Asymmetric Synthesis of α-Alkyl-α-phenylglycines

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α,α-Disubstituted α-amino acids are popular replacements for naturally occurring amino acids in peptides.[1] Peptide analogs, containing these substitutions, often have useful enzyme inhibitory and other important biological properties.[2] In recent years, a number of methods to construct chiral α,α-disubstituted α-amino acids have been developed.[3] In most approaches, the stereogenic center is established in alkylation reactions of chiral, nonracemic enolates, *e.g.*, those derived from 5,6-diphenyl,[4] 5-phenyl,[5] and 6-phenyl-1,4-oxazin-2-ones.[6] However, removal of the chiral auxiliaries is known to be problematic in routes where α-alkyl-α-arylglycines are the targets.

Recent studies in our laboratory have led to the development of a new route for asymmetric synthesis of α-alkyl-α-phenylglycines. The sequence involves sequential arylation of the Williams oxazinone **1** generating 3-phenyloxazinone **2**, alkylation to form intermediate 3-alkyl-3-phenyloxazinones **3**, and stepwise removal of *N*-BOC group and the chiral auxiliary.

To begin the sequence, (3*S*)-3-phenyloxazinone **2** is prepared by using the reported method.[7] Treatment of **2** with NaHMDS or KHMDS at -78 °C in THF, followed by addition of the alkyl halide, stirring at room temperature, and quenching with saturated aq. NH_4Cl at -78 °C, yields the corresponding 3-alkyl-3-phenyloxazinones **3** in moderate to high yields and with high diastereomeric purities (Scheme 1, Table 1).[9] High diastereoselectivities are observed even in processes where small alkyl halides (*e.g.*, methyl iodide) are employed. Interestingly, attempts to run the alkylation reaction at -78 °C met with failure with only epimerized (3*R*)-3-phenyloxazinone **2** being recovered.[6,8]

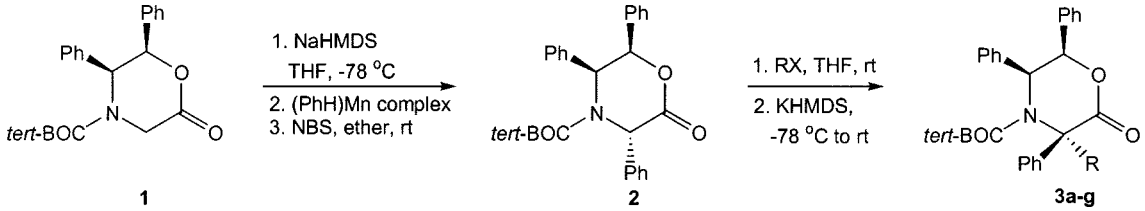
For the purpose of determining the level of diastereoselectivity associated with the alkylation reactions, (3*S*)-3-methyl-3-phenyloxazinone **5** was prepared by using the reverse sequence (*i.e.*, alkyation followed by arylation) to introduce the 3-substituent (Scheme 2). Analysis of the ^{1}H NMR spectra of the oxazinones **3a** and **5** showed that both methylation of **2** and phenylation of **4** yield single diastereomers (**3a** and **5**, respectively) of the 3,3-disubstituted products. However, in contrast to the high efficiency of the methylation reaction of **2**, phenylation of **4** is a low yielding (44%) process.

When the 5,6-diphenyloxazinone template is used for α-arylglycines synthesis, new methods are needed to bring

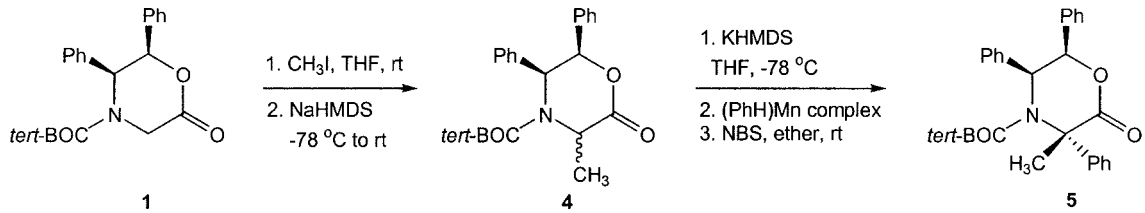
Table 1. Alkylation Reactions of 3,5,6-Triphenyloxazinone (**2**)

Entry	RX	Product	Yield (%)[a]	%de
1	CH_3I	**3a**	99	>95
2	$CH_3CH_2CH_2I$	**3b**	82	>95
3	H_2C=$CHCH_2Br$	**3c**	95	>95
4	HC≡CCH_2Br	**3d**	98	>95
5[b]	CH_3OCH_2Cl	**3e**	75	>95
6	$BrCH_2CO_2CH_2CH_3$	**3f**	88	>95
7[c]	C_4H_9I	**3g**	96	>95

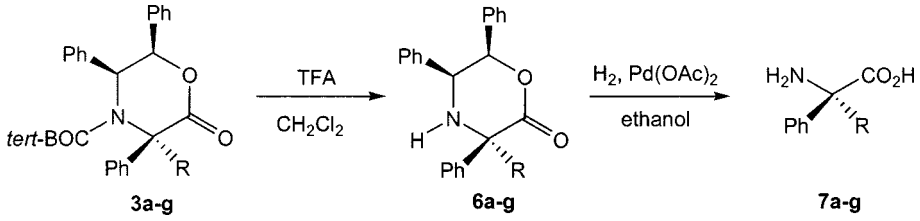
[a]Isolated yields. [b]Some starting material is recovered. [c]Since *n*-butyl bromide does not react, the corresponding iodide, prepared by treatment of the bromide with NaI in acetone, was used instead.



Scheme 1



Scheme 2



Scheme 3

about selective cleave of the benzylic C-O and C-N bonds in order to liberate the amino acid targets. Williams has developed both a dissolving metal reduction and a catalytic hydrogenolysis method for this purpose.[4d] Also, Remuzon showed that the chiral auxiliary in 3-alkyl-3,6-diphenyl-1,4-oxazin-2-ones is removed selectively by catalytic hydrogenolysis.[6] Finally, Hegedus reported that *syn*-3,5,6-triphenyloxazinone isomers are selectively cleaved to form the amino acid in high yield under mild reductive conditions (1 atm of H_2, $PdCl_2$).[10]

However, our attempts to use the hydrogenolysis process for removal of the chiral auxiliary present in *tert*-BOC protected 3-alkyl-3,5,6-triphenyloxazinones **3** gave none or only low yields (*ca.* 10%) of the desired products. We believed that this process might be more successful if it were applied to *N*-deprotected oxazinones. We first tried to remove the *tert*-BOC group by using TMSI in CH_2Cl_2,[4d] but low yields (40% and 32%) were encountered for the allyl and propargyl-oxazinones, **3c** and **3d**. Moreover, deprotection of oxazinones **3e** and **3f** failed completely. In contrast, removal of *tert*-BOC group with TFA in dichloromethane[4e] in all cases cleanly furnishes the deprotected 3-alkyl-3-phenyl-1,4-oxazin-2-ones **6** (Scheme 3 and Table 2). Importantly, hydrogenolysis of the deprotected oxazinones **6** under mild conditions (1 atm H_2, 0.5 equiv $Pd(OAc)_2$, 25 °C, 4h) affords the desired α-alkyl-α-phenylglycines **7** in moderate yields (Scheme 3 and Table 2).[11] The enantiomeric purity of (*R*)-α-methyl-α-phenylglycine **7a** ($[\alpha]_D^{25}$ -94.5), generated by use of this route, was determined to be *ca.* 100% by comparison of its specific rotation to the reported value (lit.[6,12] $[\alpha]_D^{20}$ -98).

In conclusion, we have demonstrated that 3-alkyl-3-phenyloxazinones can be prepared in high yields and with high diastereomeric purities by alkylation reactions of chiral 3-phenyloxazinone. Also, removal of *tert*-BOC group followed by selective hydrogenolysis is an effective procedure to efficiently transform 3-alkyl-3,5,6-triphenyloxazinones to the corresponding α-alkyl-α-phenylglycines without accompanying racemization.

Table 2. *N*-BOC Removal and Hydrogenolysis of **3**

Entry	R	**6** (%)[a]	**7** (%)[a]
1	CH_3	94	75
2	$CH_3CH_2CH_2$	90	82
3	H_2C=$CHCH_2$	90	82[b]
4	HC≡CCH_2	93	75[b]
5	CH_3OCH_2	87	83
6	$CH_2CO_2CH_2CH_3$	90	75
7	C_4H_9	92	71

[a] Isolated yields. [b]Allyl and propargyl groups are reduced to propyl group under this reaction conditions.

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9. Spectroscopic data for (3*R*,5*S*,6*R*)-4-(*tert*-butyloxycarbonyl)-2,3,5,6-tetrahydro-3-methyl-3,5,6-triphenyl-1,4-oxazin-2-one (**3a**): mp 72-74 °C; $[\alpha]_D^{25}$ = -18.8 (c 0.8, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50-7.10 (m, 15H), 6.23 (d, *J* = 2.8 Hz, 1H), 5.28 (s, 1H), 2.39 (s, 3H), 1.09 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.72, 153.89, 142.35, 135.16, 134.80, 129.82, 128.32, 128.17, 128.13, 128.09, 127.74, 127.00, 126.81, 125.93, 81.64, 80.39, 64.73, 59.56, 27.83, 26.42.; IR (KBr) 3076, 2975, 1751, 1688, 1454, 1347, 1164, 1082, 880, 698 cm^{-1}; Anal. Calcd for $C_{28}H_{29}NO_4$: C, 75.82; H, 6.59; N, 3.16. Found: C, 75.81; H, 6.61; N, 3.21.
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