Asymmetric Synthesis and Epimerization of Aryloxazinones

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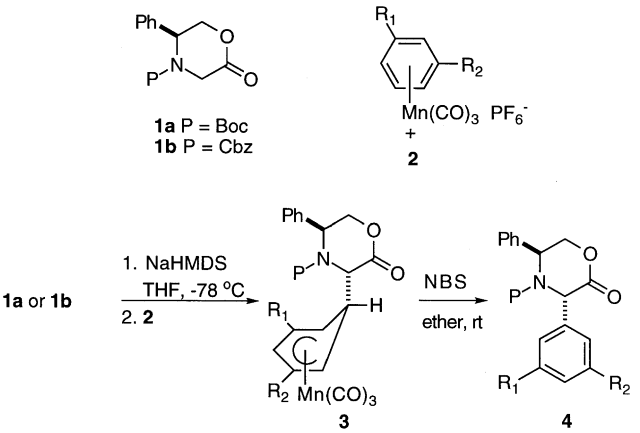
An interesting and important nonproteinogenic class of amino acids is the arylglycines[1] which are found in a wide range of bioactive compounds such as nocardicines[2] and glycopeptide antibiotics[3] (e.g. vancomycin, teicoplanin, ristocetin, β-avoparcin, and actaplanin). However, the arylglycines are difficult to synthesize in optically pure form due to the ease at which the α-methine proton can undergo base-catalyzed racemization.[4]

Numerous approaches to the asymmetric synthesis of arylglycines have appeared, including: asymmetric Strecker synthesis;[5] arylation or alkylation of nucleophilic glycinates;[6] arylation of electrophilic glycinates;[7] electrophilic amination of chiral enolates;[8] and nucleophilic amination of α-substituted acids[9] and others.[10]

Some of these works use the chiral 5,6-diphenyloxazinones as a glycine equivalent. Williams reported the asymmetric synthesis of several arylglycines *via* the cuprate or Friedel-Crafts couplings to chiral 3-bromooxazinone.[7d] Also the photolysis of [(amino)(aryl)carbene]chromium complexes having the optically active amino alcohol were reported to give the aryloxazinones.[10b] However these methodologies limit the general synthesis of various arylglycines due to the availability of aryl metal compounds.

We report herein our preliminary studies on the conversion of (arene)$Mn(CO)_3^+$ PF_6^- complexes to aryloxazinones, which can be converted to arylglycines, *via* their reaction with the chiral glycine equivalent, 5-phenyloxazinone (**1a** or **1b**).[11]

Preparation of the arene-manganese complexes were accomplished in high yields on using a modification of the procedure described by Rybinskaya *et al.*[12] Benzene-manganese complex was obtained by means of the conventional procedure [$Mn(CO)_5Br$-$AlCl_3$-heat].[13] (Arene)$Mn(CO)_3$ complexes (**2**) were treated with enolate of **1a** or **1b** to give the substituted cyclohexadienyl-$Mn(CO)_3$ complexes (**3**). We could not separate the cyclohexadienyl-$Mn(CO)_3$ complexes since significant decomposition of cyclohexadienyl-$Mn(CO)_3$ complexes occurs upon attempted silica gel chromatography. So direct treatment of these reaction mixture with *N*-bromosuccinimide (NBS) effected oxidative demetallation to give the *anti*-aryloxazinones (**4**) in moderate yields and high diastereoselectivities (Scheme 1).



Scheme 1

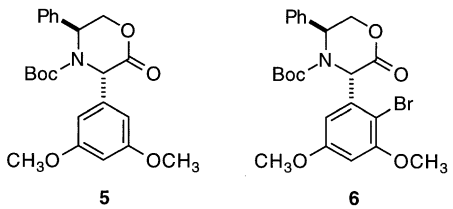
The results were summarized in Table 1. We have examined the various bases and solvents (NaHMDS/DME, NaHMDS/THF, KHMDS/THF, LiHMDS/THF, and LDA/THF) for the reaction and found that they gave the similar yields (61-67%). Also addition of HMPA did not improve the yields and diastereoselectivities. The electrophile approaches from the less hindered face of the oxazinone enolate giving the *anti*-aryloxazinone.

Table 1. Arylation of Oxazinones Using (Arene)$Mn(CO)_3$ Complexes

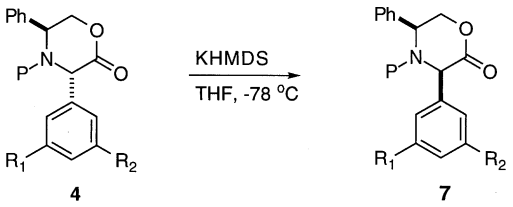
entry	P	Mn complexes (**2**)	product	yield (%)[a]	de (%)[b]
1	Boc	R_1=R_2=H	**4a**	63	95
2	Boc	R_1=H, R_2=OCH_3	**4b**	65	90
3	Boc	R_1=H, R_2=OPh	**4c**	49	75
4	Boc	R_1=H, R_2=O(*p*-$CH_3OC_6H_4$)	**4d**	55	99
5	Boc	R_1=H, R_2=O(*p*-$PhCH_2OC_6H_4$)	**4e**	44	81
6	Cbz	R_1=R_2=H	**4f**	60	89
7	Cbz	R_1=H, R_2=OCH_3	**4g**	55	94
8	Cbz	R_1=R_2=OCH_3	**4h**	62	87

[a] Yield of isolated, pure *anti*-isomer. [b] Determined from isolated yields of pure *anti*- and *syn*-isomers.

In case of the (1,3-dimethoxycyclohexadienyl)Mn complex (P=Boc, R_1=R_2=OCH_3), use of 1 equivalent of NBS gave the complicated reaction mixture. However, use of 2 equivalents of NBS gave the mixture of *anti*-aryloxazinone **5** (25%) and monobrominated aryloxazinone **6** (30%). Brominated aryloxazinone **6** might be formed by electrophilic substitution of aryloxazinone **5** which has the electron-rich aromatic ring.



We tried the alkylation of the enolates of *anti*-3-aryloxazinones with alkyl halide to prepare the 3-alkyl-3-aryloxazinones. However, the reaction gave the epimerized *syn*-3-



Scheme 2

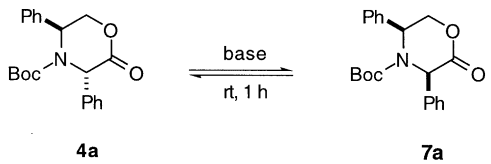
Table 2. Epimerization of *anti*-3-Aryloxazinones

entry	*anti*-oxazinone (4)	*syn*-oxazinone (7)	ratio (7 : 4)[a]
1	**4a**	**7a**	87:13
2	**4b**	**7b**	81:19
3	**4c**	**7c**	70:30
4	**4d**	**7d**	72:28
5	**4e**	**7e**	70:30
6	**4f**	**7f**	56:44
7	**4g**	**7g**	88:12
8	**4h**	**7h**	74:26

[a] Determined from isolated yields of pure *anti*- and *syn*-isomers.

aryloxazinones instead at -78 °C. Therefore, we studied the conversion of *anti*-3-aryloxazinones to *syn*-3-aryloxazinones at low temperature. *Anti*-aryloxazinones **4**[14] were treated with KHMDS in THF at -78 °C and quenched with saturated ammonium chloride solution at -78 °C to give the epimerized *syn*-aryloxazinones **7**[15] in moderate yields (Scheme 2, Table 2). The treatment of *syn*-3-aryloxazinones with base at -78 °C gave the similar *syn*/*anti* ratios. The results show that the enolate anion of 3-aryloxazinone is stabilized by the aryl group and attacked by proton from the opposite side of the 5-phenyl group to afford the *syn*-3-aryloxazinone as a major isomer.

The equilibration experiments were done using several bases to show whether the *syn*-3-aryloxazinones were the kinetic or thermodynamic products (Scheme 3). The results show that *anti*-3-aryloxazinones are thermodynamic products (Table 3). Thus, the epimerization of the arylglycine enolate synthons demonstrated to be the result of kinetic control by equilibration experiments for phenyl adduct **4a**.

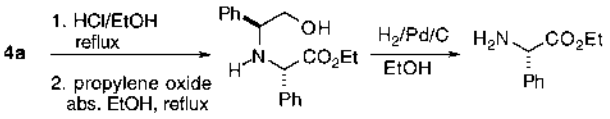


Scheme 3

Table 3. Thermodynamic Equilibration Studies

entry	base	ratio (**4a** : **7a**)[a]
1	NaOEt/EtOH	2.7 : 1
2	LDA/THF	1 : 1
3	NaHMDS/THF	1.1 : 1

[a] Ratios were determined by isolated yields.



Scheme 4

A simple deprotection scheme was used for the Boc-protected phenyl adduct (Scheme 4).[11] Exposure of *anti*-phenyloxazinone **4a** to excess refluxing ethanolic hydrogen chloride for 2 h and removal of the volatiles provided the ethyl ester HCl salt which was neutralized by refluxing in absolute ethanol containing propylene oxide to afford **8a** in 96% yield. Hydrogenolysis of **8a** under influence of 5% Pd/C and hydrogen (15 psi) at room temperature gave the phenylglycine ethyl ester. Determination of optical purity of the final phenylglycine derivative is underway.

In conclusion, the *anti*-aryloxazinones were prepared in moderate yields and high diastereoselectivities from the nucleophilic substitution of chiral glycine enolate equivalents with (arene)$Mn(CO)_3^+$ complexes. Also, *syn*-aryloxazinones were obtained in moderate yields *via* epimerization of *anti*-aryloxazinones. Investigations concerning the conversion of aryloxazinones to arylglycines are underway.

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14. **(3*S*,5*S*)-4-*tert*-Butyloxycarbonyl-3,5-diphenyl-2,3,5,6-tetrahydro-4H-1,4-oxazin-2-one (4a).** mp 176-177 °C, $[\alpha]^{25}_{D}$=-92.5 (c 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, DMSO-d_6, at 298 K) δ 7.46-7.20 (m, 10H), 5.99 (s) and 5.91 (s) (1H, $O_2CCHPhN$), 5.55 (s) and 5.43 (s) (1H, $NCHPhCHHO$), 4.76 (d) and 4.57 (d) (1H, *J*=11.0 Hz, $NPhCHCHH$), 4.54 (d) and 4.38 (d) (1H, *J*=10.8 Hz, $NPhCHCHH$), 1.16 and 1.15 (s, 9H, $C(CH_3)_3$); ^{1}H NMR (400 MHz, DMSO-d_6, at 373 K) δ 7.46-7.20 (m, 10H), 5.95 (s, 1H, $O_2CCHPhN$), 5.47 (s, 1H, $NCHPhCHHO$), 4.66 (br s) and 4.46 (br s) (2H, $PhCHCHHO$), 1.15 (s, 9H, $C(CH_3)_3$); IR (KBr) 1756, 1706 cm^{-1}. Anal. Calcd. for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96. Found: C, 71.20; H, 6.81; N, 4.06.
15. **(3*R*,5*S*)-4-*tert*-Butyloxycarbonyl-3,5-diphenyl-2,3,5,6-tetrahydro-4H-1,4-oxazin-2-one (7a).** $[\alpha]^{25}_{D}$=+89 (c 0.4, CH_2Cl_2); ^{1}H NMR (400 MHz) δ 7.48-7.39 (m, 5H), 7.25-7.23 (m, 3H), 7.08-7.05 (m, 2H), 6.27(s) (1H, $O_2CCHPhN$), 4.96 (dd, 1H, *J*=12.0, 5.0 Hz, $NPhCH-CHHO$), 4.19 (dd, 1H, *J*=12.4, 5.6 Hz, $NPhCHCHHO$), 4.13(t, *J*=12.2 Hz, $NPhCHCHH$), 1.25 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (75 MHz) δ 168.6, 155.6, 138.2, 137.1, 129.7, 129.0, 128.9, 128.4, 127.2, 126.9, 82.3, 69.0, 59.7, 58.7, 28.4; IR (KBr) 1772, 1697 cm^{-1}. Anal. Calcd. for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96. Found: C, 70.95; H, 7.02; N, 3.88.