Asymmetric Catalysis

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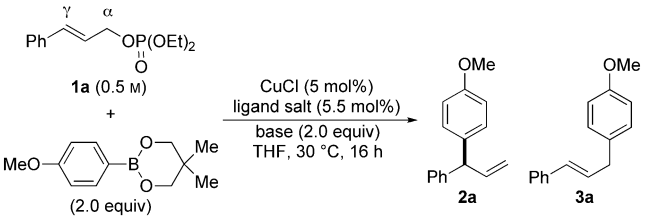
Copper-Catalyzed Asymmetric Allylic Substitution of Allyl Phosphates with Aryl- and Alkenylboronates**

Ryo Shintani, Keishi Takatsu, Momotaro Takeda, and Tamio Hayashi**

Catalytic asymmetric allylic substitution with organometallic reagents is one of the efficient ways of constructing enantioenriched chiral compounds by the formation of a new carbon–carbon bond. Although a significant number of reports have been made on this reaction, particularly using chiral copper complexes as catalysts,[1] the organometallic reagents that can be employed are mostly limited to highly reactive ones, such as Grignard,[2] diorganozinc,[3] and triorganoaluminum reagents.[4] In contrast, the use of milder nucleophiles, such as organoboronic acid derivatives, has been much less explored despite their availability, stability, and ease of handling.[5] In fact, the asymmetric substitution of simple allylic electrophiles with organoboronic acids has been addressed only in the context of nickel-catalyzed reactions with moderate enantioselectivity,[6] and rhodium-catalyzed reactions using *cis*-2-butene-1,4-diol derivatives as substrates.[7,8] In addition to the limited number of methods, most of the organometallic nucleophiles that have been employed in asymmetric allylic substitution reactions are alkylmetals; the successful employment of aryl nucleophiles has begun to appear only recently.[2d–f,3a,4c,6–9] Herein we describe the development of a copper/N-heterocyclic carbene complex catalyzed asymmetric allylic substitution of allyl phosphates with aryl- and alkenylboronic acid esters to construct both tertiary and quaternary carbon stereocenters with high regio- and enantioselectivity.[10]

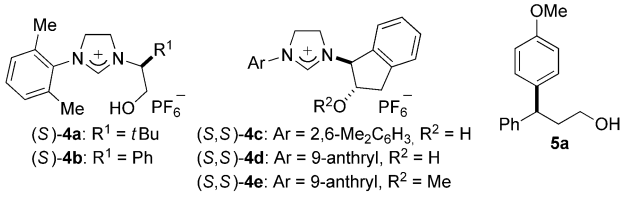
In 2010, two research groups independently reported that arylboronic acid esters are competent nucleophiles in copper-catalyzed allylic substitution reactions using achiral catalysts.[11] Based on this precedent, as well as our recent success in the copper-catalyzed asymmetric addition of organoboronates using Mauduit-type chiral N-heterocyclic carbene (NHC) ligands,[12,13] we initially conducted the reaction of cinnamyl phosphate (**1a**) with 4-methoxyphenylboronic acid neopentylglycol ester in the presence of CuCl (5 mol%), chiral NHC salt (*S*)-**4a** (5.5 mol%),[12a] and KO*t*Bu (2.0 equiv) in THF at 30°C (Table 1, entry 1). Under these reaction conditions, the reaction proceeded smoothly to give a 41:59 mixture of the γ-substitution product **2a** and the α-substitution product **3a** in 95% combined yield; the thus obtained **2a** had a moderate *ee* value of 56%.[14] We subsequently found that the choice of metal alkoxide base had a significant impact on the reaction outcome. For example, when NaO*t*Bu was used there was a higher selectivity toward **2a** over **3a** (86:14), but the enantioselectivity of **2a** became significantly lower (Table 1, entry 2). On the other hand, the reaction with NaOMe resulted in preferential formation of **2a** (**2a**/**3a** = 78:22) with 48% *ee* (Table 1, entry 3). On the basis of these results, we decided to employ NaOMe as the base in investigations to examine the effect of different chiral NHC ligands. As shown in entry 4 (Table 1), the change of substitutent on the ligand tether from *tert*-butyl to phenyl ((*S*)-**4b**)[12a] improved both the γ selectivity (86:14) and enantioselectivity (76% *ee*), and even higher selectivities were observed when using a tether derived from

Table 1: A study of the base and ligand used in the copper-catalyzed asymmetric allylic substitution of **1a** with 4-methoxyphenylboronate.



Entry	Ligand salt	Base	Yield of **2a** + **3a** [%][a]	**2a**/**3a**[b]	*ee* of **2a** [%][c]
1	(*S*)-**4a**	KO*t*Bu	95	41:59	56
2	(*S*)-**4a**	NaO*t*Bu	92	86:14	32
3[d]	(*S*)-**4a**	NaOMe	91	78:22	48
4[d]	(*S*)-**4b**	NaOMe	85	86:14	76
5	(*S*,*S*)-**4c**	NaOMe	92	97:3	91
6	(*S*,*S*)-**4d**	NaOMe	92	99:1	92
7[e,f]	(*S*,*S*)-**4d**	NaOMe	75	99:1	81
8[f]	(*S*,*S*)-**4e**	NaOMe	68	94:6	78

[a] Yield of the isolated product. [b] Determined by ^{1}H NMR spectroscopy. [c] Determined by HPLC on a Chiralpak AS-H column with hexane/2-propanol = 95:5 after converting **2a** into alcohol **5a** by hydroboration/oxidation. [d] The reaction was conducted for 40 h. [e] 4-Methoxyphenylboronic acid pinacol ester was used as the nucleophile. [f] The reaction was conducted for 30 h. THF = tetrahydrofuran.



[*] Dr. R. Shintani, Dr. K. Takatsu, M. Takeda, Prof. Dr. T. Hayashi
Department of Chemistry, Graduate School of Science
Kyoto University, Sakyo, Kyoto 606-8502 (Japan)
E-mail: shintani@kuchem.kyoto-u.ac.jp
thayashi@kuchem.kyoto-u.ac.jp

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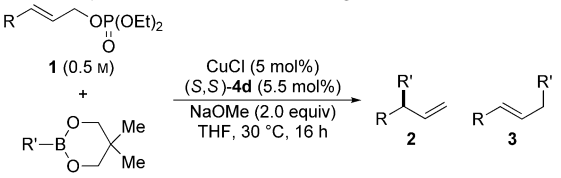
trans-1-amino-2-indanol ((*S*,*S*)-**4c**;[12b] Table 1, entry 5). The highest regio- and enantioselectivities were realized when the 2,6-dimethylphenyl group on (*S*,*S*)-**4c** was changed to a 9-anthryl group ((*S*,*S*)-**4d**;[12b] Table 1, entry 6). The reaction with 4-methoxyphenylboronic acid pinacol ester as the nucleophile, in place of neopentylglycol ester, also led to the formation of **2a** with high regioselectivity, but the yield and the enantioselectivity was somewhat lower (Table 1, entry 7). Also, the use of the NHC salt (*S*,*S*)-**4e**, which has a methoxy group instead of a hydroxy group ((*S*,*S*)-**4c**), slightly diminished the regioselectivity (94:6), and the yield and enantioselectivity were lower (Table 1, entry 8).

Under the reaction conditions in which (*S*,*S*)-**4d** was used as the ligand precursor, several arylboronic acid neopentylglycol esters can react with cinnamyl phosphate **1a** to give products **2** with high regio- and enantioselectivities (Table 2, entries 1–6). Heteroaryl- and alkenylboronates can also be employed to give the substitution products in high yield, although either the regio- or enantioselectivity decreases (Table 2, entries 7 and 8). With regard to the γ substituent of the allyl phosphates, various aryl groups including 2-naphthyl and 3-thienyl groups are tolerated in the reaction with phenylboronate, and the corresponding 1-(hetero)aryl-1-phenyl-2-propenes are obtained in high yield with uniformly high regio- and enantioselectivities (Table 2, entries 9–14). Highly regio- and enantioselective preparation of 1,1-diaryl-2-propenes having substituents on both of the aryl groups is also possible, as exemplified in entry 15 (Table 2). In addition to these cinnamyl phosphate derivatives, γ-alkylated or γ-silylated allyl phosphates are also suitable substrates for the present catalysis and give products **2** with high regioselectivity and with moderate to good enantioselectivity (Table 2, entries 16–19).

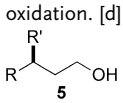
As demonstrated in Table 1, both regio- and enantioselectivity in the product formation are highly dependent on the nature of the metal alkoxide base, and the ester portion of the organoboronate as well as the hydroxy tether of the ligand also affected the reaction outcome. Although no conclusive evidence about the mechanism has been obtained to date, on the basis of these experimental results and a recent report by Nakamura and co-workers on the copper-catalyzed asymmetric allylic substitutions using diorganozinc reagents,[3b] a possible catalytic cycle for the present catalysis using Cu/(*S*,*S*)-**4d** is illustrated in Scheme 1. A mixture of CuCl, (*S*,*S*)-**4d**, and NaOMe generates the chelated copper(I)/NHC complex **A**,[15] which undergoes transmetalation with organoboronate to give organocopper(I) species **B**.[10d,11b,12] Interaction of NaOMe with the pendant boron atom of intermediate **B** would form intermediate **C**. The sodium moiety of

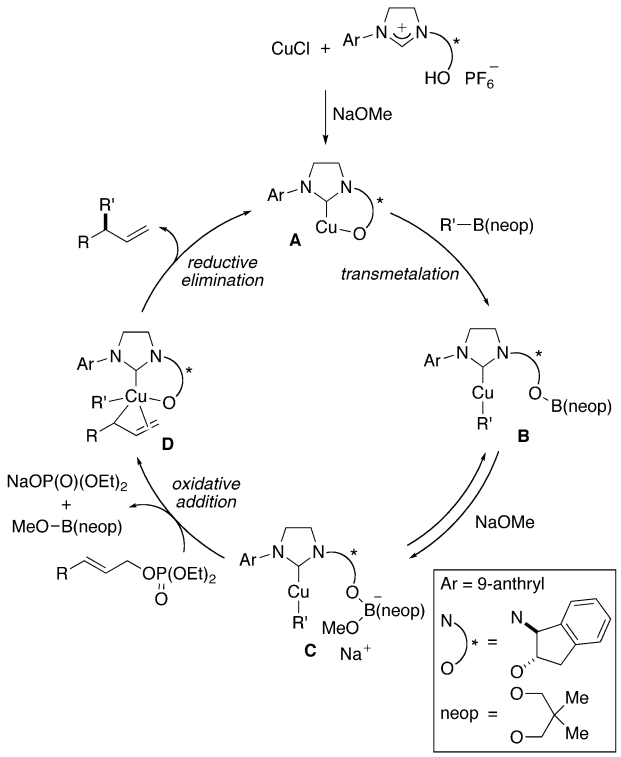
Table 2: Investigation of the substrate scope for the copper-catalyzed asymmetric allylic substitution of **1** with organoboronates.



Entry	**1**	R′	Product	Yield of **2**+**3** [%][a]	**2**/**3**[b]	*ee* of **2** [%][b]
1	**1a**	4-MeOC$_6$H$_4$	(*S*)-**2a**	92	99:1	92
2	**1a**	4-MeC$_6$H$_4$	(*S*)-**2b**	93	99:1	91
3	**1a**	4-ClC$_6$H$_4$	(*S*)-**2c**	88	98:2	93
4	**1a**	4-MeO$_2$CC$_6$H$_4$	(*S*)-**2d**	89	96:4	91
5	**1a**	3-MeC$_6$H$_4$	(*S*)-**2e**	91	>99:1	94
6	**1a**	2-naphthyl	(*S*)-**2f**	92	99:1	94
7	**1a**	3-thienyl	(*S*)-**2g**	93	85:15	93
8	**1a**	1-cyclohexenyl	(*R*)-**2h**	84	99:1	73
9	**1b**	Ph	(*R*)-**2b**	93	99:1	91
10	**1c**	Ph	(*R*)-**2c**	93	97:3	90
11	**1e**	Ph	(*R*)-**2e**	92	99:1	91
12	**1i**	Ph	(*R*)-**2i**	95	>99:1	93
13	**1f**	Ph	(*R*)-**2f**	90	99:1	91
14	**1g**	Ph	(*R*)-**2g**	90	98:2	89
15[d]	**1i**	2-naphthyl	(*R*)-**2j**	84	>99:1	96
16	**1k**	Ph	(*R*)-**2k**	87	99:1	68
17	**1l**	Ph	(*S*)-**2l**	93	>99:1	85
18	**1m**	Ph	(*S*)-**2m**	83	>99:1	85
19	**1n**	Ph	(*R*)-**2n**	74	>99:1	84

[a] Yield of the isolated product. [b] Determined by ^{1}H NMR spectroscopy. [c] Determined by HPLC using a chiral stationary phase with hexane/2-propanol after converting **2** into alcohol **5** by hydroboration/oxidation. [d] The reaction was conducted for 40 h. Cy = cyclohexyl.



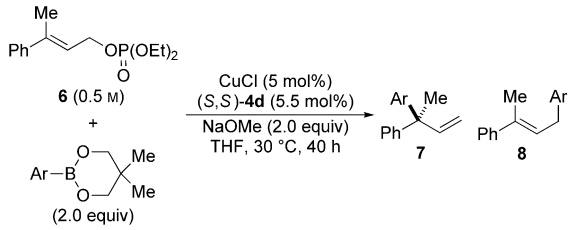


Scheme 1. A possible catalytic cycle for the copper-catalyzed allylic substitution of allyl phosphates with organoboronates.

C guides the orientation of the allyl phosphate in the subsequent oxidative addition to the organocopper center, thus giving the allylcopper(III) species **D**[3b] along with the formation of sodium diethyl phosphate and trialkoxyborane. Reductive elimination of **D** then gives the substitution product, and copper(I) complex **A** is regenerated. The step from **C** to **D** of this catalytic cycle is presumably the regio- and stereodetermining step, and this scheme can explain why the selectivities are strongly dependent on the base, the boronic ester, and the hydroxy tether of the ligand.

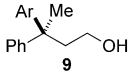
Having established a copper-catalyzed asymmetric allylic substitution of γ-monosubstituted allyl phosphates with organoboronates, we applied this method to the construction of quaternary carbon stereocenters by using γ,γ-disubstituted allyl phosphates.[3a,4c-e,16] As shown in Table 3, entry 1, the

Table 3: Copper-catalyzed asymmetric allylic substitution of **6** with arylboronates.



Entry	Ar	Product	Yield of **7** [%][a]	**7**/**8**[b]	*ee* of **7** [%][c]
1	4-$MeOC_6H_4$	(*S*)-**7a**	90	>99:1	86
2	4-ClC_6H_4	(*S*)-**7b**	84	96:4	86
3	3-MeC_6H_4	(*S*)-**7c**	89	>99:1	90
4	2-naphthyl	(*S*)-**7d**	95	>99:1	89

[a] Yield of the isolated product. [b] Determined by ^{1}H NMR spectroscopy. [c] Determined by HPLC using a chiral stationary phase with hexane/2-propanol after converting **7** into alcohol **9** by hydroboration/oxidation.



reaction of compound **6** with 4-methoxyphenylboronate smoothly proceeded in the presence of Cu/(*S*,*S*)-**4d** to give γ-substitution product **7a** exclusively with reasonably high enantioselectivity (86% *ee*). Similarly, several other arylboronates can also be employed, giving 2,2-diaryl-3-butenes **7** in high yield with up to 90% *ee* (Table 3, entries 2–4).

In summary, we have developed a copper/N-heterocyclic carbene catalyzed asymmetric allylic substitution of allyl phosphates with organoboronates to give the γ-substitution products with high enantioselectivity. We have also proposed a catalytic cycle to explain the observed influence of the reaction parameters. Future studies will be directed toward mechanistic investigations to establish the detailed catalytic cycle and to understand the origin of the stereoselectivity in the present catalysis.

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