Development of copper-mediated allylation of γ-activated-α,β-unsaturated lactam toward peptide mimetic synthesis

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Abstract—Reactions of γ-activated-α,β-unsaturated lactams with allylboronate in the presence of LiOi-Pr and CuX (stoichiometric or catalytic amount) proceed in an *anti*-S_N2' manner to yield α-allylated compounds that serve as a potential synthetic intermediate for *cis*-aminoacyl-Pro mimetics.
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The introduction of allyl units into an organic functional group serves as a versatile transformation, which allows a molecule to be subjected to further synthetic manipulations.[1] Numerous studies on allylations of aldehydes,[2] ketones[3] or imines[4] with allylic metal reagents, including catalytic and asymmetric versions,[5] have appeared in the literature. Although 1,4-[6] or S_N2'-sense reactions[7] of allylic metals in the presence of copper salts also constitute an indispensable part of allylation, many controversial issues regarding the regioselectivity of the reaction (1,2- vs 1,4-addition or S_N2 vs S_N2') and nature of the reagent (σ-allyl vs π-allyl) remain.[8]

Recently, we prepared configuration-fixed *cis*-aminoacyl-Pro dipeptide mimetics **6**,[9] which is a useful bioprobe for evaluating the structure–function relationships of Pro-containing peptides/proteins,[10] where (*Z*)-alkenes are substituted for the cis-peptide bond that is in equilibrium with the corresponding trans-peptide bond[11] (Scheme 1). A key transformation in our synthesis is the construction of a five-membered ring, which corresponds to the Pro moiety on unsaturated lactam **1**. Such five-membered ring formation involves the incorporation of a C3 unit at the α-position of **1**, fol-
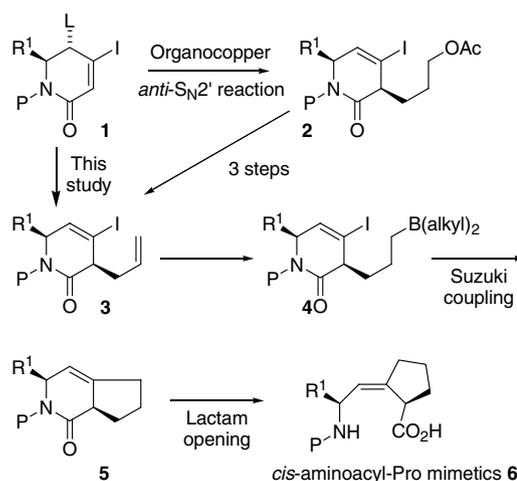
Scheme 1. Outline for the synthesis of *cis*-aminoacyl-Pro mimetics.

lowed by intramolecular Suzuki coupling, to give bicyclic lactam **5** as a crucial precursor of the (*Z*)-Pro mimetic. The 'CH$_2$CH$_2$CH$_2$OAc' group as the C3 unit is incorporated at the α-position in regio- and diastereoselective manners with the aid of zinc–copper reagents[12] (e.g., (IZn)$_2$Cu(CN)[(CH$_2$)$_3$OAc]$_2$·2LiCl) and is subsequently converted to the corresponding C3-borane moiety via an allyl group (Scheme 1, **1** to **4** via **2** and **3**). Directly incorporating the allyl group into **1** could decrease the synthetic steps; however, attempted reaction using allyl Grignard reagents in the presence of a copper

salt met with failure to give desired product in 9% yield with concomitant formation of various compounds including a reductive product. This situation prompted us to reconsider the feasibility of copper-mediated S_N2'-type allylation, which is applicable to the Pro-mimetic synthesis in the light of recent progress in the allylation reaction.

γ-Phosphoryloxy-α,β-unsaturated lactams[13] **7a–c** were selected as substrates for the examined reactions. Although non-β-halogenated substrate **7a** does not have potential as a precursor for mimetic synthesis, it is read-ily available. Using these substrates, we explored suit-able reaction conditions (Table 1). Treatment of **7a** and **7b** with the allyl Grignard reagent in the presence of CuCN·2LiCl following methods described in the liter-ature[7b–d] gave desired products **8a** and **8b**, respectively, in unacceptable yields accompanied by a non-negligible amount of reduced compound **10a** or **10b** (Table 1, entries 1 and 2). The addition of $ZnCl_2$ to the above reaction of **7a** improved the reaction outcomes, whereas the same tuning was unsatisfactory for the reaction of **7b** (Table 1, entries 3 and 4). Therefore, we next examined other allylmetal reagents as alternatives to the Grignard reagent.

Recently, Shibasaki's group has disclosed the synthetic utility of allylsilanes or allylboronates in the presence of copper salts and chiral ligands in the allylation of carbonyl compounds.[5] Inspired by their reports, we explored the synthetic applicability of a combination of allylsilanes (or allylboronates) and copper salts to the S_N2'-conversions. Treatment of **7a** with a reagent that consisted of allyltrimethoxysilane, tetrabutylammo-nium difluorotriphenylsilicate (TBAT), and CuCN in THF gave a mixture, which contained *anti*-S_N2' product **8a** (44%) and S_N2 product **9a** (23%) (Table 1, entry 5). In our previous study on the *anti*-S_N2' reaction on unsaturated lactams,[11b] the addition of lithium salts into the reaction mixture suppressed the formation of S_N2 products. However, the presence of lithium salts in the allylsilane–TBAT system inhibited the reaction, which was also the case for the allylboronate–TBAT system as discussed later (Table 1, entries 6 and 8). Our exten-sive search for suitable reaction conditions using allyl-silanes was fruitless.

Table 1. Examination of *anti*-S_N2' allylation with various allylmetal reagents in the presence of copper salts

Substrates
7a (X = H, R = Me, P = Bzl)
7b (X = I, R = Me, P = DMB)
7c (X = I, R = CH_2OBzl, P = DMB)

anti-S_N2' products: **8a**, **8b**, **8c**
S_N2 products: **9a**, **9b**, **9c**
Reduction products: **10a**, **10b**

Entry	Sub.	Allylmetal reagent[a] (equiv)	Cu salt (equiv)	Additive(s) (equiv)	Conditions	Solvent(s)	Products (isolated yield %)
1	7a	Allyl Grignard (4)	CuCN (2)	LiCl (4)	−78 °C, 30 min	THF	8a (43), 10a (27)
2	7b	Allyl Grignard (2)	CuCN (2)	LiCl (4)	−78 °C, 30 min	THF	8b (9), 10b (12)
3	7a	Allyl Grignard (4)	CuCN (2)	$ZnCl_2$ (4), LiCl (4)	0 °C, 30 min	THF	8a (81), 9a (6), 10a (4)
4	7b	Allyl Grignard (4)	CuCN (2)	$ZnCl_2$ (4), LiCl (4)	0 °C, 30 min	THF	8b (22), 9b (5), 10b (24)
5	7a	Allylsilane (4)	CuCN (2)	TBAT (4)	0 °C, 1 h	THF	8a (44), 9a (23)
6	7a	Allylsilane (4)	CuCN (2)	TBAT (4), LiCl (4)	0 °C, 1 h	THF	—[b]
7	7a	Allylboronate (4)	CuCN (2)	TBAT (4)	0 °C, 1 h	THF	8a (72), 9a (16)
8	7a	Allylboronate (4)	CuCN (2)	TBAT (4), LiCl (4)	0 °C, 1 h	THF	—[b]
9	7a	Allylboronate (4)	CuCl (2)	TBAT (4)	0 °C, 1 h	THF	8a (72), 9a (15)[c]
10	7a	Allylboronate (4)	CuBr (2)	TBAT (4)	0 °C, 1 h	THF	8a (68), 9a (19)[c]
11	7a	Allylboronate (4)	CuSCN (2)	TBAT (4)	0 °C, 1 h	THF	8a (64), 9a (8)[c]
12	7b	Allylboronate (4)	CuCN (2)	TBAT (4)	0 °C, 1 h	THF	8b (15), 9b (39)
13	7b	Allylboronate (4)	CuCN (2)	TBAT (4)	0 °C, 1 h	DMF	8b (28), 9b (42)
14	7c	Allylboronate (4)	CuCN (2)	TBAT (4)	0 °C, 1 h	DMF	8c (67), 9c (20)
15	7c	Allylboronate (4)	CuCl (2)	TBAT (4)	0 °C, 1 h	DMF	8c (56), 9c (28)
16	7c	Allylboronate (4)	CuBr (2)	TBAT (4)	0 °C, 1 h	DMF	8c (40), 9c (25)
17	7a	Allylboronate (4)	CuSCN (2)	TBAF (4)	0 °C, 1 h	THF	8a (72), 9a (4)
18	7b	Allylboronate (4)	CuSCN (2)	TBAF (4)	0 °C, 1 h	DMF–THF	8b (61), 9b (21)
19	7c	Allylboronate (4)	CuSCN (2)	TBAF (4)	0 °C, 1 h	DMF–THF	8c (73), 9c (11)
20	7a	Allylboronate (4)	CuCN (2)	LiO*i*-Pr (4)	0 °C, 1 h	THF	8a (81), 9a (1)
21	7b	Allylboronate (4)	CuCN (2)	LiO*i*-Pr (4)	rt, 6 h[d]	THF	8b (73), 9b (24), 7b (3)
22	7c	Allylboronate (4)	CuCN (2)	LiO*i*-Pr (4)	rt, 6 h[d]	THF	8c (72), 9c (4), 7c (17)
23	7b	Allylboronate (4)	CuCN (0.1)	LiO*i*-Pr (4)	rt, 2 h[d]	THF	8b (92), 9b (4)
24	7c	Allylboronate (4)	CuCN (0.1)	LiO*i*-Pr (4)	rt, 2 h[d]	THF	8c (84), 9c (4), 7c (10)

[a] Allyl magnesium chloride (allyl Grignard), allyltrimethoxysilane (allylsilane), or pinacol 2-propenylboronic ester (allylboronate) was used.
[b] Starting material was recovered.
[c] α-Phenylated material (ca. 5% (CuCl and CuBr) and 21% (CuSCN)) was detected.
[d] Because the starting materials were observed after 1 h, the reaction times were increased. However, the reactions are yet to be optimized.

Next, we examined the synthetic applicability of pinacol 2-propenylboronic ester as an allylboronate to the *anti*-S_N2' reaction. Reactions of **7a** with the allylboronate in the presence of various copper salts (CuCN, CuCl, CuBr, or CuSCN) and TBAT gave desired **8a** in moderate isolated yields (64–72%) with the accompanying S_N2 product (8–19%) (Table 1, entries 7, 9–11). In these reactions, an α-phenyl product was also formed. Especially, the use of CuSCN gave the phenyl product in 21% isolated yield, but a good regioselectivity was observed.[14] Encouraged by the fact that the desired product was obtained in moderate yield, we attempted reactions of **7b** and **7c** with CuX (X = Cl, Br or CN)–TBAT–allylboronate mixtures to prepare proline mimetics. Reaction of **7b** (Ala-Pro type) gave the *anti*-S_N2'/S_N2 mixture, but the S_N2 product was preferentially formed (Table 1, entries 12 and 13). Although treatment of **7c** (Ser-Pro type) afforded the *anti*-S_N2' product as the main compound, the conversion efficiency and *anti*-S_N2'/S_N2 selectivity remained unsatisfactory (Table 1, entries 14–16).

Hence, we reconsidered the reaction conditions in connection with the formation of the α-phenyl product. We speculated that the reaction of allylboronate with TBAT gave a mixture of the borate and silicate, and the remaining silicate formed of the α-phenyl product via a phenyl copper reagent (Fig. 1). Therefore, we initially examined the use of tetrabutylammonium fluoride (TBAF) as a non-silicate type fluoride source with the aid of CuSCN. Reactions of **7a–c** with the allylboronate–CuSCN–TBAF proceeded with moderate regioselectivities to afford the corresponding *anti*-S_N2' product **8a–c**,[15] respectively, without the accompanying α-phenylated product (Table 1, entries 17–19). Furthermore, to improve the regioselectivity, we employed an alkoxide (LiO*i*-Pr), which has been reported to effectively convert the borane to the corresponding borate.[5c] Fortunately, the reaction of **7a** with allylboronate–CuCN in the presence of LiO*i*-Pr in THF proceeded with almost perfect selectivity to furnish **8a** in 81% isolated yield (*anti*-S_N2':S_N2 = 81:1) (Table 1, entry 20). Applying this system to the reaction of **7b** and **7c** improved the products distribution, albeit some of the starting material remained (Table 1, entries 21 and 22).[16]

In order to demonstrate the synthetic usefulness of this system, we planned to use a catalytic amount of CuCN (10 mol %). It should be noted that the attempted reac-
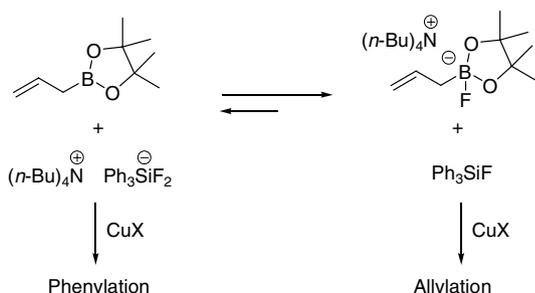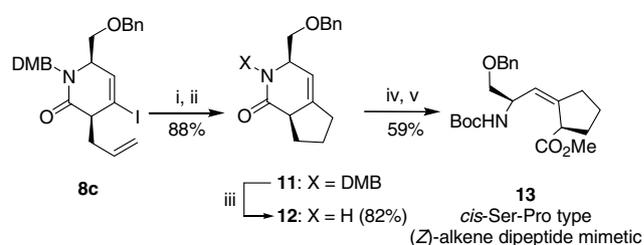
Scheme 2. Conversion of **8c** to *cis*-Ser-Pro mimetic **13**. Reagents and conditions: (i) 9-BBN–H (6 equiv) in THF at room temperature for 7 h; (ii) CsF (6 equiv) and PdCl₂(dppf) (10 mol %) in DMF at 50 °C for 3.5 h; (iii) TFA at 0 °C for 2 h then at room temperature for 4 h; (iv) Me₃O·BF₄ (3 equiv) and 2,6-di-*t*-butylpyridine (1.1 equiv) in CH₂Cl₂ at room temperature for 5 h; (v) 0.1 M HCl in CH₂Cl₂–THF–MeOH–H₂O at 0 °C to room temperature for 12 h then Boc₂O (5.4 equiv) and Et₃N (5.0 equiv) for 5 h.

tion of **7b** with allylboronate (4 equiv) and LiO*i*-Pr (4 equiv) in the presence of 10 mol % CuCN yielded **8b** in 92% isolated yield with concomitant formation of **9b** (4%) (Table 1, entry 23). Application of this catalytic system to the conversion of **7c** also gave satisfactory results to give the desired **8c** in 84% isolated yield (S_N2'/S_N2 = 21:1 in Table 1, entry 24).

At this stage, origin of the improvement of the *anti*-S_N2'/S_N2 ratio in the use of allylboronate–CuCN–LiO*i*-Pr remains to be disclosed. Analysis of reagent formed in the reaction mixture by spectroscopic measurements would give some insight to clarify the factors responsible for the reaction outcomes.

Finally, the conversion of **8c** to the Ser-Pro type alkene dipeptide mimetic was conducted according to our previous synthetic protocol[9b] for the *cis*-Ala-Pro mimetic (Scheme 2).

In summary, we have developed a reliable *anti*-S_N2' allylation of γ-activated-α,β-unsaturated lactams using allylboronate and LiO*i*-Pr in the presence of a stoichiometric or catalytic amount of copper salt. Although the reason for the observed high regioselectivity has yet to be elucidated, the developed reactions have shortened the route to *cis*-Pro mimetics. Finally, our protocol may provide valuable insight into the development of copper-mediated allylation protocols on a wide variety of substrates.

Acknowledgements

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.03.017.

Figure 1. Plausible explanation for the formation of the α-phenylated product.

References and notes

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14. In terms of the product distribution (*anti*-S_N2' vs S_N2), the use of CuSCN as a copper salt gave the best result among the examined conditions, which shows sharp contrast to the experimental results in Ref. 7d.
15. Relative configuration of **8b** was established by the comparison with the authentic sample in Ref. 9b. Reduction of the halogen in **8b** afforded **8b′** (*N*-DMB). On the basis of both NMR analyses of **8b** and **8b′** and the empirical rule mentioned below, cis-configuration was established. To our knowledge, copper-mediated S_N2'-reaction to the allyl phosphate proceeds in *anti*-manner with no exceptions.[7b,11a,b,13a,b] Therefore, relative configuration of **8c** was also tentatively assigned as cis.
16. The use of CuCN is critical in the allylboronate–LiO*i*-Pr system: reaction of **7b** with CuSCN resulted in the decrease in regioselectivity (**8b/9b** = 2.4:1); reaction with CuCl did not complete the reaction (**7b** (25%) was recovered).