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COMMUNICATION

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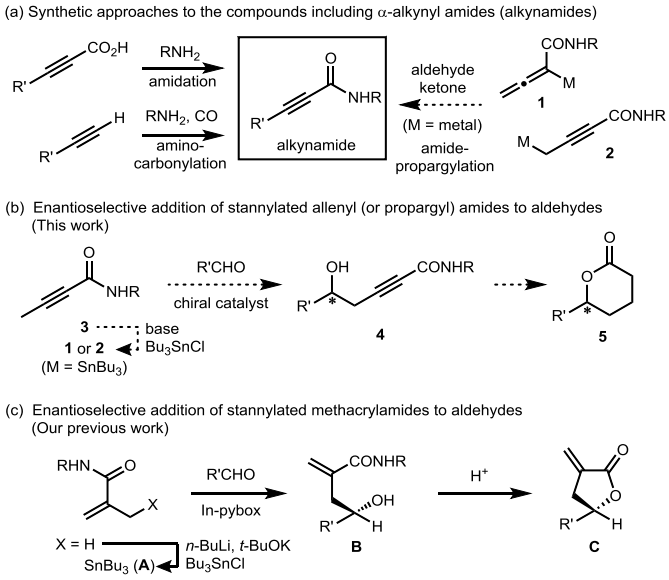
Catalytic enantioselective propargylation of aldehydes with newly prepared stannyl allenyl amide is described. The reaction has been accomplished by using catalytic amounts of indium chloride, zinc chloride, and a chiral BINOL derivative, affording amide-functionalized homopropargyl alcohols in excellent yields and enantioselectivities.



Scheme 1. Syntheses and reactions of allyl/allenyl amides

α-Alkynyl amide (alkynamide) is a useful unit for the synthesis of heterocyclic systems. For instance, compounds bearing this unit can be converted to biologically relevant lactams through metal-catalyzed cyclization.[1] Alkynamide also serves as an electron-deficient alkyne in [3+2] cycloadditions with dipoles or ylides to furnish a variety of heteroaromatic systems such as pyrazole,[2] isoxazole,[3] triazole,[4] pyrrole,[5] and indolizine.[6] The great synthetic potential of alkynamide has attracted the attention of synthetic chemists, and therefore various derivatives have been stepwisely synthesized through amidation of alkynyl acids or aminocarbonylation of terminal alkene (Scheme 1a).[7]

Meanwhile, direct installation of an alkynyl amide unit through amido-functionalized propargylation of aldehydes or ketones (we call them amide propargylation) is attractive in terms of step economy because it is possible to prepare homopropargyl alcohols **4** bearing a synthetically useful amide functionality in two steps starting from alkynamide **3** (Scheme 1b).[8] However, to our knowledge, no reports describing successful studies on amide propargylation have appeared previously, probably due to the lack of suitable synthetic methodologies that enable an access to amide-functionalized propargylating agents such as **1** and **2**.[9,10] In the meantime, during our continuing efforts to develop carbonyl-functionalized allylation, we have shown that stannylated methacrylamides **A**[11] and their analogous boronates[12] are available through stannylation or boration of dianion intermediates generated by deprotonation of methacrylamides (Scheme 1c). These reagents underwent addition to aldehydes under the influence of chiral catalyst to give enantioenriched allyl adducts **B**, which were efficiently converted into methylene lactones **C** in acidic media.[11b–e] Considering the superior acidity of the propargylic proton of 2-butynamides **3** relative to that of the allylic proton in methacrylamides, we assumed that comparable dianion approach starting from **3** would lead to stannylated allenyl amides **1** or propargyl amides **2**. These reagents would react with aldehydes to provide amide-functionalized homopropargyl alcohols **4**, which should be transformed into δ-lactones **5** through hydrogenation followed by cyclization (Scheme 1b). In this communication, we report the preparation of a new series of stannylated allenyl amides and successful application to the enantioselective amide propargylation of aldehydes.

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Electronic Supplementary Information (ESI) available: X-ray data for compound **7**. Experimental details, characterisation data, ^{1}H and ^{13}C NMR spectra and HPLC charts of new compounds. See DOI: 10.1039/x0xx00000x

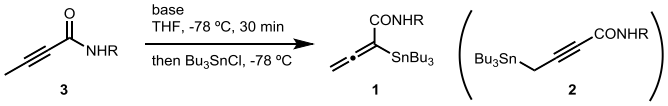


Table 1. Stannylation of **3** under various basic conditions[a]

Entry	**3** (R)	Base (eq)	Time [h]	**1** [%]	**2** [%]
1	**3a** (Ph)	*n*-BuLi (2.3) *t*-BuOK (2.8)	1	**1a** (22)	-
2	**3a**	LDA (3.0) LiCl (1.0)	1	**1a** (28)	-
3	**3a**	LDA (3.0) HMPA (4.5)	1	**1a** (7)	-
4	**3a**	LDA (3.0)	1	**1a** (45)	-
5	**3a**	LiHMDS (3.0)	2	**1a** (4)	-
6	**3a**	NaHMDS (3.0)	2	**1a** (trace)	-
7	**3b** (*p*-Cl-C_6H_4)	LDA (3.0)	1[b]	**1b** (23)	-
8	**3c** (*p*-MeO-C_6H_4)	LDA (3.0)	1	**1c** (52)	-
9	**3d** (*p*-Me-C_6H_4)	LDA (3.0)	1	**1d** (38)	-

[a] All reactions were carried out with **3** (1.0 equiv.), base, and Bu_3SnCl (3.0 equiv.) in dry THF at -78 °C. [b] The reaction mixture was warmed to 0 °C over 1 h.

Inspired by the previous works relating ester-functionalized propargylating agents,[13] we expected that reaction of aldehydes with **1** would efficiently provide **4** in the presence of Lewis acid. Therefore, our first objective was to develop a scalable synthetic method for **1** (Table 1). In the initial attempt to carry out the stannylation of **3a** under the same reaction conditions for the synthesis of **A**, the reaction proceeded sluggishly with poor conversion after 2 h. The desired product **1a** could be readily isolated as air-insensitive solid through silica gel column chromatography (22% yield, entry 1). Use of LDA–LiCl that is the literature conditions employed for the synthesis of ester analogs[9e] resulted in 28% yield of the product (Table 1, entry 2). After further screening of bases and additives (Table 1, entries 3–6), it was revealed that deprotonation with 3 equivalents of LDA was the key to obtaining the good yield of **1a** (45% yield) as shown in entry 4 of Table 1.[14] Thus, we established a new synthetic procedure that allows access to sufficient quantities (hundreds of milligrams) of *N*-aryl-substituted stannyl allenyl amides **1a–d**.[15,16]

With the stannylated allenyl amide **1** in hand, we attempted amide propargylation by mixing benzaldehyde and **1a** (molar ratio 1:1.2) in acetonitrile. In the absence of any additives, the aldehyde was gradually consumed with predominant formation of the allenyl adduct **6a** (22% yield). Similar results were obtained by using scandium triflate or ytterbium triflate as an additive, giving **6a** in respective yields of 37 and 32% (Table S1, entries 1 and 2). As a result of our screening of metal additives, we fortunately found that a selectivity switch occurred on the reaction performed with zinc or indium reagent, in which the desired propargyl product **4a** was obtained as a major regioisomer (Table S1, entries 3–6). Among them, the case with indium triflate gave the best result by enabling **4a** to be formed in 61% yield (Table S1, entry 4).[17]

We then examined enantioselective synthesis of **4a** by adding a chiral ligand to the reaction using indium triflate (Table 2). On the basis of our successful results on the enantioselective

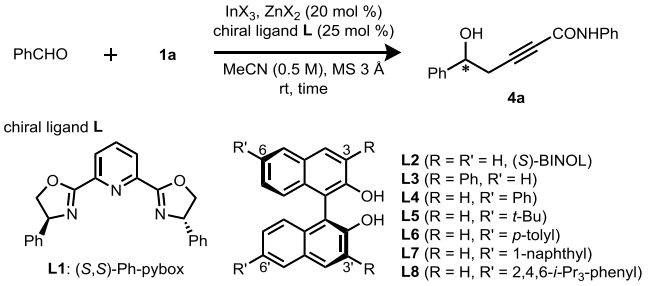


Table 2. Screening of metal reagents and chiral ligands in the reaction of benzaldehyde with **1a**[a]

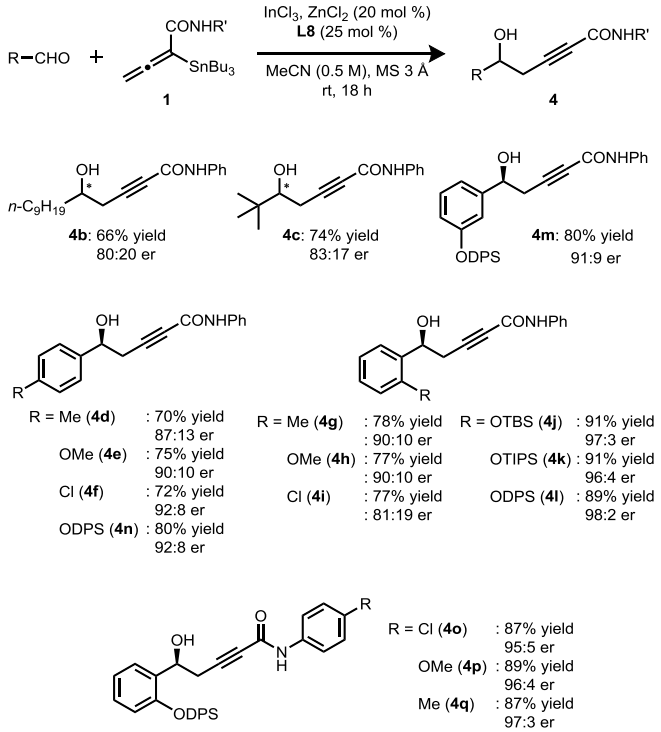
Entry	InX_3	ZnX_2	**L**	Time [h]	Yield[b] [%]	Er[c]
1	$In(OTf)_3$	–	**L1**	18	65	43:57
2	$In(OTf)_3$	–	**L2**	18	31	62:38
3	$In(OTf)_3$	$ZnCl_2$	**L1**	18	40	49:51
4	$In(OTf)_3$	$ZnCl_2$	**L2**	18	76	80:20
5	$In(OTf)_3$	$Zn(OTf)_2$	**L2**	18	73	70:30
6	$InCl_3$	$ZnCl_2$	**L2**	18	72	86:14
7	$InCl_3$	$Zn(OTf)_2$	**L2**	18	63	81:19
8	$InCl_3$	–	**L2**	18	38	84:16
9	$InCl_3$	$ZnCl_2$	**L3**	18	64	58:42
10	$InCl_3$	$ZnCl_2$	**L4**	18	74	90:10
11	$InCl_3$	$ZnCl_2$	**L5**	18	75	88:12
12	$InCl_3$	$ZnCl_2$	**L6**	18	82	90:10
13	$InCl_3$	$ZnCl_2$	**L7**	18	74	88:12
14	$InCl_3$	$ZnCl_2$	**L8**	18	82	94:6
15	$InCl_3$	–	**L8**	18	55	88:12
16	–	$ZnCl_2$	**L8**	18	51	52:48

[a]All reactions were carried out with benzaldehyde (1.0 equiv.) and **1a** (1.2 equiv.) in dry MeCN in the presence of InX_3 (20 mol %), ZnX_2 (20 mol %), **L** (25 mol %), and MS 3 Å at rt. [b]Isolated yield of **4a**. [c]The er values were determined by HPLC analysis using Daicel Chiralpak IC.

allylation with **A**,[11] chiral pybox and BINOL ligands **L1**,**2** were expected to serve as a potential ligand for controlling facial selectivity on the carbonyl plane. In fact, they had a positive effect on the stereochemical outcome of the reaction between benzaldehyde and **1a**, albeit the observed enantioselectivities were very low (Table 2, entries 1 and 2). The selectivity was significantly enhanced to 80:20 by adding zinc chloride as a cocatalyst for the reaction using BINOL ligand (Table 2, entry 4), although the reaction in the presence of indium triflate, zinc chloride, and pybox gave an almost racemic product (Table2, entry 3). Further improvement was realized by varying indium and zinc reagents (Table 2, entries 5–7) with the best result (72% yield, 86:14 er) being obtained using a pair of catalytic indium chloride and zinc chloride (Table 2, entry 6). We also performed the reaction only in the presence of indium chloride and BINOL as a control experiment (Table 2, entry 8). In this case, **1a** was isolated in poor yield (38%), although the product enantioselectivity was detected at the same level as that observed in entry 6.[18]

Subsequently, we optimized the substituents of the BINOL ligand in order to further improve enantioselectivity. Screening

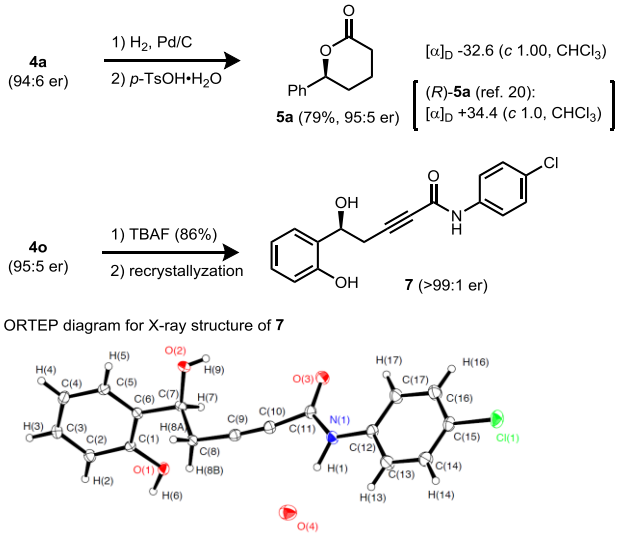
of the reactions with 6,6'-disubstituted BINOLs were made because 6,6'-diphenyl BINOL **L4** exhibited greater



Scheme 2. Scope of amide propargylation: The er values were determined by HPLC analysis using Daicel Chiralpak IC. The absolute configurations of **4d–n, p** and **q** were tentatively assigned by analogy (see Scheme 3)

enantioselectivity than 3,3'-diphenyl derivative **L3** (Table 2, entries 9 and 10). Use of BINOL derivatives bearing phenyl, *t*-butyl, *p*-tolyl or 1-naphthyl substituents at the 6 and 6' positions (**L4–L7**) led to a modest increase in selectivity to give **4a** in 88:12–90:10 ers (Table 2, entries 10–13). The selectivity reached up to 94:6 er without compromising the yield by using 2,4,6-triisopropylphenyl derivative **L8** (Table 2, entry 14). Notably, in control experiments in the absence of each metal reagent, enantiomeric ratios of **4a** were 88:12 (only with indium chloride, table 2, entry 15) and 52:48 (only with zinc chloride, table 2, entry 16), respectively. These results suggest that the stereoselectivity should be mainly ascribed to the formation of indium-BINOL complex.[19,20] Then, we turned our efforts to optimize the reaction solvent under the comparable conditions in entry 14. However, reactions in all the tested solvents such as dichloromethane, chloroform, and toluene resulted in poor yields and low selectivities (28–41% yields, 60:40–78:22 ers). Thus, we decided to employ the conditions in entry 14 for further investigations.

Next, we evaluated the substrate scope of the reaction (Scheme 2). Under the optimum reaction conditions, alkyl substrates such as decanal and pivalaldehyde provided the corresponding adducts **4b**,**c** with moderate enantioselectivities (80:20 and 83:17 ers, respectively). Benzaldehydes bearing electron-donating or electron-withdrawing groups at the *para*- or *ortho*-position gave comparable results to that with benzaldehyde (**4d–i**, 70–77% yields, 81:19–92:8 ers). We have to point out that *ortho*-siloxy substituent, especially *tert*-butyldiphenylsilyloxy (DPSO) group at the *ortho*-position, exerted a beneficial effect on the enantioselectivity (**4l**, 98:2 er). Analogously, the products



Scheme 3. Determination of the absolute configurations of **4a** and **4o**

4j,**k** were obtained in 97:3 and 96:4 ers, respectively. As for the amide substituents on **1**, both electron-donating and electron-withdrawing groups were tolerated, and **4o–q** were produced in high yields and excellent er values.[21,22]

Finally, we focused on the confirmation of the absolute configuration of the newly formed stereocenter (Scheme 3). In order to probe this issue, we examined the transformation of **4a** into known compound **5a**.[23] Alkyne moiety in **4a** (94:6 er) was successfully hydrogenated in the presence of Pd/C in methanol to give the corresponding saturated amide, which was in turn subjected to lactone cyclization under acidic conditions to afford **5a** in 64% two-step yield with no erosion of stereointegrity (95:5 er). The spectral data for **5a** were identical to those in the literature except for the opposite sign of optical rotation. Thus, the absolute configuration of the major enantiomer of **4a** was determined to be *S*. Furthermore, as part of efforts to provide mechanistic insight for the unique *ortho*-siloxy effect, we attempted to determine the stereochemistry of **4o** through the single-crystal X-ray diffraction analysis using the anomalous dispersion method.[24] The DPS group of **4o** (95:5 er) was removed by treatment with tetrabutylammonium fluoride (TBAF). The product **7**, whose enantiomeric purity was maintained during the deprotection, was further purified by recrystallization from ethyl acetate/hexane to afford X-ray quality crystals (>99:1 er). The single-crystal X-ray diffraction analysis showed that the molecules adopt the chiral orthorhombic space group $P2_12_12_1$ with the Flack parameter as low as 0.03(5), clearly demonstrating that the absolute configuration of the newly formed stereocenter is *S*.[24,25] The results suggests that the amide propargylation of aryl aldehydes would proceed in the same manner to give the *S* adducts as a major enantiomer.[26]

In conclusion, we have developed the catalytic enantioselective propargylation of aldehydes with stannyl allenyl amides newly prepared from propargyl amides. A variety of aldehydes were efficiently coupled with the

propargylating reagents under the influence of $InCl_3$, $ZnCl_2$, and a chiral BINOL derivative to afford the corresponding amide-functionalized homopropargyl alcohols directly in excellent yields and enantioselectivities. This report represents the first example of catalytic enantioselective amide propargylation, which will provide new opportunities for the future development of pharmaceutically attractive molecules. Further investigations on mechanistic details of catalytic asymmetric process and synthetic application of this work are currently underway.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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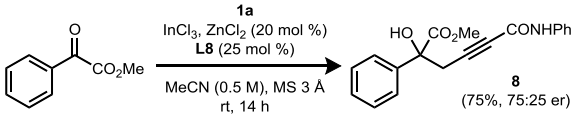
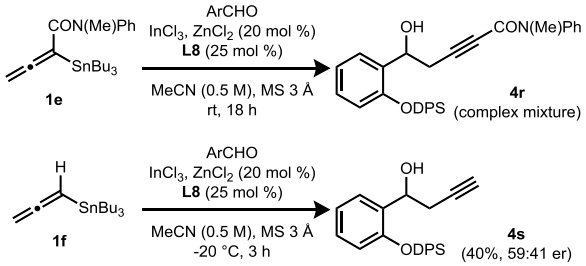
14 Regioisomer **2** was not observed throughout these investigations.
15 The preparation of an ester analog of **1a** resulted in failure because stannylation of α-alkynyl ester gave complex mixture under the comparable conditions.
16 Preparation of *N*-pentyl derivative of **3** met with failure because purification of the reaction products was hampered by their poor stability to silica gel. We also attempted to synthesize γ-ethyl derivative of **1**, however, stannylation of *N*-phenyl-2-hexynamide under the optimized conditions resulted in a complex mixture.
17 The reaction of acetophenone with **1a** in the presence of catalytic $In(OTf)_3$ resulted in decomposition of the stannyl reagent, indicating the high chemoselectivity of the reaction.
18 On the basis of the results in entries 2, 4, 6 and 8, transition state of the reaction catalyzed with $InCl_3$ and $ZnCl_2$ is presumed to be similar, but not identical, to that with $In(OTf)_3$ and $ZnCl_2$. It seems that the main role of $ZnCl_2$ in the former reaction is not to affect the stereochemistry but simply to increase the reaction rate.
19 (*a*) R. Takita, K. Yakura, T. Ohshima and M. Shibasaki, *J. Am. Chem. Soc.*, 2005, **127**, 13760–13761; (*b*) Y.-C. Teo and T.-P. Loh, *Org. Lett.*, 2005, **7**, 2539–2541; (*c*) Y.-C. Teo, J.-D. Goh and T.-P. Loh, *Org. Lett.*, 2005, **7**, 2743–2745; (*d*) Y.-C. Teo, K.-T. Tan and T.-P. Loh, *Chem. Commun.*, 2005, 1318–1320.
20 Zinc chloride seems to promote dissociation of the allenyl carbon-stannane bond based on the results of NMR experiments (see Figure S1 in the Supporting Information).
21 The reaction of α-ketoester with **1a** provided the corresponding adduct **8** in good yield (75%), albeit with 75:25 er.



22 We attempted to evaluate the effect of the amide N–H group of **1** on the stereochemical outcome of the propargylation. The reaction of benzaldehyde with **1e** under the optimum conditions resulted in a complex mixture. Meanwhile, nonsubstituted allenyl stannane **1f** gave the corresponding product **4s** in an almost racemic form. These results indicate that the amide N–H group would play an important role in good reaction efficiency as well as high stereodifferentiation.



23 D. Koszelewski, D. Paprocki, A. Brodzka and R. Ostaszewski, *Tetrahedron: Asymmetry*, 2017, **28**, 809–818.
24 H. D. Flack, *Acta Crystallogr., Sect. A: Fundam. Crystallogr.*, 1983, **39**, 876–881.
25 Crystal data for **6**: orthorhombic, space group $P2_12_12_1$, a = 5.7177(5) Å, b = 7.7029(6) Å, c = 35.315(3) Å, V = 1555.4(2) $Å^3$, Z = 4, ρ = 1.425 Mgm^{-3}, μ(MoKα) = 0.265 mm^{-1}, T = 173 K; in the final least–squares refinement cycles on F^2, the model converge at R1 = 0.0461 (I > 2σ(I)), wR2 = 0.1286, and GOF = 1.077 and Flack absolute structure parameter = 0.03(5) for 3534 reflections and 220 parameters (CCDC deposition number 1878739).
26 For a possible transition state, see Figure S2 in the Supporting Information.