Enantioselectivity

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Construction of Chiral Tri- and Tetra-Arylmethanes Bearing Quaternary Carbon Centers: Copper-Catalyzed Enantioselective Propargylation of Indoles with Propargylic Esters

*Kouhei Tsuchida, Yasushi Senda, Kazunari Nakajima, and Yoshiaki Nishibayashi**

Abstract: *Copper-catalyzed enantioselective propargylation of indoles with propargylic esters and sequential Huisgen cycloaddition with azides lead to the construction of chiral triarylmethanes, bearing a quaternary carbon center, with high to excellent enantioselectivities. The result described herein can be used in the enantioselective preparation of a tetraarylmethane.*

Development of the asymmetric synthesis of all-carbon quaternary stereocenters in a catalytic manner is one of the most important subjects in modern organic chemistry because the all-carbon quaternary stereocenter is involved as a universal structure in many natural products and pharmaceuticals.[1] Particularly, the construction of tri- and tetra-arylmethanes bearing a quaternary carbon center remains a significant challenge in materials science and medicinal chemistry.[2,3]

Transition metal-catalyzed allylic substitution reactions are well known as one of the most reliable strategies for the enantioselective construction of all-carbon quaternary stereocenters at the allylic position of allyllic substituted products with high enantioselectivity.[1a,b,4] In sharp contrast to the allylic substitution reactions, the enantioselective construction of all-carbon quaternary stereocenters at the propargylic position of propargylic substituted products has not yet been achieved, although various propargylic substitution reactions have been reported by using a variety of transition metals as catalysts.[5] Especially, ruthenium- and copper-catalyzed substitution reactions of propargylic alcohol derivatives bearing a terminal alkyne moiety with various nucleophiles gave the corresponding propargylic substituted products with a high enantioselectivity, where transition metal–allenylidene complexes were key reactive intermediates.[5–9]

One of synthetic advantages of propargylic substitution reactions is that propargylic substituted products possess a terminal alkyne moiety, which can be easily converted into various groups in a single step. Typically, Huisgen cycloaddition between terminal alkynes and azides gives the corresponding 1,2,3-triazoles in high yields with an excellent selectivity and is widely used as a synthetic tool for the construction of target molecules in many research areas.[10,11]

[*] K. Tsuchida, Y. Senda, Dr. K. Nakajima, Prof. Dr. Y. Nishibayashi
Department of Systems Innovation, School of Engineering
The University of Tokyo
Hongo, Bunkyo-ku, Tokyo 113-8656 (Japan)
E-mail: ynishiba@sys.t.u-tokyo.ac.jp

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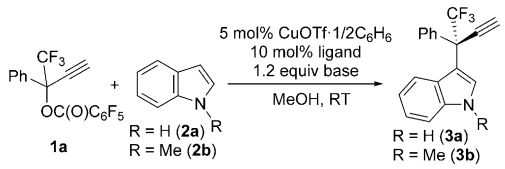
Based on this background, we envisaged the catalytic propargylation of aromatic compounds with tertiary propargylic alcohol derivatives bearing an aromatic moiety at the propargylic position, and subsequent Huisgen cycloaddition to realize the enantioselective preparation of triarylmethanes bearing a quaternary carbon center. In fact, the copper-catalyzed enantioselective propargylation of indoles with propargylic esters bearing aromatic and trifluoromethyl moieties at the propargylic position and sequential Huisgen cycloaddition with azides proceeded to give the corresponding triarylmethanes bearing a quaternary carbon center in high yields with excellent enantioselectivities (up to 97% *ee*). Furthermore, the present reaction system can be applicable to the enantioselective preparation of a tetraarylmethane (78% *ee*) when a tertiary propargylic ester, bearing two different aromatic moieties at the propargylic position, is used as a substrate. This reaction is the first successful example of the enantioselective preparation of a tetraarylmethane. Herein, we describe preliminary results.

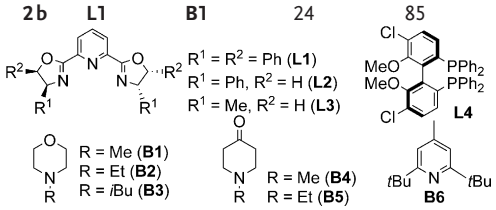
At first, we investigated the copper-catalyzed propargylation of indoles with tertiary propargylic esters because this transformation is considered to be a key step towards the construction of chiral triarylmethanes bearing a quaternary carbon center. Treatment of 1,1,1-trifluoro-2-phenylbut-3-yn-2-yl perfluorobenzoate (**1a**) with 2 equivalents of indole (**2a**) and 1.2 equivalents of *N*,*N*-diisopropylethylamine in the presence of 5 mol% of CuOTf·1/2 C_6H_6 and 10 mol% of (4*S*,5*R*)-diPh-Pybox (**L1**) in methanol at room temperature for 1 hour gave 3-(1,1,1-trifluoro-2-phenylbut-3-yn-2-yl)-1*H*-indole (**3a**) in 41% yield with 47% *ee* (*S*; Table 1, entry 1). Unfortunately, other propargylic esters such as acetate and *tert*-butyl carbonate were not applicable. The reactivity and enantioselectivity dramatically depend on the nature of the base employed. In fact, cyclic amines worked as more effective bases to promote the catalytic reactions smoothly (Table 1, entries 2–8). Especially, the use of 4-methylmorpholine (**B1**) as a base achieved the best reactivity and enantioselectivity (Table 1, entry 2).

The use of other pybox ligands such as (*S*)-Ph-Pybox (**L2**), (*S*)-Me-Pybox (**L3**), and (*R*)-Cl-MeO-BIPHEP (**L4**), which were previously reported to work as effective optically active ligands toward copper-catalyzed enantioselective propargylic amination and etherification,[8] did not give satisfactory results (Table 1, entries 9–11). When the reaction using **L1** was carried out at a lower reaction temperature, such as 0 °C, **3a** was obtained in 81% yield with 91% *ee* (Table 1, entry 12). Use of a larger amount of **B1** (2 equiv) was effective in leading to the reaction completion in a shorter reaction time (Table 1, entry 13). The highest enantioselec-

Table 1: Copper-catalyzed enantioseletive propargylation of indole with 1,1,1-trifluoro-2-phenylbut-3-yn-2-yl perfluorobenzoate (**1a**).[a]



Entry	**2**	Ligand	Base	*t* [h]	Yield [%][b]	*ee* [%][c]
1	**2a**	**L1**	*i*Pr$_2$NEt	1	41	47 (*S*)
2	**2a**	**L1**	**B1**	6	81	86 (*S*)
3	**2a**	**L1**	**B2**	39	71	87 (*S*)
4	**2a**	**L1**	**B3**	14	80	84 (*S*)
5	**2a**	**L1**	**B4**	6	72	85 (*S*)
6	**2a**	**L1**	**B5**	11	79	85 (*S*)
7	**2a**	**L1**	**B6**	18	20	72 (*S*)
8	**2a**	**L1**	DABCO	0.5	42	80 (*S*)
9	**2a**	**L2**	**B1**	7	38	34 (*S*)
10	**2a**	**L3**	**B1**	6	13	28 (*S*)
11	**2a**	**L4**	**B1**	5	trace	–
12[d]	**2a**	**L1**	**B1**	92	81	91 (*S*)
13[d,e]	**2a**	**L1**	**B1**	48	79	91 (*S*)
14[d,e]	**2b**	**L1**	**B1**	24	85	95 (*S*)



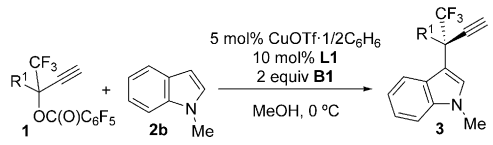
[a] Reaction of **1a** (0.20 mmol) with **2a** (0.40 mmol) in the presence of CuOTf·1/2 C_6H_6 (0.010 mmol), ligand (0.020 mmol), and base (0.24 mmol) in methanol (2 mL) at room temperature. [b] Yield of isolated product. [c] Determined by HPLC. [d] At 0 °C. [e] 2 equiv of **B1**. DABCO = 1,4-diazabicyclo[2.2.2]octane, Tf = trifluoromethanesulfonyl.

tivity (95% *ee*) was observed in the reaction of **1a** with 1-methylindole (**2b**) under the same reaction conditions (Table 1, entry 14).

Reactions of other propargylic perfluorobenzoates with **2b** were carried out by using **L1** as an optically active ligand at 0 or −10 °C in methanol. Typical results are shown in Table 2. Introduction of a substituent such as fluoro, chloro, bromo, methoxy, phenyl, and methyl group at the *para*-position of the benzene ring of the propargylic perfluorobenzoates (**1b**–**g**) gave a similarly high enantioselectivities (93–96% *ee*) (Table 2, entries 1–6).[12,13] Although the presence of a methyl group at the *meta*-position of the benzene ring of the propargylic perfluorobenzoate **1h** gave the highest enantioselectivity (97% *ee*; Table 2, entry 7), no reaction occurred at all with that bearing the *ortho*-methyl-substituted benzene ring (Table 2, entry 8). A similarly high enantioselectivity was observed in the use of either 2-naphthyl or 2-thienyl group at the propargylic position of the propargylic perfluorobenzoate (Table 2, entries 9 and 10).

In contrast to the reaction of 2-phenylbut-3-yn-2-yl perfluorobenzoate (**1l**) with 2 equivalents of **2a** under similar reaction conditions, where **3l** was obtained in a low yield together with the formation of the corresponding methyl ether (2-phenylbut-3-yn-2-yl methyl ether) and 2-phenylbut-1-en-3-yne as shown in Eq 1, the reaction of 3-ethynyl-1-

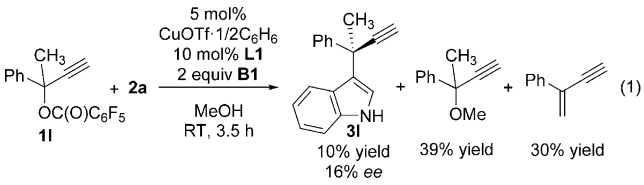
Table 2: Enantioseletive propargylation of 1-methylIndole (**2b**) with propargylic perfluorobenzoates (**1**).[a]

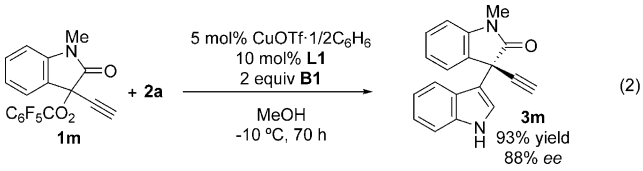


Entry	R^1 (**1**)	*t* [h]	Yield [%][b]	*ee* [%][c]
1[d]	4-FC_6H_4 (**1b**)	64	76 (**3c**)	95
2	4-ClC_6H_4 (**1c**)	24	71 (**3d**)	93
3[d]	4-BrC_6H_4 (**1d**)	110	82 (**3e**)	94
4[d]	4-MeOC_6H_4 (**1e**)	72	82 (**3f**)	95
5	4-PhC_6H_4 (**1f**)	72	59 (**3g**)	94
6[d]	4-MeC_6H_4 (**1g**)	72	86 (**3h**)	96
7[d]	3-MeC_6H_4 (**1h**)	72	75 (**3i**)	97
8[e]	2-MeC_6H_4 (**1i**)	30	0	–
9[d]	2-naphthyl (**1j**)	192	85 (**3j**)	95
10[d]	2-thienyl (**1k**)	64	84 (**3k**)	97

[a] Reaction of **1** (0.20 mmol) with **2b** (0.40 mmol) in the presence of CuOTf·1/2 C_6H_6 (0.010 mmol), **L1** (0.020 mmol), and **B1** (0.40 mmol) in methanol (2 mL) at 0 °C. [b] Yield of isolated product. [c] Determined by HPLC. [d] At −10 °C. [e] At room temperature.

methyl-2-oxoindolin-3-yl perfluorobenzoate (**1m**) with 2 equivalents of **2a** at −10 °C gave the corresponding propargylated indole **3m** in 93% yield with 88% *ee* (*R*) [Eq. 2].[12] This result indicates that a propargylic ester bearing a cyclic moiety at the propargylic position is applicable as a substrate.

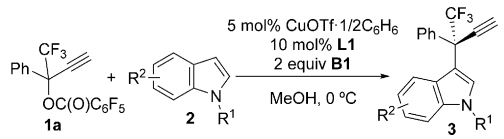




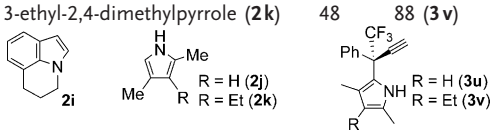
Propargylation of other indoles (**2c**–**i**) also proceeded smoothly to give the corresponding propargylated indoles (**3n**–**t**) in good to high yields with an excellent enantioselectivity (89–96% *ee*; Table 3, entries 1–7). Reactions of **1a** with 2,4-dimethylpyrroles (**2j** and **2k**) gave the corresponding propargylated pyrroles (**3u** and **3v**) in high yields with a slightly lower enantioselectivity (Table 3, entries 8 and 9).

To obtain more information on the reactive species of the real copper catalyst, we prepared the copper-pybox complex $[Cu_2(\mathbf{L1})_2(\mu\text{-Cl})][CuCl_2]$[13,14] (**4**) from the reaction of CuCl with 0.7 equivalents of **L1** in acetone at room temperature for 24 hours (Scheme 1a). The molecular structure of **4** was unambiguously characterized by X-ray crystallography, and an ORTEP drawing of the cationic part of **4** is shown in

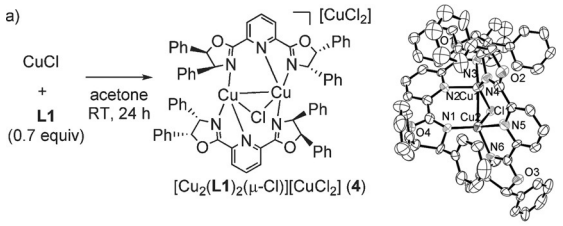
Table 3: Enantioseletive propargylation of indoles and pyrroles (**2**) with propargylic perfluorobenzoates (**1a**).[a]



Entry	R^1	R^2 (**2**)	t [h]	Yield [%][b]	*ee* [%][c]
1	H	6-Me (**2c**)	17	90 (**3n**)	90
2	H	7-Me (**2d**)	20	86 (**3o**)	93
3	H	7-OMe (**2e**)	22	82 (**3p**)	89
4[d]	Me	7-OMe (**2f**)	120	61 (**3q**)	96
5	Et	– (**2g**)	20	86 (**3r**)	89
6[d]	allyl	– (**2h**)	20	57 (**3s**)	92
7[d]	lilolidine (**2i**)		72	86 (**3t**)	96
8	2,4-dimethylpyrrole (**2j**)		20	83 (**3u**)	80
9[d]	3-ethyl-2,4-dimethylpyrrole (**2k**)		48	88 (**3v**)	80



[a] Reaction of **1a** (0.20 mmol) with **2** (0.40 mmol) in the presence of CuOTf·1/2 C_6H_6 (0.010 mmol), **L1** (0.020 mmol), and **B1** (0.40 mmol) in methanol (2 mL) at 0 °C. [b] Yield of isolated product. [c] Determined by HPLC. [d] At −10 °C.



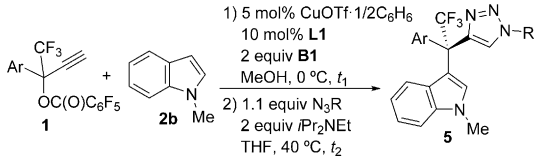
Scheme 1. Preparation of a dinuclear copper complex bearing a pybox ligand, and its catalytic activity.

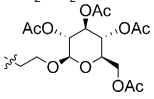
Scheme 1a. Then, we carried out the catalytic reaction by using **4** as a catalyst as shown in Scheme 1b. Although the enantioselectivity of the product **3b** is almost the same with that obtained by using the copper complex formed in situ from CuCl and **L1**, the yield of **3b** is lower. At present, we have not yet discovered the reason, but the anion $[CuCl_2]^-$ in **4** may inhibit the catalytic reaction. This result indicates that the dinuclear copper complex bearing 2 equivalents of **L1** may work as a reactive species.

A proposal of the dicopper complex, such as **4**, as a reactive species in the present propargylation is also supported by a nonlinear relationship[15] between the *ee* value of optically active ligand **L1** and the *ee* value of **3a**, which is produced by treatment of **1a** with **2a** in methanol at 0 °C for 48 hours in the presence of 5 mol% of CuOTf·1/2 C_6H_6 and 10 mol% of **L1** as shown in Scheme 1c. This result provides direct evidence that a dinuclear copper complex works as a key reactive species in the propargylation.[8k]

Based on the results of enantioselective propargylation of indoles shown in Tables 2 and 3, we subjected propargylation products to a subsequent Huisgen cycloaddition to obtain chiral triarylmethanes bearing a trifluoromethyl moiety. Typical results are shown in Table 4. Treatment of **1a** with

Table 4: One-pot enantioselective synthesis of triayrlmethane (**5**).[a]

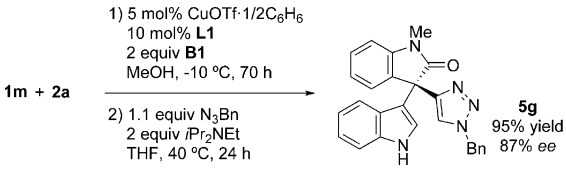


Entry	Ar (**1**)		R	t_1, t_2 [h]	Yield [%][b]	*ee* [%][c]
1	Ph	(**1a**)	Bn	24, 40	89 (**5a**)	96
2[d]	2-thienyl	(**1k**)	Bn	72, 24	86 (**5b**)	97
3	Ph	(**1a**)	CH_2(4-C_6H_4Me)	24, 20	88 (**5c**)	95
4	Ph	(**1a**)	CH_2(1-pyrenyl)	24, 24	77 (**5d**)	96
5	Ph	(**1a**)	CH_2CO_2Me	24, 24	85 (**5e**)	95
6	Ph	(**1a**)		24, 24	84 (**5f**)	20:1[e]

[a] After reaction of **1** (0.20 mmol) with **2b** (0.40 mmol) in the presence of CuOTf·1/2 C_6H_6 (0.010 mmol), **L1** (0.020 mmol), and **B1** (0.40 mmol) in methanol (2 mL) at 0 °C, treatment with azides (0.30 mmol) and iPr_2NEt (0.40 mmol) was carried out in one pot. [b] Yield of isolated product. [c] Determined by HPLC. [d] At −10 °C for propargylation reaction. [e] Diastereomeric ratio. THF = tetrahydrofuran.

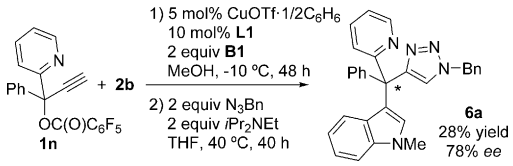
2 equivalents of **2b** and 2 equivalents of **B1** in the presence of 5 mol% of CuOTf·1/2 C_6H_6 and 10 mol% of **L1** in methanol at 0 °C for 24 hours, followed by treatment with 1.1 equivalents of benzyl azide and 2 equivalents of *N*,*N*-diisopropylethylamine in THF at 40 °C for 40 hours gave 3-(1-(1-benzyl-1*H*-1,2,3-triazol-4-yl)-2,2,2-trifluoro-1-phenylethyl)-1-methyl-1*H*-indole (**5a**) in 89% yield with 96% *ee* (Table 4, entry 1). Separately, we carried out the reaction of **3b** (95% *ee*) with 1.1 equivalents of benzyl azide and 2 equivalents of *N*,*N*-diisopropylethylamine in the presence of 5 mol% of CuOTf·1/2 C_6H_6 and 10 mol% of **L1** in THF at 40 °C for 20 hours to give **5a** in 99% yield with 95% *ee*. This result indicates that the Huisgen cycloaddition between **3b** and benzyl azide took place without loss of the optical purity. A similarly high enantioselectivity was observed in the use of a 2-thienyl group at the propargylic position of the propargylic perfluorobenzoate (Table 4, entry 2). The use of other substituents, such as *p*-tolyl, 1-pyrenyl, and methoxycarbonyl groups, on the azide under the same reaction conditions gave the corresponding triarylmethanes in high yields with an

excellent enantioselectivity (Table 4, entries 3–5). Here, the reaction with optically active 2-azidoethyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside also proceeded smoothly with an excellent diastereoselectivity (Table 4, entry 6). When **1m** was used as propargylic ester bearing a cyclic moiety at the propargylic position, the corresponding triarylmethane was obtained in 95% yield with 87% *ee* (*R*) [Eq. 3]. The result of the sequential reactions provides a synthetically useful approach to construct chiral triarylmethanes bearing a quaternary carbon center.



(3)

Finally, we applied the present reaction system to the enantioselective preparation of a tetraarylmethane by using a tertiary propargylic esters, bearing two different aromatic moieties at the propargylic position, as substrates. We investigated the copper-catalyzed propargylation of indoles with 1-phenyl-1-(pyridin-2-yl)prop-2-ynyl perfluorobenzoate (**1n**) with 2 equivalents of **2b** and 2 equivalents of **B1** in the presence of 5 mol% of CuOTf·1/2 C_6H_6 and 10 mol% of **L1** in methanol at −10 °C for 48 hours followed by treatment with 2 equivalents of benzyl azide and 2 equivalents of *N*,*N*-diisopropylethylamine in THF at 40 °C for 40 hours to give 3-((1-benzyl-1*H*-1,2,3-triazol-4-yl)(phenyl)(pyridin-2-yl)methyl)-1-methyl-1*H*-indole (**6a**) in 28% yield with 78% *ee* (Scheme 2). Unfortunately, the sequential Huisgen cycloaddition did not proceed smoothly, probably because of the steric hindrance at the propargyl position of the indole, even though the propargylation took place with a high enantioselectivity.



Scheme 2. Enantioselective synthesis of tetra-arylmethane.

In summary, we have succeeded in novel enantioselective copper-catalyzed proparygylation of indoles with propargylic esters. This reaction is the first successful example of enantioselective construction of an all-carbon quaternary stereocenter based on a propargyl substitution strategy. The major advantage of this strategy is that a further derivatization of the terminal alkyne moiety, into an aromatic ring, which is quite useful for the construction of chiral all-carbon substituted tri- and tetra-arylmethanes. The one-pot procedure demonstrated in this manuscript provides the first successful example of the enantioselective preparation of a tetraarylmethane. We consider the methodology described herein as opening a new synthetic route towards chiral tri- and tetra-arylmethanes. Further application of this methodology is now in progress.

Acknowledgments

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Keywords: alkynes · copper · cycloadditions · enantioselectivity · synthetic methods

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