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In situ Catalytic Generation of Allylcopper Species for Asymmetric Allylation: Toward 1*H*-Isochromene Skeletons**

Junya Kawai, Prasanna Kumara Chikkade, Yohei Shimizu, and Motomu Kanai**

Asymmetric allylation of carbonyl groups has been extensively studied because of the high versatility of enantiomerically enriched homoallylic alcohols.[1] There are four main methods for catalytic asymmetric carbonyl allylation: a) using allylmetal species (such as allyl tin, allyl silicon, and allyl boron reagents),[2] b) using the catalytic variant of the Nozaki–Hiyama reaction,[3] c) using reductive generation of nucleophilic π-allyl palladium from allylic alcohols or acetates,[4] and d) using catalytic transfer hydrogenation[5] of various precursors, such as allyl acetates,[6] allenes,[7] and dienes[8] in a waste-minimal manner. Those methods are reliable and widely used in organic synthesis. In contrast, despite potential utility, in situ generation of nucleophilic allylmetal species by oxymetallation has been less explored.

Herein we report the sequential intramolecular oxycupration of allenes[9–11] and subsequent asymmetric addition of the in situ generated allylcopper intermediates to carbonyl compounds (Figure 1).[12] This method has four characteristic features compared to current catalytic asymmetric allylation chemistry. First, a nucleophilic allylcopper species is generated from stable organic molecules, allenes. Second, the thus generated chiral allylcopper species is used for catalytic asymmetric C–C bond formation.[13] Third, along with asymmetric allylation, an additional heterocycle can also be procured, a heterocycle which is ubiquitous in natural products. Finally, this transformation does not generate stoichiometric waste throughout the cascade.

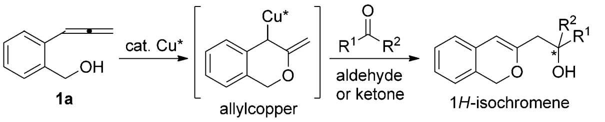
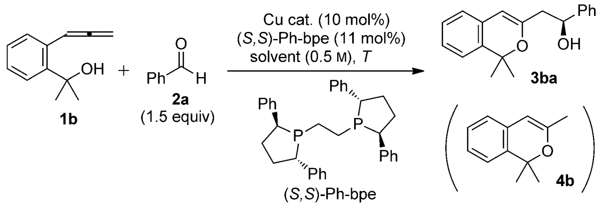


Figure 1. Catalytic intramolecular oxycupration of allenes and subsequent asymmetric carbonyl allylation toward 1*H*-isochromene derivatives

We chose the 1*H*-isochromene ring formation as the first target for our reaction development.[14] Initial optimization for the reaction between the allenic alcohol **1b** and benzaldehyde (**2a**) using copper-conjugated Brønsted base catalysts generated in situ from CuX and LiO*t*Bu is summarized in Table 1.[15] Preliminary ligand screening suggested that electron-rich aliphatic diphosphine ligands were suitable and Ph-bpe was proven to be the best for the desired transformation. Among the copper sources screened (entries 1–4), cationic copper (CuPF$_6$) markedly improved the yield and enantioselectivity (entry 4) compared with those obtained using CuCN or copper halides. The addition of in situ generated allylcopper species to aldehydes proceeded with exclusive regioselectivity at the terminal position of the allene, rather than at the benzylic position, to give the desired **3ba**. The possible regioisomeric isobenzofuran product, generated through the 5-*exo*-trig cyclization of **1b**, was not detected for any of the reactions.[16] In contrast, when the yield was moderate, one of the major side products was **4b**, which was generated by oxycupration and subsequent protonation of the resulting allylcopper species from the substrate alcohol.[17] To reduce

Table 1: Initial optimization of catalytic asymmetric construction of 1*H*-isochromene derivative **3ba**.



Entry	Cu cat.	Solvent	*T* [°C]	*t* [h]	Yield [%][a]	*ee* [%][b]
1[d]	CuCN	NMP	RT	24	33	3
2[d]	CuCl	NMP	RT	24	33	14
3[d]	CuBr	NMP	RT	22	23	38
4[d]	CuPF$_6$[g]	NMP	RT	28	77	74
5	CuO*t*Bu	NMP	RT	16	71	74
6	CuO*t*Bu	HMPA/THF (1:9)	RT	20	89	85
7[e,f]	CuO*t*Bu	HMPA/THF (1:19)	0	2	97 (87)[c]	92
8[e,f]	MesCu	HMPA/THF (1:19)	0	4	98 (92)[c]	92

[a] Determined by ^{1}H NMR spectroscopy using *t*BuOMe as an internal standard. [b] Determined by HPLC using a chiral stationary phase. [c] Yield of isolated product given within parentheses. [d] LiO*t*Bu (10 mol%) was added. [e] 0.3 M. [f] Used 2 equiv of **2a**. [g] Used CuPF$_6$(CH$_3$CN)$_4$. HMPA = hexamethylphosphoramide, NMP = *N*-methylpyrrolidone, THF = tetrahydrofuran.

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[*] J. Kawai,[+] Dr. P. K. Chikkade,[+] Dr. Y. Shimizu, Prof. Dr. M. Kanai
Graduate School of Pharmaceutical Sciences
The University of Tokyo
7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033 (Japan)
E-mail: y-shimizu@mol.f.u-tokyo.ac.jp
kanai@mol.f.u-tokyo.ac.jp
Homepage: http://www.f.u-tokyo.ac.jp/~kanai/e_index.html
Dr. P. K. Chikkade,[+] Prof. Dr. M. Kanai
JST, ERATO, Kanai Life Science Catalysis Project
7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033 (Japan)

[+] These authors contributed equally to this work.

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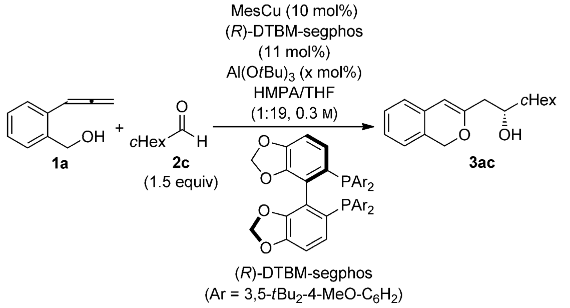
the undesired protonation pathway, the possible effects of lithium salts generated in the catalyst preparation step were assessed using salt-free CuO*t*Bu[18] (entry 5). However, the results did not change much, thus indicating that the lithium ion did not play a key role. In contrast, solvent screening revealed that the use of a HMPA/THF mixed solvent profoundly reduced the formation of **4b** and enhanced the enantioselectivity of **3ba** (entries 6 and 7).[19] Finally, **3ba** was obtained in excellent yield and enantioselectivity using mesitylcopper (MesCu)[20] as the catalyst (entry 8).

The thus developed reaction conditions, however, were not suitable for the primary allenic alcohol **1a**. Therefore, we investigated the reaction conditions again using **1a** and cyclohexanecarboxaldehyde (**2c**) as substrates (Table 2).

Table 2: Optimization of the reaction between **1a** and cyclohexanecarboxaldehyde (**2c**).



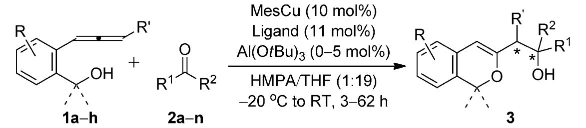
Entry	*x*	*T* [°C]	*t* [h]	Yield [%][a]	*ee* [%][c]
1	0	RT	37	25	88
2	2	RT	37	70	89
3[d]	2	RT	> 37	0	n.d.
4	5	RT	15	79	89
5	5	15	24	66[b]	91

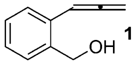
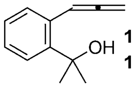
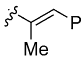
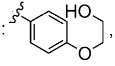
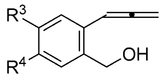
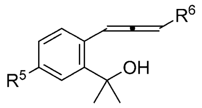
[a] Determined by ^{1}H NMR spectroscopy using *t*BuOMe as an internal standard. [b] Yield of isolated product. [c] Determined by HPLC using a chiral stationary phase. The absolute configuration of the product **3ac** was estimated from that of **3aa**. [d] Neither mesitylcopper nor ligand was added as a control experiment. n.d. = not determined.

DTBM-segphos was found to be superior, in terms of enantioselectivity, to other ligands examined.[21] The reactivity was not satisfactory (entry 1) despite further screening of catalysts. To improve the reactivity, we studied additive effects. Pleasingly, the addition of 2 mol% of Al(O*t*Bu)$_3$ dramatically improved the reactivity without affecting the enantioselectivity (entry 2). Al(O*t*Bu)$_3$ alone in the absence of the copper catalyst promoted no reaction at all (entry 3).[22] Finally, the reaction proceeded at 15 °C to give the desired product **3ac** in 66 % yield with 91 % *ee* (entry 5).

With the optimized reaction conditions in hand, we studied the substrate scope of this asymmetric carbonyl allylation (Table 3). Both aromatic and aliphatic aldehydes were competent (entries 1–16). Excellent enantioselectivity was generally produced, especially for the combination of aliphatic aldehydes with **1a** (entries 2–6) and aromatic aldehydes with **1b** (entries 8–16). The catalyst loading could be reduced to 5 mol% in an ideal case without decreasing enantioselectivity (entry 9). Heteroaromatic aldehydes can also be utilized (entries 13 and 14). The α,β-unsaturated aldehyde **2m** exclusively produced the corresponding 1,2-adduct (entry 15), thus implying that the addition of allylcopper to aldehydes proceeds via a six-membered transition state. The reaction with the aldehyde **2n**, possessing an additional unprotected hydroxy group, was noteworthy as it afforded the target product **3bn** in 79 % yield and 89 % *ee* (entry 16). Moreover, acetophenone (**2g**), a significantly less reactive electrophile than aldehydes, also gave the desired product in 77 % yield, albeit with moderate enantioselectivity

Table 3: Substrate scope.



Entry	1	2: R^1, R^2	Cond.[a]	3	Yield[b] [%]	*ee*[c] [%]
1	 **1a**	**2a**: Ph, H	B	**3aa**	70	81
2	**1a**	**2b**: *t*Bu, H	B	**3ab**	77	91
3	**1a**	**2c**: cyclohexyl, H	B	**3ac**	66	91
4	**1a**	**2d**: cyclopentyl, H	B	**3ad**	60	89
5	**1a**	**2e**: 3-pentyl, H	B	**3ae**	91	93
6	**1a**	**2f**: cyclopropyl, H	B	**3af**	78	84
7[d]	**1a**	**2g**: Ph, Me	B	**3ag**	77	76
8	 **1b**	**2a**	A	**3ba**	92	92
9[e]	**1b**	**2a**	A	**3ba**	84	92
10	**1b**	**2h**: 4-MeOC$_6$H$_4$, H	A	**3bh**	91	90
11	**1b**	**2i**: 4-*t*BuC$_6$H$_4$, H	A	**3bi**	90	91
12	**1b**	**2j**: 4-FC$_6$H$_4$, H	A	**3bj**	85	90
13	**1b**	**2k**: 2-thienyl, H	A	**3bk**	92	94
14	**1b**	**2l**: 2-furanyl, H	A	**3bl**	91	91
15	**1b**	**2m**:  , H	A	**3bm**	96	91
16[d,f]	**1b**	**2n**:  , H	A	**3bn**	79	89
						
17	**1c**: R^3 = H, R^4 = Cl	**2c**	B	**3cc**	72	86
18	**1c**: R^3 = H, R^4 = Cl	**2e**	B	**3ce**	76	91
19	**1d**: R^3 = H, R^4 = Br	**2e**	B	**3de**	77	88
20	**1e**: R^3 = F, R^4 = H	**2e**	B	**3ee**	86	93
						
21[g]	**1f**: R^5 = OMe, R^6 = H	**2a**	A	**3fa**	69	92
22[h]	**1g**: R^5 = H, R^6 = Me	**2a**	A	**3ga**	98 (79:21)[i]	97/82
23	**1h**: R^5 = H, R^6 = Ph	**2a**	A	**3ha**	99 (65:35)[i]	81/95

[a] Conditions A: Using 2.0 equiv of aldehyde in the absence of Al(O*t*Bu)$_3$. Ligand = (*S*,*S*)-Ph-bpe. Conditions B: Using 1.5 equiv of aldehyde and 5 mol% Al(O*t*Bu)$_3$. Ligand = (*R*)-DTBM-segphos. See the Supporting Information for more details. [b] Yield of the isolated product. [c] Determined by HPLC using a chiral stationary phase. [d] HMPA/THF (1:4) was used as a solvent. [e] Used 5 mol% of CuO*t*Bu instead of MesCu. [f] Used 1.5 equiv of aldehyde. [g] Added 2 mol% of Al(O*t*Bu)$_3$. [h] Added 5 mol% of Al(O*t*Bu)$_3$. [i] Diastereomeric ratio was determined from ^{1}H NMR analysis of the crude reaction mixture.

(76 % *ee*; entry 7). Together, the allylcopper species was tolerant to protic functional groups, and still exhibited high nucleophilicity to carbonyl groups.

As for the scope of the allenic alcohols, the substrates **1c**–**e** having an electron-withdrawing halogen substituent at the *meta*- or *para*-position to the allene moiety had good reactivity and afforded the desired products in good yield with high enantioselectivity (Table 3, entries 17–20). The electron-donating group at the *para*-position of the allene moiety in the substrate **1f** led to a slower reaction, but the product was still obtained with excellent enantioselectivity (entry 21). Next we examined the reaction with the racemic, disubstituted allenic alcohols **1g** and **1h** and the results obtained were also noteworthy (entries 22 and 23). Although the methyl-substituted substrate **1g** had lower reactivity (entry 22) than **1b** (entry 8), the reaction proceeded in the presence of Al(O*t*Bu)$_3$ as a cocatalyst and the product **3ga** was obtained in high yield (98 %) as a mixture of diastereomers (79:21) with high enantioselectivity (97 % *ee*/82 % *ee*). X-ray crystallographic analysis unambiguously revealed the absolute and relative configurations of the major isomer to be *syn*-(*S*,*S*).[21] Therefore, this transformation can be regarded as stereoconvergent. The chirality of the substrate was lost at the allycopper stage, and enantioselective allylation of the aldehyde proceeded under chiral ligand control.[21] The phenyl-substituted allenic alcohol **1h** was a highly reactive substrate, and the product **3ha** was obtained at −10 °C in almost quantitative yield with 81/95 % *ee* (entry 23). Despite the nearly symmetric structure of the allene moiety of **1h**, only a single regioisomer was exclusively observed as a product.

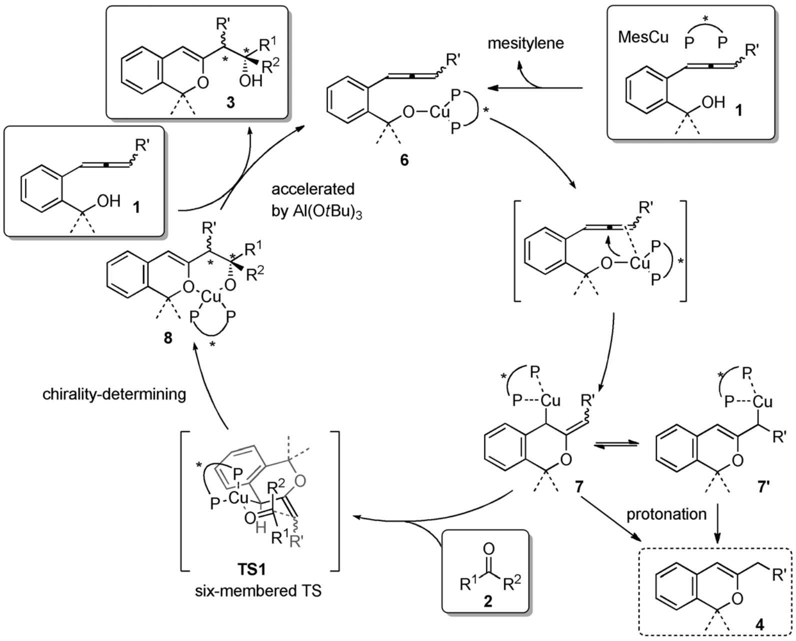
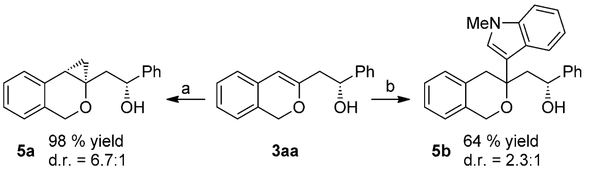


Figure 2. Proposed catalytic cycle of 1*H*-isochromene-constructing asymmetric allylation between **1** and **2**.

These molecules can be versatile chiral building blocks for potential drug candidates. Typical synthetically useful transformations of **3aa** producing isochroman skeletons[23] are summarized in Scheme 1. Cyclopropanation of **3aa** proceeded in excellent yield with a 6.7:1 diastereoselectivity, thus giving the (*R*,*R*,*S*) isomer **5a** with a tricyclic scaffold.[24] The addition of an indole nucleophile to the enol ether moiety of **3aa** proceeded using cationic gold catalysis, and the coupling product **5b**, possessing a tetrasubstituted carbon center, was generated.[25]



Scheme 1. Derivatizations of 1*H*-isochromene scaffold. Reagents and conditions: a) Et$_2$Zn (4 equiv), CH$_2$I$_2$ (4 equiv), TFA (4 equiv), DME, 0 °C, 5 h; (b) *N*-methylindole (1.5 equiv), [AuCl(PPh$_3$)] (0.1 equiv), AgSbF$_6$ (0.1 equiv), toluene, RT, 4 h. DME = 1,2-dimethoxyethane, TFA = tetrafluoroacetic acid.

Based on our current observations and previous findings in the reactions using allylcopper species,[12] we propose a catalytic cycle as shown in Figure 2. First, the copper allenic alkoxide **6** is generated through deprotonation of the hydroxy group by the catalyst. Then, either the allylcopper **7** or **7′** is formed through oxycupration of the allene.[26] The addition of the thus generated allylcopper to the aldehyde **2** would proceed through a six-membered transition state (**TS1**) to give the enantiomerically enriched copper alkoxide **8**. Ligand exchange between **8** and **1** yields the product **3**, and the active catalyst **6** is regenerated at the same time. Considering the fact that enantioselectivity was not affected by the addition of Al(O*t*Bu)$_3$ (Table 2, entry 1 versus 2), the aluminum additive would accelerate this ligand exchange step after the enantioselectivity was determined, by facilitating liberation of the copper catalyst from **8**.

In summary, we developed an efficient catalytic method to generate reactive allylcopper species by the intramolecular oxycupration of allenes. The resulting allylcopper can be used for subsequent asymmetric carbonyl allylation, thus providing 1*H*-isochromene derivatives in excellent enantioselectivity. Three characteristics of this reaction are: 1) tolerance to existing free hydroxy groups, 2) stereoconvergency when applied to racemic disubstituted allenes, and 3) no need to prefunctionalize or preactivate substrates for the generation of the allylcopper. Application and extension of this minimal-waste-producing allylcopper generation method to asymmetric synthesis of biologically important molecules are currently ongoing.

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[17] Other significant side reactions were isomerization of the allene to alkyne and oxygenation of the allylcopper intermediate with unintentionally contaminated oxygen molecule.

[18] Salt-free CuO*t*Bu was prepared in situ from mesitylcopper and the same molar amount of *t*BuOH.

[19] Generation of the byproduct **4b** was minimized in aprotic polar solvents, such as DMF and DMSO. The mixture of THF and a small amount of HMPA, however, produced higher enantioselectivity than any other solvent system.

[20] T. Tsuda, K. Watanabe, K. Miyata, H. Yamamoto, T. Saegusa, *Inorg. Chem.* **1981**, *20*, 2728.

[21] See the Supporting Information for details.

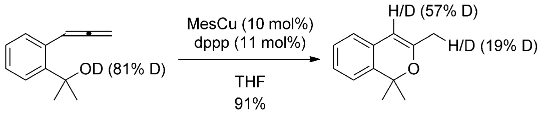
[22] Other additives produced less satisfactory results (see the Supporting Information). Considering the fact that enantioselectivity was not affected by the addition of $Al(OtBu)_3$ (Table 2, entry 1 versus 2), the aluminum additive would accelerate the catalyst turnover step after the enantioselectivity was determined. See the Supporting Information for the proposed catalytic cycle.

[23] For representative examples, see: a) R. E. TenBrink, C. L. Bergh, J. N. Duncan, D. W. Harris, R. M. Huff, R. A. Lahti, C. F. Lawson, B. S. Lutzke, I. J. Martin, S. A. Rees, S. K. Schlachter, J. C. Sih, M. W. Smith, *J. Med. Chem.* **1996**, *39*, 2435; b) C. F. Bender, F. Yoshimoto, C. L. Paradise, J. K. De Brabander, *J. Am. Chem. Soc.* **2009**, *131*, 11350; c) M. Leibeling, D. C. Koester, M. Pawliczek, S. C. Schild, D. B. Werz, *Nat. Chem. Biol.* **2010**, *6*, 199, and references cited therein.

[24] Z. Yang, J. C. Lorenz, Y. Shi, *Tetrahedron Lett.* **1988**, *29*, 8621. For details about X-ray analysis, see the Supporting Information.

[25] N. T. Patil, V. S. Raut, R. D. Kavthe, V. V. N. Reddy, P. V. K. Raju, *Tetrahedron Lett.* **2009**, *50*, 6576. Moderate stereoselectivity of **5b** is due to the relative thermodynamic stability of the two diastereomers. Two diastereomers of **5b** (vinylogous aminal) equilibrated even under treatment using silica gel.

[26] When we conducted the reaction with the deuterated substrate **1i** in the absence of an aldehyde, oxycupration/deuteration proceeded to give **4c**. This result supports the existence of equilibrium between **7** and **7′**.



1i **4c**