[4+2] Cycloadditions

Functionalized 1,2-Dihydronaphthalenes from the Cu(OTf)$_2$-Catalyzed [4+2] Cycloaddition of *o*-Alkynyl(oxo)benzenes with Alkenes**

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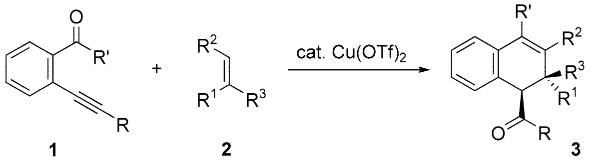
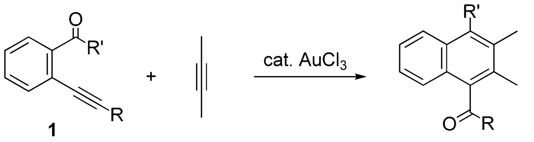
As dihydronaphthalene derivatives are useful starting materials for the synthesis of biologically active cyclic molecules, numerous synthetic approaches to these compounds have been reported. Among them, the dearomatization of naphthalene derivatives by the nucleophilic addition of certain organometallic reagents is one of the most useful and convenient methods.[1–6] However, to enhance the electrophilicity of naphthalene derivatives, the presence of electron-withdrawing groups such as oxazolino and imino groups on the naphthalene ring is required. A drawback of the nucleophilic-addition method is the difficulty in application to a wide range of substrates. In this contribution we report an unprecedented Cu(OTf)$_2$-catalyzed cycloaddition between *o*-(alkynyl)benzaldehydes (or *o*-(alkynyl)phenyl ketones) **1** and olefins **2**, which affords 1,2-dihydronaphthalene derivatives **3** bearing a ketone function at the 1-position [Eq. (1)].



(1)

We recently reported that the AuCl$_3$-catalyzed reaction of *o*-(alkynyl)benzaldehydes with alkynes produces the [4+2] benzannulation products, naphthalene derivatives, in good to high yields [Eq. (2)].[7] We thought that if we could use alkenes, instead of alkynes, dehydronaphthalene derivatives would be obtained, and the scope of [4+2] cycloaddition would be expanded greatly. The reaction of *o*-(phenylethynyl)benzaldehyde (**1a**, R = Ph, R′ = H) with 1.2 equiv styrene (**2a**, R^1 = Ph, R^2 = H, R^3 = H) in the presence of 10 mol% AuCl$_3$ in THF at 90 °C for 20 h gave 1-benzoyloxy-2-phenyl-1,2-dihydronaphthalene (**3a**) in 25% yield (Table 1, entry 1). The stereochemical relationship between benzoyl group and phenyl group was *trans*. To improve the yield of **3a**, we examined several other Lewis acids. Although the CuOTf-catalyzed reaction gave **3a** in 51% yield, the *cis* isomer of **3a** was also produced in 20% yield (entry 2). When the reaction was carried out with Cu(OTf)$_2$ as the catalyst, the yield of **1a** increased dramatically up to 96% without the formation of the *cis* isomer (entry 3). Besides THF, other solvents such as 1,2-dimethoxyethane and 1,4-dioxane could be used for the present reaction (entries 4 and 5). However, less polar solvents such as toluene and 1,2-dichloroethane gave **3a** in lower yields (entries 6 and 7).



(2)

We next examined the Cu(OTf)$_2$-catalyzed reaction of aldehydes and ketones **1b–e** with olefins **2a–k** (Table 2). The

Table 1: The Lewis acid catalyzed reaction of *o*-(phenylethynyl)benzaldehyde (**1a**) with styrene (**2a**) to give **3a** (R = R^1 = Ph, R′ = R^2 = R^3 = H).[a]

Entry	Catalyst	Solvent	Conditions	Yield of **3a** [%][b]
1	AuCl$_3$	THF	90 °C, 20 h	25
2	CuOTf	THF	80 °C, 15 h	51[c]
3	Cu(OTf)$_2$	THF	80 °C, 10 h	96
4	Cu(OTf)$_2$	(CH$_2$OMe)$_2$	80 °C, 10 h	92
5	Cu(OTf)$_2$	1,4-dioxane	80 °C, 10 h	90
6	Cu(OTf)$_2$	toluene	80 °C, 15 h	62
7	Cu(OTf)$_2$	(CH$_2$Cl)$_2$	60 °C, 3 h	72

[a] The reaction was carried out with **1a** (1 equiv) and **2a** (1.2 equiv) in the presence of the Lewis acid (10 mol%). [b] Yield of isolated product. [c] The *cis* isomer of **3a** was obtained in 20% yield.

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[**] OTf = Trifluoromethylsulfonate.

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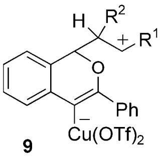
Table 2: The Cu(OTf)$_2$-catalyzed reaction of **1** with olefins **2** to give products **3**.[a]

Entry	1	R	R′	2	R^1	R^2	R^3	3	R	R′	R^1	R^2	R^3	Yield [%][b]
1	**1b**	Bu	H	**2a**	Ph	H	H	**3b**	Bu	H	Ph	H	H	56
2	**1c**	H	H	**2a**	Ph	H	H	**3c**	H	H	Ph	H	H	49
3	**1d**	Ph	Ph	**2a**	Ph	H	H	**3d**	Ph	Ph	Ph	H	H	86
4	**1e**	Ph	Me	**2a**	Ph	H	H	**3e**	Ph	Me	Ph	H	H	26
5	**1e**	Ph	Me	**2a**	Ph	H	H	**3e**	Ph	Me	Ph	H	H	51[c]
6	**1a**	Ph	H	**2b**	p-MeC$_6$H$_4$	H	H	**3f**	Ph	H	p-MeC$_6$H$_4$	H	H	98
7	**1a**	Ph	H	**2c**	p-CF$_3$C$_6$H$_4$	H	H	**3g**	Ph	H	p-CF$_3$C$_6$H$_4$	H	H	82
8	**1a**	Ph	H	**2d**	2-naphthyl	H	H	**3h**	Ph	H	2-naphthyl	H	H	56
9	**1a**	Ph	H	**2d**	2-naphthyl	H	H	**3h**	Ph	H	2-naphthyl	H	H	90[c]
10	**1a**	Ph	H	**2e**	C$_4$H$_9$	H	H	**3i**	Ph	H	C$_4$H$_9$	H	H	90
11	**1a**	Ph	H	**2f**	-(CH$_2$)$_6$-		H	**3j**	Ph	H	-(CH$_2$)$_6$-		H	44
12	**1a**	Ph	H	**2f**	-(CH$_2$)$_6$-		H	**3j**	Ph	H	-(CH$_2$)$_6$-		H	75[c]
13	**1a**	Ph	H	**2g**	Ph	H	Ph	**3k**	Ph	H	Ph	H	Ph	88
14	**1a**	Ph	H	**2h**	Ph	H	Me	**3l**	Ph	H	Ph	H	Me	76
15	**1a**	Ph	H	**2i**	H	Me	Ph	**3m**	Ph	H	Ph	Me	H	65
16	**1a**	Ph	H	**2j**	Ph	Me	H	**3m**	Ph	H	Ph	Me	H	62
17	**1a**	Ph	H	**2k**	Me	Me	Me	**3n**	Ph	H	Me	Me	Me	67

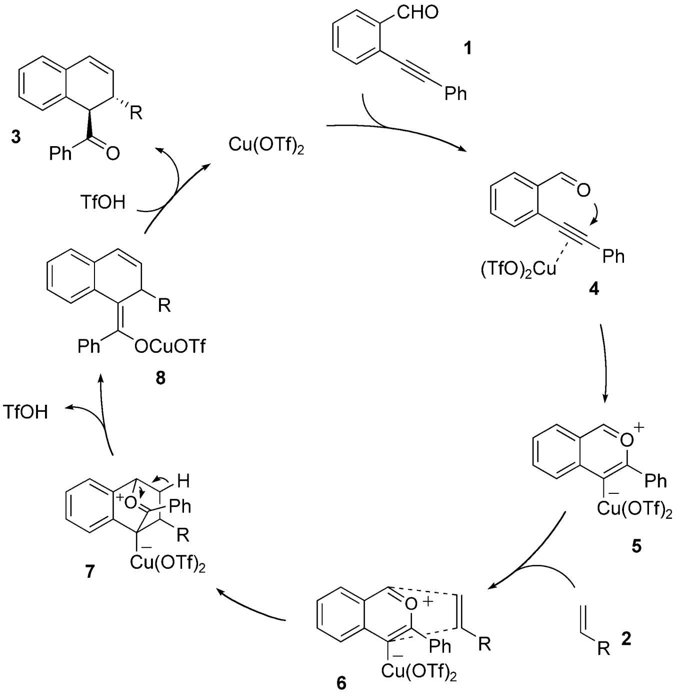
[a] The reaction was carried out with **1** (1 equiv) and **2** (1.2 equiv) in the presence of Cu(OTf)$_2$ (10 mol%) in THF at 80 °C unless otherwise noted. [b] Yield of isolated product. [c] The reaction was performed in the presence of 10 mol% CF$_3$CO$_2$H as an additive.

reaction of **1b**, bearing a hexynyl group at the *ortho* position, with **2a** gave **3b** in 56% yield (entry 1). The dihydronaphthalene derivative **3c** bearing a formyl substituent was prepared by the reaction of **1c**, which has a terminal alkyne (R = H), with styrene (**2a**) (entry 2). The substrate with a ketone function (**1d**, R′ = Ph) can be used for the present reaction, and **3d** was obtained in a high yield (entry 3). Although the reaction of **1e**, which has an acyl group, with **2a** afforded **3f** in low yield (entry 4), the yield was increased up to 51% when the reaction was carried out in the presence of 10 mol% CF$_3$CO$_2$H (entry 5). Not only styrene (**2a**) but also the mono-, di-, and trisubstituted olefins **2b**–**k** could be employed in the present reaction, and the corresponding products were obtained in good to high yields (entries 6–17). In entries 9 and 12, the yields of **3h** and **3j** were increased by addition of a catalytic amount of CF$_3$CO$_2$H.

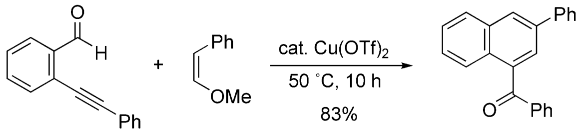
A plausible mechanism for the present reaction is shown in Scheme 1. The coordination of the triple bond of **1** to Cu(OTf)$_2$ enhances the electrophilicity of the alkyne, and the subsequent nucleophilic attack (as shown in **4**) of the carbonyl oxygen atom on the electron-deficient alkyne forms the cupric ate complex **5**. The Diels–Alder reaction of **5** with olefin **2** gives the intermediate **7** through **6**. Due to the instability of **7**, the cleavage of the carbon–oxygen bond followed by elimination of proton occurs to give the copper enolate **8** and TfOH. Protonation of **8** by TfOH gives **3**, and the copper catalyst is regenerated. In all cases with Cu(OTf)$_2$ as a catalyst, the *trans* isomer was obtained as the sole product. When the *cis* isomer of **3a** was treated with a catalytic amount of Cu(OTf)$_2$ in THF at 80 °C, the isomerization to the *trans* isomer **3a** occurred. This result clearly shows that the exclusive formation of the *trans* products is due to their thermodynamic stabilities. The regioselective formation of **3** in the [4+2] cycloaddition [Eq. (1)] is accounted for by considering a carbocation intermediate **9** on the way from **6** to **7**. In the reaction with olefins bearing aryl groups (entries 1–9), the carbocation **9** stabilized by neighboring aryl groups (R^1 = aryl) is preferable to the alternative regioisomeric carbocation in which R^2 is adjacent to the carbocation. In the reaction of hexene (entry 10) the formation of **9** with a butyl group at R^1 is preferred owing to its electron-donating effect.



Interestingly, the reaction of **1a** with β-methoxy-styrene **2l** did not give the corresponding 1,2-dihydronaphthalene but afforded the naphthalene derivative **10** in 83% yield [Eq. (3)]. Perhaps the expected [4+2] cycloaddition took place in a similar way as mentioned above, and the resulting 2-



Scheme 1. Plausible reaction mechanism.



1a **2l** **10** (3)

methoxydehydronaphthalene underwent elimination of methanol to give **10**.

A novel and efficient synthetic method for 1,2-dihydronaphthalenes has been developed. We are now at a position to synthesize regioselectively functionalized 1,2-dihydronaphthalene derivatives starting from *o*-(alkynyl)benzaldehydes and *o*-(alkynyl)aryl ketones. Further studies to elucidate the mechanism of this novel reaction and to extend the scope of its synthetic utility are in progress in our laboratory.

Experimental Section

Typical experimental procedure: Synthesis of **3a**: To a solution of $Cu(OTf)_2$ (18.0 mg, 10 mol%) in THF (2 mL) were added **1a** (103 mg, 0.5 mmol) and **2a** (0.07 mL, 0.6 mmol) successively at room temperature under Ar atmosphere. The resulting mixture was stirred at 80°C for 10 h and then cooled to room temperature. A saturated aqueous solution of NH_4Cl was added, and the mixture was extracted with ether three times. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated to dryness to leave the crude product, which was purified by silica gel column chromatography using hexane/EtOAc (8:1) as the eluent to give **3a** (149 mg, 0.48 mmol) in 96% yield.

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Keywords: cycloaddition · dihydronaphthalene · Lewis acids

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