum condition for the diastereoselective allylation.

Table 1. Nucleophilic allylation of camphorsultam derived glyoxylic oxime ether **3a** with allyltributylstannane in the presence of a Lewis acid[a]



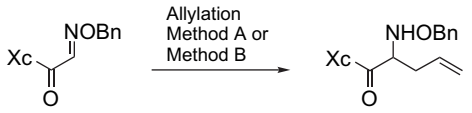
3a **4a**

Entry	Lewis acid	Solvent	*T* (°C)	*t* (h)	Yield[b] (%)	de[c] (%)
1	$Sc(OTf)_3$	CH_3CN	rt	24	0	
2	$Yb(OTf)_3$	CH_3CN	rt	24	0	
3	$Eu(OTf)_3$	CH_3CN	rt	24	0	
4	$Sm(OTf)_3$	CH_3CN	rt	24	0	
5	$La(OTf)_3$	CH_3CN	rt	24	0	
6	$PdCl_2$	CH_3CN	rt	24	0	
7	$Zn(OTf)_2$	CH_3CN	rt	2	88	87 (*S*)
8	$Zn(OTf)_2$	CH_3CN	0	7	89	92 (*S*)
9	AgOTf	CH_3CN	rt	6	87	93 (*S*)
10	$Sn(OTf)_2$	CH_3CN	rt	1/2	92	56 (*S*)
11	$Sn(OTf)_2$	CH_3CN	0	1	90	74 (*S*)
12	$Sn(OTf)_2$	CH_3CN	−25	1	91	78 (*S*)[d]
13	$Sn(OTf)_2$	CH_3CN	−40	1	90	91 (*S*)[d]
14	$Sn(OTf)_2$	EtCN	−60	3	84	82 (*S*)
15	$Sn(OTf)_2$	EtCN	−80	12	68	87 (*S*)

[a] Unless otherwise specified, all reactions were carried out using **3a** (0.13 mmol), allyltributylstannane (2.0 equiv) and $Sn(OTf)_2$ (1.0 equiv) under the solvent and temperature indicated.
[b] Isolated yield.
[c] Absolute configuration was assigned by single crystal X-ray analysis.
[d] See Ref. 13.

The scope and generality of the present method was investigated by performing allylation reactions of various glyoxylic oxime ethers under the optimum conditions. The efficient allylation of an aldehyde with allyldiethylaluminum has been reported.[16] The use of triallylaluminum for the allylation of carbonyl/aldimine/ketimine group to give the corresponding homoallylic alcohols and amines with excellent material yields was recently reported.[17] Stereoselective allylation by allyl metals such as Mg, Zn, B, Sn have been extensively studied while the use of economical allylaluminum reagents have received relatively less attention.[18] To the best of our knowledge, the diastereoselective allylation of the electron deficient C═N bond by triallylaluminum has not been reported in the literature. In our previous study, no desired product was isolated when glyoxylic oxime ether **3a** was treated with allyltributylstannane in the absence of $Sn(OTf)_2$ in CH_3CN at −40 °C, while excellent yield and a high diastereoselectivity was achieved in the presence of $Sn(OTf)_2$ (Table 1, entry 13). Treatment of **3a** with freshly prepared triallylaluminum in ether at −78 °C resulted in no reaction (Table 2, entry 1). On the other hand, reasonable stereoselectivity was obtained when the reaction was carried out in THF (Table 2, entry 2). Both the chemical yield and diastereoselectivity were further improved when **3a** was treated with triallylaluminum in CH_2Cl_2 at −78 °C for 10 min (Table 2, entry 4). The operationally simple procedure provided an attractive alternative for the allylation of the imine bond. A similar result was obtained by the slow addition of triallylaluminum using a syringe pump under the same reaction conditions. Dichloromethane was found to be the solvent of choice for the allylation of **3a** when triallylaluminum was used. The absolute stereochemistry of the newly generated stereogenic center was assigned as an *S* configuration, which is the same as that obtained when allyltributylstannane is used. These results encouraged us to evaluate and compare the efficiency of the allylation of a C═N bond using two different allylating methods (method A: allyltributylstannane (2.0 equiv) and $Sn(OTf)_2$ (1.0 equiv) and method B: triallylaluminum). A direct comparison of the reactivity and stereochemical course between allyltributylstannane and triallylaluminum is of interest. Various chiral glyoxylic oxime ethers were then subjected to the above

Table 2. Diastereoselective allylation of glyoxylic oxime ethers **3a–h** with allyltributylstannane, $Sn(OTf)_2$, and triallylaluminum[a]



3a-h **4a-h**

Entry	Substrate	Method[b] (equiv)	Solvent	T (°C)	Yield[c] (%)	de[d] (%)
1	**3a**	B (2.0)	Ether	−78	0	
2	**3a**	B (2.0)	THF	−78	87	60 (*S*)
3	**3a**	B (2.0)	CH_3CN	−40	83	50 (*S*)
4	**3a**	B (2.0)	CH_2Cl_2	−78	89	82 (*S*)[e]
5	**3b**[f]	A	CH_3CN	−40	92	>99 (*S*)[e]
6	**3b**	B (1.2)	CH_2Cl_2	−78	50	57 (*S*)
7	**3b**	B (2.2)	CH_2Cl_2	−78	81	67 (*S*)
8	**3c**[f]	A	CH_3CN	−40	94	>99 (*S*)[g]
9	**3c**	B (2.2)	CH_2Cl_2	−78	84	>99 (*S*)
10	**3d**	A	CH_3CN	−78	90	33 (*S*)
11	**3d**	B (2.2)	CH_2Cl_2	−78	81	76 (*S*)
12	**3e**	A	CH_3CN	−78	55	10
13	**3e**	B (2.2)	CH_2Cl_2	−78	82	37
14	**3f**	A	CH_3CN	−78	62	<10
15	**3f**	B (2.2)	CH_2Cl_2	−78	75	10
16	**3g**	B (2.2)	CH_2Cl_2	−78	82	>99[h]
17	**3h**	B (2.2)	CH_2Cl_2	−78	80	90[h]

[a] Unless otherwise specified, all reactions were carried out using **3a–h** (0.13 mmol) under the solvent and temperature indicated.
[b] Method A: allyltributylstannane (2.0 equiv) and $Sn(OTf)_2$ (1.0 equiv) were used under the reaction conditions for 1 h; Method B: triallylaluminum (1.0 M) was used under the reaction conditions for 10 min.
[c] Isolated yield.
[d] Diastereoselectivity was determined by 400 MHz ^{1}H NMR.
[e] Absolute configuration was assigned by single crystal X-ray analysis.
[f] See Ref. 13.
[g] Absolute stereochemistry was assigned by analogy.
[h] Absolute configuration was not assigned.

two allylation reaction conditions. Excellent stereoselectivity was achieved when *N*-phenyl camphorpyrazolidinone derived glyoxylic oxime ether was treated with allyltributylstannane in the presence of $Sn(OTf)_2$ while only moderate stereoselectivity was found when triallylaluminum was used (Table 2, entries 5 and 6). The stereoselectivity was improved when the amount of triallylaluminum was increased (Table 2, entry 7). Excellent diastereoselectivity was achieved when the *N*-tosyl camphorpyrazolidinone derived glyoxylic oxime ether was treated with either of the allylating reagents (Table 2, entries 8 and 9). Allylation of (*S*)-(+)-4-phenyl-oxazolidin-2-one derived glyoxylic oxime ether with triallylaluminum gave the desired product with 76% de compared to 33% de when allyltributylstannane was used (Table 2, entries 10 and 11). Poor diastereoselectivities were observed when 10,10-diphenyl-2,10-camphandiol and the (−)-menthol derived glyoxylic oxime ether was used under either of the reaction conditions (Table 2, entries 12–15). Finally, excellent stereoselectivities were achieved when the ester linked auxiliaries ((−)-borneol and (−)-pinanediol) derived glyoxylic oxime ethers were treated with triallylaluminum at −78 °C (Table 2, entries 16 and 17). The reaction proceeded to completion at −78 °C in 10 min when triallylaluminum was used, compared to an hour when allyltributylstannane was used. It can thus be concluded from the above results that triallylaluminum is more reactive than allyltributylstannane in the presence of $Sn(OTf)_2$.

We previously proposed that $Sn(OTf)_2$ coordinates to the sulfonyl group in camphorsultam (**3a**) and *N*-tosyl camphorpyrazolidinone (**3c**) while forming a chelate with the oxime ether nitrogen and adjacent carbonyl group in *N*-phenyl camphorpyrazolidinone (**3b**) derived substrates.[13] The Sn atom coordinates strongly with the carbonyl and α-oxime ether groups in **3b** that serves both to activate and restrict the conformational populations in the transition state.[19] The observed diastereoselectivity for the triallylaluminum allylation of **3a–c** can be explained by a similar argument as proposed in Figure 1. We propose that the Lewis acid nature of the aluminum reagent coordinates strongly with the sulfonyl oxygen atoms in **3a** and **3c**, similar to $Sn(OTf)_2$. On the other hand, the aluminum atom coordinates weakly to the α-oxime ether groups compared with that of $Sn(OTf)_2$ in the case of **3b**. The *s*-cis/*s*-trans transition state conformations then reach an equilibrium, which accounts for the low diastereoselectivity (67% de) when **3b** was treated with triallylaluminum. The chelation of the aluminum atom to the Lewis bases also accelerates the release of the allylating group in the reaction. The allyl group delivered from the *si* face to the α-imino carbon, leading to the desired major products with high to excellent stereoselectivities. The mechanistic explanation for the high to excellent stereoselectivity of the two ester linkage auxiliaries (**3g** and **3h**) remains unclear at this moment. The coordination of the aluminum reagent to the hydroxy group and the structural skeleton of **3g** and **3h** may be responsible for the stereoselectivity.

3. Conclusions

In conclusion, the diastereoselective allylation of various chiral glyoxylic oxime ethers was examined using allyltributylstannane and triallylaluminum as the allylating reagents. This is the first example of the diastereoselective allylation of chiral glyoxylic oxime ether derivatives with triallylaluminum. Allylation of a sulfonyl group containing (**3a** and **3c**) and (−)-borneol and (−)-pinanediol derived glyoxylic oxime ethers (**3g** and **3h**) provided the corresponding homoallylic amines in high to excellent diastereoselectivities (up to >99%). The coordination of the aluminum reagent to the

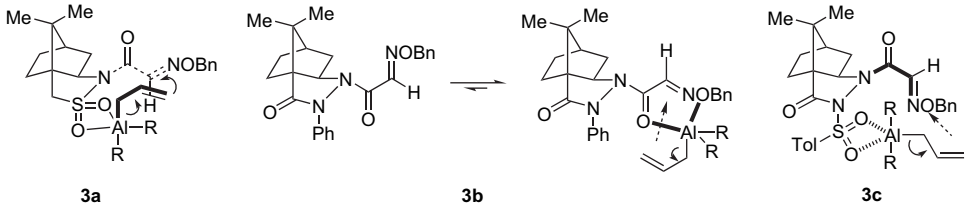


Figure 1. Proposed mechanism for triallylaluminum allylation of glyoxylic oxime ethers **3a–c**.

Lewis base atoms of the substrates may account for the rapid reaction rate. Further investigations of the use of organoaluminum as a reactive reagent are currently in progress.

4. Experimental

4.1. General methods

All reagents were used as purchased from the commercial suppliers without further purification. NMR spectra were recorded on a Bruker Avance 400 NMR spectrometer (400 MHz for ^{1}H, and 100 MHz for ^{13}C). Chemical shifts are reported in δ parts per million referenced to an internal TMS standard for ^{1}H NMR and chloroform-*d* (δ 77.0) for ^{13}C NMR. Optical rotations were measured on a JASCO P-1010 polarimeter. EI mass spectra were recorded on a Finnigan TSQ-700 instrument at an ionizing energy of 70 eV and HRMS spectra were recorded on JEOL SX-102A. Routine monitoring of reactions was performed using silica gel, glass-backed TLC plates (Merck Kieselgel 60 F_{254}) and visualized by UV light (254 nm). Analytical high performance liquid chromatography was performed on a JASCO PU-1580 HPLC. Solutions were evaporated to dryness under reduced pressure using a rotary evaporator and the residue was purified by flash column chromatography on silica gel (230–400 mesh) with the indicated eluents. Air and/or moisture sensitive reactions were performed under inert atmosphere conditions.

Crystallographic data for the structures in this paper have been deposited at the Cambridge Crystallographic Data Center and allocated the CCDC deposit numbers.[20]

4.1.1. Synthesis of glyoxylic oxime 2. To a solution of *O*-benzylhydroxylamine hydrochloride (1.0 g, 6.2 mmol) in H_2O (15 mL) was added glyoxylic acid (0.92 g, 12.5 mmol) in one portion. The reaction mixture was stirred at ambient temperature. After 2 h, CH_2Cl_2 (20 mL) was added to the reaction mixture and the aqueous layer was extracted with CH_2Cl_2 (2×15 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ and after evaporation of the solvent, a white solid product (1.0 g, 90%) was obtained: ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.9 (s, 1H), 7.53 (s, 1H), 7.37–7.33 (m, 5H), 5.30 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 140.2, 135.6, 128.6 (×4), 78.5.

4.1.2. Typical procedure for the synthesis of glyoxylic oxime ether 3a–h. Under a N_2 atmosphere, a mixture of glyoxylic oxime ether **2** (1.0 g, 5.58 mmol) and thionyl chloride (3.0 mL, 41.96 mmol) was refluxed at 75 °C for 2 h and concentrated on a rotary evaporator to remove the excess $SOCl_2$. The resulting residue was dissolved in THF (5 mL) and added to a mixture of camphorsultam (0.6 g, 2.78 mmol) and NaH (0.1 g, 4.16 mmol) in THF (5 mL) at 0 °C. The reaction mixture was then stirred at 0 °C for 2 h. The reaction mixture was quenched with H_2O (20 mL) and extracted with EtOAc (3×20 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ and concentrated in vacuo. The crude products were further purified by flash column chromatography eluted with hexanes/EtOAc (4:1) to give the product as a white solid (0.91 g, 87%).

Compound **3a**: R_f=0.58 (4:1 hexanes/EtOAc); $[\alpha]_D^{31}$ −79.7 (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (s, 1H), 7.39–7.32 (m, 5H), 5.31 (s, 2H), 3.97 (dd, 1H, *J*=7.6, 5.0 Hz), 3.52 (d, 1H, *J*=13.8 Hz), 3.44 (d, 1H, *J*=13.8 Hz), 2.13–2.11 (m, 1H), 2.06 (dd, 1H, *J*=13.9, 7.6 Hz), 1.92–1.86 (m, 3H), 1.43–1.30 (m, 2H), 1.15 (s, 3H), 0.96 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.4, 143.2, 138.1, 130.0, 129.9, 129.8, 78.9, 66.1, 53.9, 50.5, 49.0, 46.3, 39.5, 33.5, 27.2, 21.7, 20.5; LRMS (FAB) [M+1] *m/z* (relative intensities) 377.2 (100), 347.3 (2), 307.2 (2), 289 (2), 242.2 (3), 214.3 (2), 214.3 (2), 154.2 (13), 107 (11) (calcd for $C_{19}H_{24}N_2O_4S$: 377.15). Crystal data for **3a** at 27 °C: $C_{19}H_{24}N_2O_4S$, *M* 376.46, monoclinic, $P2_1$, *a*=7.8927 (2) Å, *b*=23.0682 (6) Å, *c*=10.9889 (4) Å, *V*=1899.78 (10) Å^3, *Z*=4, D_x=1.316 Mg/m^3, μ=0.197 mm^{-1}, 5846 reflections, 470 parameters, *R*=0.0988, R_w=0.1889 for all of the data.

Compound **3b**: R_f=0.52 (4:1 hexanes/EtOAc); $[\alpha]_D^{32}$ +61.2 (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (s, 1H), 7.39–7.33 (m, 7H), 7.30–7.28 (m, 2H), 7.20–7.16 (m, 1H), 5.22 (d, 1H, *J*=12.0 Hz), 5.17 (d, 1H, *J*=12.0 Hz), 4.21 (dd, 1H, *J*=7.8, 5.0 Hz), 2.27–2.21 (m, 2H), 1.95–1.94 (m, 1H), 1.86–1.84 (m, 1H), 1.41–1.35 (m, 2H), 1.20 (m, 1H), 1.11 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 158.9, 144.2, 139.6, 138.6, 130.5, 130.0, 129.9, 129.8, 129.7, 127.0, 78.5, 69.9, 60.4, 53.4, 48.2, 40.4, 29.0, 27.3, 21.1, 20.7; HRMS (EI) *m/z* 417.2044 (calcd for $C_{25}H_{27}N_3O_3$: 417.2047). Crystal data for **3b** at 20 °C: $C_{25}H_{27}N_3O_3$, *M* 417.5, orthorhombic, $P2_1$, 2_12_1, *a*=9.1750 (2) Å, *b*=10.3510 (2) Å, *c*=23.4620 (5) Å, *V*=2228.20 (8) Å^3, *Z*=4, D_x=1.245 Mg/m^3, μ=0.083 mm^{-1}, 5011 reflections, 281 parameters, *R*=0.0609, R_w=0.1125 for all of the data.

Compound **3c**: R_f=0.3 (2:1 hexanes/EtOAc); $[\alpha]_D^{32}$ −124.7 (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.3–7.85 (m, 3H), 7.38–7.28 (m, 6H), 5.29 (m, 2H), 3.68 (br s, 1H), 2.62 (br s, 1H), 2.46 (s, 3H), 2.03–1.86 (m, 3H), 1.20 (m, 1H), 1.85 (m, 2H), 1.6 (m, 1H), 1.01 (s, 3H), 1.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.3, 162.0, 148.4, 143.8, 138.5, 135.7, 131.6, 130.2, 130.0, 129.9, 129.8, 79.6, 78.6, 71.9, 61.4, 53.8, 48.5, 29.9, 27.4, 22.3, 20.9, 20.7; HRMS (EI) *m/z* 495.1826 (calcd for $C_{26}H_{29}N_3O_5S$: 495.1828).

Compound **3d**: R_f=0.4 (4:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.37–7.28 (m, 10H), 5.43 (dd, 2H, *J*=8.7, 4.0 Hz), 5.26 (s, 1H,), 4.67 (t, 1H, *J*=8.8 Hz), 4.27 (dd, 1H, *J*=9.0, 4.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 153.5, 141.5, 137.9, 135.9, 129.1, 128.8, 128.5, 128.46, 128.36, 128.30, 126.1, 78.1, 70.5, 57.4; HRMS (EI) *m/z* 324.1114 (calcd for $C_{18}H_{16}N_2O_4$: 324.1105).

Compound **3e**: R_f=0.8 (10:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67–7.63 (m, 4H), 7.47–7.33 (m, 5H), 7.24–7.21 (m, 2H), 7.14–7.11 (m, 4H), 7.08–7.5 (m, 1H), 5.28 (m, 2H), 5.22 (m, 1H), 4.13 (s, 1H), 2.34–2.27 (m, 1H), 2.00–1.89 (m, 2H), 1.85–1.80 (m, 1H), 1.67–1.64 (m, 1H), 1.55–1.49 (m, 4H), 1.18 (m, 1H), 0.65 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.5, 148.8, 143.6, 140.1, 136.0, 129.1, 128.7, 125.5, 127.7, 126.7, 126.4, 126.2, 126.1, 82.2, 81.0, 78.3, 59.2, 51.3, 47.8, 38.2, 30.9, 27.0, 24.4, 22.6; HRMS (EI) *m/z* 483.2418 (calcd for

$C_{31}H_{33}NO_4$:483.2404). Crystal data for **3e** at 20 °C: $C_{31}H_{33}NO_4$, M 483.58, orthorhombic, $P2_12_12_1$, a=10.6150 (10) Å, b=11.0210 (2) Å, c=44.3470 (7) Å, V=5188.06 (13) Å^3, Z=8, D_x=1.238 Mg/m^3, μ=0.081 mm^{-1}, 2064 reflections, 281 parameters, R=0.0681, R_w=0.1479 for all of the data.

Compound **3f**: R_f=0.83 (10:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (s, 1H), 7.36–7.28 (m, 5H), 5.26 (s, 2H), 4.88–4.81 (m, 1H), 2.05–2.02 (m, 1H), 1.90–1.84 (m, 1H), 1.70–1.67 (m, 2H), 1.52–1.43 (m, 2H), 1.10–1.02 (m, 2H), 0.91–0.82 (m, 7H), 0.77 (d, 3H, J=7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.25, 141.2, 135.9, 128.4, 128.3, 128.2, 77.2, 75.5, 60.9, 52.2, 46.7, 40.5, 33.0, 31.2, 26.1, 23.4, 21.8, 20.5, 16.2; HRMS (EI) m/z 317.1983 (calcd for $C_{19}H_{27}NO_3$: 317.1985).

Compound **3g**: R_f=0.8 (10:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (s, 1H), 7.40–7.32 (m, 5H), 5.29 (s, 2H), 5.38 (m, 1H), 2.43–2.37 (m, 1H), 2.00–1.94 (m, 1H), 1.85–1.80 (m, 1H), 1.70 (t, 1H, J=9.0 Hz), 1.29–1.22 (m, 2H), 1.05 (dd, 1H, J=13.9, 3.5 Hz), 0.92 (s, 3H), 0.89 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9, 141.1, 135.9, 128.5, 128.3, 128.2, 81.0, 76.7, 48.8, 47.7, 44.7, 36.4, 27.8, 26.8, 19.5, 18.7,13.3; HRMS (EI) m/z 315.1848 (calcd for $C_{19}H_{25}NO_3$: 315.1829).

Compound **3h**: R_f=0.75 (10:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (s, 1H), 7.38–7.33 (m, 5H), 5.28 (s, 2H), 5.27–5.23 (m, 1H), 2.57–2.53, (m, 2H), 2.6 (m, 1H), 2.02 (t, 1H, J=5.7 Hz), 1.78–1.73 (m, 1H), 1.52 (d, 2H, J=10.6 Hz), 1.34 (s, 3H), 1.3 (s, 3H), 1.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.2, 140.8, 135.9, 128.6, 128.5, 128.4, 117.1, 73.9, 73.2, 54.1, 40.2, 38.7, 34.4, 29.7, 28.0, 27.8, 24.2; HRMS (EI) m/z 331.1809 (calcd for $C_{19}H_{25}N_2O_4$: 331.1778).

4.1.3. Typical procedure for the allylation of glyoxylic oxime ethers 3a–h using allyltributylstannane in the presence of Sn(OTf)$_2$ (method A) and triallylaluminum (method B). Method A. To a solution of **3a** (50 mg, 0.13 mmol) in CH_3CN (5 mL) $Sn(OTf)_2$ (55.5 mg, 0.13 mmol) was added. The reaction mixture was stirred for 10 min at ambient temperature. The solution was cooled to −40 °C and allyltributylstannane (81 μL, 0.26 mmol) was added and the stirring continued for 1 h. The reaction mixture was quenched with H_2O (15 mL) and extracted with CH_2Cl_2 (3×20 mL). The organic layers were separated and dried over anhydrous $MgSO_4$ and concentrated. The resulting crude products were subject to flash column chromatography purification eluted with hexanes/EtOAc (3:1) to afford **4a** as a white solid (50 mg, 90% yield, ratio of diastereomers 91% de).

Method B. A solution of **3a** (50 mg, 0.13 mmol) in CH_2Cl_2 (5 mL) was cooled to −78 °C and triallylaluminum (1.0 M, 0.26 mL, 0.26 mmol) was added dropwise over a period of 20 min. After 10 min, the reaction mixture was quenched with H_2O (5 mL) and aq HCl (1.0 mL, 2 N) was then added at −78 °C. The mixture was stirred for an additional 10 min and warmed to 0 °C. The mixture was further diluted with H_2O (10 mL) and extracted with CH_2Cl_2 (3×20 mL). The organic layers were separated and dried over anhydrous $MgSO_4$ and concentrated in vacuo. The resulting crude products were subject to flash column chromatography eluted with hexanes/EtOAc (3:1) to give **4a** as a white solid (45 mg, 89% yield, ratio of diastereomers 82% de).

Compound **4a**: R_f=0.60 (4:1 hexanes/EtOAc); $[\alpha]_D^{30}$ −46.7 (c 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.25 (m, 5H), 5.77–5.68 (m, 1H), 5.07 (d, 1H, J=16.9 Hz), 5.03 (d, 1H, J=9.8 Hz), 4.73 (d, 1H, J=11.7 Hz), 4.66 (d, 1H, J=11.7 Hz), 4.46 (t, 1H, J=6.4 Hz), 3.96 (t, 1H, J=6.4 Hz), 3.51 (d, 1H, J=13.8 Hz), 3.46 (d, 1H, J=13.8 Hz), 2.41–2.30 (m, 2H), 2.06 (d, 2H, J=6.8 Hz), 1.94–1.85 (m, 4H), 1.44–1.32 (m, 2H), 1.13 (s, 3H), 0.96 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 137.9, 132.9, 128.8, 128.4, 127.8, 118.6, 76.1, 65.3, 62.6, 53.2, 48.8, 47.9, 44.8, 38.5, 35.0, 33.0, 26.6, 21.0, 20.1; HRMS (EI) m/z 418.1929 (calcd for $C_{22}H_{30}N_2O_4S$ 418.1926). Crystal data for **4a** at 27 °C: $C_{22}H_{30}N_2O_4S$, M 418.5, orthorhombic, $P2_1$, a=7.6150 (5) Å, b=16.0100 (6) Å, c=17.8800 (7) Å, V=2179.86 (19) Å^3, Z=4, D_c=1.275 Mg/m^3, μ=0.179 mm^{-1}, 3808 reflections, 263 parameters, R=0.1220, R_w=0.1976 for all of the data.

Compound **4b**: R_f=0.53 (4:1 hexanes/EtOAc); $[\alpha]_D^{31}$ −24.2 (c 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.29 (m, 5H), 7.28–7.26 (m, 5H), 7.18–7.14 (m, 1H), 5.75 (m, 1H), 5.13–5.09 (m, 2H), 4.71 (d, 1H, J=11.3 Hz), 4.66 (d, 1H, J=11.3 Hz), 4.07 (dd, 1H, J=7.9, 5.0 Hz), 3.79 (t, 1H, J=6.5 Hz), 2.75–2.71 (m, 1H), 2.30–2.21 (m, 3H), 2.04–1.94 (m, 2H), 1.90 (t, 1H, J=3.9 Hz), 1.43–1.30 (m, 2H), 1.05 (s, 3H), 1.0 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 170.5, 138.5, 137.5, 133.3, 128.9, 128.5, 128.4, 128.2, 126.0, 122.1, 118.7, 76.4, 66.0, 61.8, 59.2, 53.8, 46.7, 39.5, 33.8, 28.5, 27.0, 20.3, 20.2; HRMS (EI) m/z 459.2507 (calcd for $C_{28}H_{33}N_3O_3$: 459.2516). Crystal data for **4b** at 20 °C: $C_{28}H_{33}N_3O_3$, M 459.57, monoclinic, $P2_1$, a=10.4820 (11) Å, b=10.8420 (11) Å, c=11.3590 (16) Å, V=1290.5 (3) Å^3, Z=2, D_c=1.183 Mg/m^3, μ=0.077 mm^{-1}, 3671 reflections, 308 parameters, R=0.2229, R_w=0.2971 for all the data.

Compound **4c**: R_f=0.3 (2:1 hexanes/EtOAc); $[\alpha]_D^{30}$ −46.9 (c 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (m, 2H), 7.36–7.28 (m, 7H), 5.91 (br s, 1H), 5.18–5.10 (m, 2H), 4.70 (s, 2H), 4.14 (br s, 1H), 3.80 (br s, 1H), 2.86–2.83 (m, 2H), 2.48 (dd, 1H, J=15.0, 7.1 Hz), 2.43 (s, 3H), 2.29 (br s, 1H), 2.09 (br s, 1H), 1.90–1.89 (m, 2H), 1.79 (dd, 1H, J=13.3, 8.2 Hz), 1.26–1.25 (m, 2H), 0.97 (s, 3H), 0.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 171.7, 145.5, 137.8, 137.4, 135.6, 134.0, 129.7, 129.2, 129.0, 128.4, 128.0, 118.1, 76.4, 70.0, 60.9, 52.2, 47.9, 38.00, 35.2, 29.8, 29.5, 26.9, 21.9, 20.4, 19.8; HRMS (EI) [M+1] m/z 538.2371 (calcd for $C_{28}H_{36}N_3O_5S$: 538.2370).

Compound **4d**: An inseparable mixture of diastereomers was obtained. Selected peaks of the major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.38–7.27 (m, 10H), 5.60 (m, 1H), 5.48 (dd, 1H, J=8.7, 3.6 Hz), 4.95–4.89 (m, 2H), 4.32 (dd, 1H, J=8.9, 3.6 Hz), 2.35–2.30 (m, 1H), 5.23–5.19 (m, 1H); HRMS (EI) m/z 366.1576 (calcd for $C_{21}H_{22}N_2O_4$: 366.1572).

Compound **4e**: An inseparable mixture of diastereomers was obtained. Selected peaks of the major diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74–7.71 (m, 4H), 7.58–7.55 (m, 4H), 7.35 (m, 2H), 7.25–7.16 (m, 3H), 7.12–7.05 (m, 2H), 5.45–5.29 (m, 2H), 5.01–4.93 (m, 2H), 4.71 (m, 1H), 4.19 (s, 1H), 3.39 (t, 1H, J=6.1 Hz), 2.35–2.28 (m, 1H), 2.06–1.91 (m, 4H), 1.85–1.82 (m, 1H), 1.69–1.56 (m, 1H), 1.55–1.48 (m, 4H), 1.38 (m, 1H), 0.62 (s, 3H); minor diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74–7.71 (m, 4H), 7.58–7.55 (m, 4H), 7.35 (m, 2H), 7.25–7.16 (m, 3H), 7.12–7.05 (m, 2H), 5.45–5.29 (m, 2H), 5.01–4.93 (m, 2H), 4.71 (m, 1H), 4.05 (s, 1H), 3.26 (t, 1H, J=6.4 Hz), 2.35–2.28 (m, 1H), 2.06–1.91 (m, 4H), 1.85–1.82 (m, 1H), 1.69–1.56 (m, 1H), 1.55–1.48 (m, 4H), 1.38 (m, 1H), 0.62 (s,3H); HRMS (EI) [M+1] m/z 526.2973 (calcd for $C_{34}H_{40}NO_4$: 526.2952).

Compound **4f**: An inseparable mixture of diastereomers was obtained. Selected peaks of the major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (s, 1H), 7.34–7.29 (m, 5H), 5.73 (m, 1H), 5.14–5.07 (m, 2H), 4.73 (s, 2H), 3.71–3.67 (m, 1H), 2.36–2.34 (m, 2H), 2.95–1.91(m, 2H), 1.71–1.68 (m, 2H), 1.51–1.39 (m, 2H), 1.08–1.97 (m, 2H), 0.90–0.86 (m, 7H), 0.72 (d, 3H, J=7 Hz); HRMS (EI) m/z 359.2444 (calcd for $C_{22}H_{33}NO_4$: 359.2455).

Compound **4g**: R_f=0.8 (10:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.25 (m, 5H), 5.91 (br s, 1H), 5.78–5.70 (m, 1H), 5.12–5.06 (m, 1H), 5.0–4.95 (m, 1H), 4.71 (s, 3H), 3.71 (t, 1H, J=6.9 Hz), 2.35 (t, 3H, J=6.9 Hz), 1.97–2.00 (m, 1H), 1.76–1.73 (m, 1H), 1.68 (dd, 1H, J=7.8, 3.5 Hz), 1.34–1.21 (m, 2H), 1.05–0.96 (m, 1H), 0.90 (s, 3H), 0.87 (s, 3H), 0.83 (d, 3H, J=7.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 137.7, 133.1, 128.3, 127.7, 118.0, 80.6, 76.1, 63.4, 63.2, 48.8, 47.8, 44.8, 36.6, 33.9, 36.6, 33.9, 27.9, 27.1, 19.6, 18.8, 13.4; HRMS (EI) m/z 357.2309 (calcd for $C_{26}H_{31}NO_3$: 357.2298).

Compound **4h**: An inseparable mixture of diastereomers were obtained. Selected peaks of the major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.29 (m, 5H), 5.82–5.74 (m, 1H), 5.32–5.28 (m, 1H), 5.16–5.09 (m, 2H), 4.73 (m, 2H), 3.70 (t, 1H, J=7.0 Hz), 2.48–2.38 (m, 2H), 2.26–2.23 (m, 1H), 2.02–1.95 (m, 2H), 1.68–1.66 (m, 2H), 1.55 (m, 1H), 1.30 (s, 3H), 1.27 (s, 3H), 1.00 (s, 3H); HRMS (EI) [M+1] m/z 374.2326 (calcd for $C_{22}H_{32}NO_4$: 374.2326).

Acknowledgements

We wish to thank the National Science Council of the Republic of China (NSC 95-2113-M-003-003) and the National Taiwan Normal University (ORD 94-G) for financial support for this work. The X-ray crystal data, which were collected and processed by National Taiwan Normal University, are gratefully acknowledged.

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20. **3a** (CCDC 642120), **3b** (CCDC 642117), **3e** (CCDC 642121), **4a** (CCDC 642119), **4b** (CCDC 642118).