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Facile access to (*Z*)-alkene-containing diketopiperazine mimetics utilizing organocopper-mediated *anti*-S_N2' reactions

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Abstract—Regio- and stereoselective *anti*-S_N2' alkylation of γ-phosphoryloxy-α,β-unsaturated-δ-lactams with organocopper reagents allowing the preparation of *N*-alkylated-α,δ-substituted-β,γ-unsaturated-δ-lactams as highly functionalized diketopiperazine mimetics is presented.

2,5-Diketopiperazine **1** is the smallest possible cyclic peptide consisting of two α-amino acid residues. This highly constrained scaffold is seen in large numbers of biologically active compounds and serves as a privileged structure in medicinal chemistry.[1] Recently, we engaged in the development of synthetic methodologies for the preparation of (*E*)-alkene dipeptide isosteres (EADIs) as potential *trans*-peptide bond mimetics[2] along with their application to biologically active peptides.[3] On the basis of our research into EADIs, we envisioned that incorporation of (*Z*)-alkene units structurally similar to the *cis*-amide bonds in 2,5-diketopiperazines would provide diketopiperazine mimetics **2** as a novel promising scaffold for drug discovery (Fig. 1). This type of mimetic

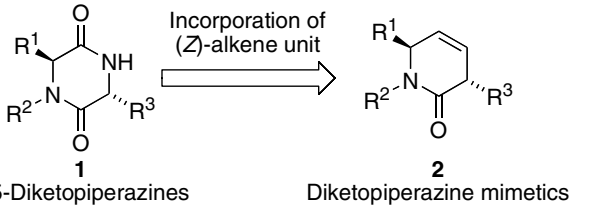

Figure 1. Diketopiperazine mimetics possessing substituted (*Z*)-alkenes as *cis*-amide bond.

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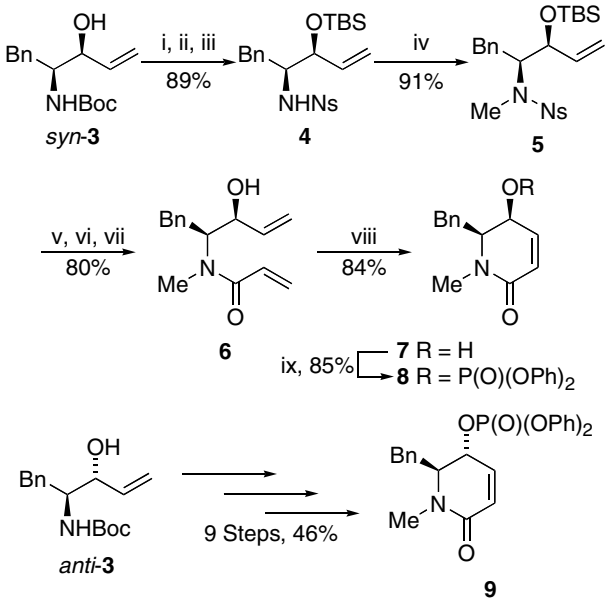
would be able to dissolve well in various media by preventing the formation of hydrogen-bonding networks that would otherwise result from the two peptide bonds. Pioneering studies were recently reported by Guibé and co-workers[4] and Knight et al.[5] for the preparation of similar structures that led to (*Z*)-alkene dipeptide isosteres and ergot alkaloids, respectively. However, stereoselective incorporation of divergent α-substituents into a common key intermediate has yet to be reported.

Our synthetic approach toward EADIs utilizes organocopper-mediated *anti*-S_N2' reaction of acyclic α,β-enoates possessing leaving groups at the γ-position. Proper choice of organocopper reagents allows a common substrate to be converted to various α-alkylated products. Development of a facile and efficient synthetic method toward functionalized diketopiperazine mimetics such as **2** is strongly desirable, since this class of compounds is of medicinal and synthetic value. In this letter, novel organocopper-mediated synthetic protocols are presented for highly functionalized diketopiperazine mimetics possessing a wide variety of α-substituents. These are discussed from the viewpoint of choice of the cyclic substrates and reagents.

The synthesis of requisite substrates for organocopper reactions is summarized in Scheme 1. The easily obtainable *N*-Boc allyl alcohol derivatives[6] *syn*-**3** and *anti*-**3** were chosen as starting materials. Conversion of the *N*-protecting group of *syn*-**3** to *N*-Ns (Ns = 2-nitrobenzenesulfonyl) followed by *O*-derivatization



Scheme 1. Synthesis of key substrates. Reagents: (i) 4 M HCl–dioxane; (ii) Ns-Cl, 2,4,6-collidine, $CHCl_3$; (iii) TBS-OTf, 2,6-lutidine, CH_2Cl_2; (iv) K_2CO_3, MeI, DMF; (v) $HSCH_2CO_2H$, LiOH, DMF; (vi) $CH_2{=}CHCOCl$, Et_3N, CH_2Cl_2; (vii) TBAF, THF; (viii) Grubbs' catalyst second generation, CH_2Cl_2; (ix) $(PhO)_2P(O)Cl$, pyridine, CH_2Cl_2. Abbreviations: Ns: 2-nitrobenzenesulfonyl; TBS: *tert*-butyldimethylsilyl.

with TBS group gave *N*-Ns amide derivative **4**. Treatment of **4** with MeI in the presence of K_2CO_3 afforded the *N*-Me sulfonamide **5**.[7] After removal of the Ns group by treatment with a thiol under basic conditions, the resulting secondary amine was acylated with acryloyl chloride followed by *O*-TBS deprotection with TBAF to afford acrylamide **6**. Ring-closing metathesis reaction of **6** with Grubbs' second-generation catalyst[8] proceeded smoothly at room temperature to yield γ-hydroxy-α,β-unsaturated-δ-lactam **7**. Although the activation of γ-hydroxy units in the acyclic enoates with the methanesulfonyl (Ms) group has afforded satisfactory results in organocopper-mediated synthesis of EADIs, attempted *O*-methanesulfonylation of **7** failed to afford any desired product due to its instability during purification over silica gel. Furthermore, *O*-acetylated derivatives proved to be inadequate for the subsequent copper-mediated α-alkylation, even though the acetylated compounds could be obtained in high yield. After extensive survey of γ-activation methodologies, we found that lactam γ-phosphoryloxy functionality[9–11] was suitable as a leaving group in terms of its stability and reactivity. Reaction of **7** with diphenylphosphoryl chloride in the presence of pyridine yielded the requisite key intermediate **8** in satisfactory isolated yield. The corresponding diastereomer **9** was also synthesized from *anti*-**3** by a sequence of reactions identical to those used for the preparation of **8**.

Next, we investigated α-alkylation of phosphate **8** with organocopper reagents (Fig. 2 and Table 1).[12] Reaction in THF of **8** with organocopper reagent prepared from equimolar amounts of MeMgCl and CuI in the presence

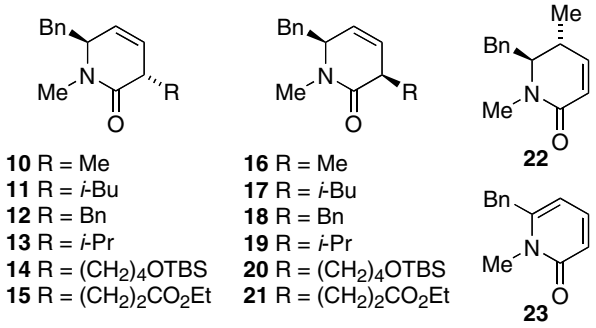


Figure 2. Structures of compounds obtained from the reaction of phosphates **8** and **9** with organocopper reagents.

Table 1. Organocopper-mediated reactions of phosphates **8** and **9**

Entry	Substrate	Reagent (2 equiv)[a,b]	Product(s) (%)[c]
1	**8**	MeCuI·MgCl·2LiCl	**10** (93)
2	**8**	MeCuI·MgCl	**10** (24), **22** (40)
3	**8**	MeCu·LiI·LiBr	**10** (83)
4	**8**	*i*-BuCu·2LiI·2LiCl	**11** (82)
5	**8**	BnCuI·MgCl·2LiCl	**12** (80)[d]
6	**8**	*i*-PrCuI·MgCl·2LiCl[e]	**23** (62)
7	**8**	*i*-PrCu(CN)·MgCl·2LiCl	**13** (81)[d]
8	**8**	$TBSOCH_2(CH_2)_2CH_2Cu{\cdot}2LiI{\cdot}2LiCl$	**14** (80)
9	**8**	$BrZnCu(CN){\cdot}CH_2CH_2CO_2Et{\cdot}2LiCl$[f]	**15** (80)
10	**9**	MeCuI·MgCl·2LiCl	**16** (73)
11	**9**	*i*-BuCuI·MgCl·2LiCl	**17** (81)
12	**9**	BnCuI·MgCl·2LiCl	**18** (85)
13	**9**	*i*-PrCu(CN)·MgCl·2LiCl	**19** (89)
14	**9**	$TBSOCH_2(CH_2)_2CH_2Cu{\cdot}2LiI{\cdot}2LiCl$	**20** (81)
15	**9**	$BrZnCu(CN){\cdot}CH_2CH_2CO_2Et{\cdot}2LiCl$[f]	**21** (79)

[a] Reaction condition (−78 °C, 20 min) was used except for entries 6, 9, and 15.
[b] THF or mixed solvent consisting of THF and Et_2O (or Et_2O–pentane) was used.
[c] Isolated yield.
[d] Small amount of S_N2 product was isolated.
[e] Reaction at −78 °C for 20 min, then at 0 °C for 40 min.
[f] Reaction at 0 °C for 60 min.

of LiCl proceeded at −78 °C in *anti*-S_N2' manner with high regio- and stereoselectivity to yield the desired α-alkylated mimetic **10** in high chemical yield (Table 1, entry 1). In contrast, organocopper-mediated reaction in the absence of LiCl afforded a mixture of *anti*-S_N2'-(**10**, 24%) and S_N2-product (**22**, 40%) (entry 2), which indicated the critical involvement of the Li salt in high α-selectivity. Whereas the role of the Li salt in affecting reaction regioselectivity is not well understood, we speculate that structural changes of the reagent/substrate complex induced by the Li salt were responsible for the observed high regioselectivity. MeCu·LiI·LiBr in THF–Et_2O derived from an equimolar mixture of MeLi·LiBr and CuI was also a useful reagent for *anti*-S_N2' alkylation of **8** (entry 3). Encouraged by these results, we examined the synthesis of other α-functionalized diketopiperazine mimetics utilizing several kinds of organocoppers prepared from equimolar amounts of organometallic reagent and copper(I) salt in the pres-

ence of Li salt. Treatment of **8** with *i*-BuCu·2LiI·2LiCl and BnCuI·MgCl·2LiCl gave the corresponding *anti*-S_N2' alkylation products **11** and **12** in reasonable yields, respectively (entries 4 and 5). Reaction of *i*-PrCuI·MgCl·2LiCl did not proceed at −78 °C, but gave predominantly the pyridinone derivative **23** at room temperature. This was probably due to the poor nucleophilicity of the reagent attributable to its steric bulkiness (entry 6). On the other hand, use of the cyanocuprate reagent, *i*-PrCu(CN)·MgCl·2LiCl, drastically improved the yield of desired *anti*-S_N2' alkylation product **13** (entry 7).

Introduction of functional groups amenable to further chemical manipulation was examined next. α-Alkylation of **8** with an *O*-TBS-protected hydroxybutyl group was possible by the use of $TBSOCH_2(CH_2)_2CH_2Cu·2LiI·2LiCl$ (entry 8). Copper–zinc mixed reagents possessing functional groups have shown synthetic usefulness through the application to various types of activated allylic compounds.[13] Recently, Knochel et al. reported that cyclic allylic phosphonates were alkylated in *anti*-S_N2' fashion by the action of functionalized copper–zinc reagents.[10] Independently, we also found that the reaction of **8** with a copper–zinc mixed reagent ($BrZnCu(CN)CH_2CH_2CO_2Et·2LiCl$) proceeded unequivocally in *anti*-S_N2' manner to yield α-substituted compound **15** possessing ester functionality (entry 9).[14] Furthermore, diastereomeric **9** was also alkylated in *anti*-S_N2' manner with various organocopper reagents to yield functionalized diketopiperazine mimetics (entries 10–15).

The absolute configurations of diketopiperazine mimetics **12** or **16** were unambiguously determined to be 3,6-*trans* (3*S*,6*S*) or 3,6-*cis* (3*R*,6*S*) by X-ray analyses.[15] Based on these results, relative configuration of the corresponding diastereomer **10** (vs **16**) or **18** (vs **12**) was assigned as 3,6-*cis* or 3,6-*trans*. ^1H NMR measurements of these diastereomeric pairs indicated that the α-protons of 3,6-*trans* compounds (**10** and **12**) appeared ca. 0.6 ppm upfield from the corresponding α-protons of the 3,6-*cis* isomers. These *trans*- and *cis*-isomers were derived from 5,6-*cis*-**8** and 5,6-*trans*-phosphate **9**, respectively, indicating that the organocopper-mediated S_N2' reactions proceeded in high *anti*-selectivity. Other S_N2'-products resulting from 5,6-*cis*-phosphate **8** also exhibited upfield chemical shifts of α-protons as compared to those of the corresponding 5,6-*trans*-derived compounds. Based on these results and the high level of stereoselectivity observed in organocopper-mediated *anti*-S_N2' reactions, compounds (**11**, **13**–**15**) and (**17**, **19**–**21**) were assigned 3,6-*trans*- and 3,6-*cis*-configurations, respectively.

In summary, reported herein are new and practical synthetic methodologies for preparation of functionalized diketopiperazine mimetics **2** containing (*Z*)-alkene units. Of note are the use of organocopper-mediated *anti*-S_N2' reactions to γ-phosphoryloxy-α,β-unsaturated-δ-lactams, which proceed with high regio- and stereoselectivities. Unequivocal access to various diastereomerically pure α-substituted mimetics is possible depending on the choice of organocopper reagents. Diversity of substituents at the 1- or 6-positions of the ring can also be assured by the selection of *N*-alkylating reagents or starting amino acids. Enhancement of α-selectivity in the organocopper-mediated reaction is attributable to the addition of Li salt, even though the basis for this effect is not well understood. Investigating the effects of Li salts and biological evaluation of these mimetics, including the conversion to linear (*Z*)-alkene-type dipeptide isosteres as a counterpart to EADIs, will be presented in due course.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version at doi:10.1016/j.tetlet.2005.04.057.

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12. Representative procedure for organocopper-mediated *anti*-S_N2' reaction of γ-phosphoryloxy-α,β-unsaturated-δ-lactams: To a stirred solution of CuI (37.3 mg, 0.196 mmol) and LiCl (16.6 mg, 0.392 mmol) in dry THF (0.75 mL) was added MeMgCl in THF (3.0 M, 0.0653 mL, 0.196 mmol) under argon at −78 °C, and the mixture was stirred for 10 min at 0 °C. To the solution of organocopper reagent was added dropwise a solution of the phosphate **8** (44.1 mg, 0.0981 mmol) in dry THF (0.75 mL) at −78 °C, and the mixture was stirred for 20 min. The reaction was quenched with a 1:1 saturated NH_4Cl–28%NH_4OH solution (2 mL). The mixture was extracted with Et_2O, and then the extract was washed with water, and dried over $MgSO_4$. Concentration under reduced pressure followed by flash chromatography over silica gel with *n*-hexane–EtOAc (1:1) yielded mimetic **10** (19.6 mg, 0.0910 mmol, 93%) as colorless oil.
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15. Crystal data for **12** (ref. CCDC 259902) and **16** (ref. CCDC 259903) can be obtained on request form the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EW, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].