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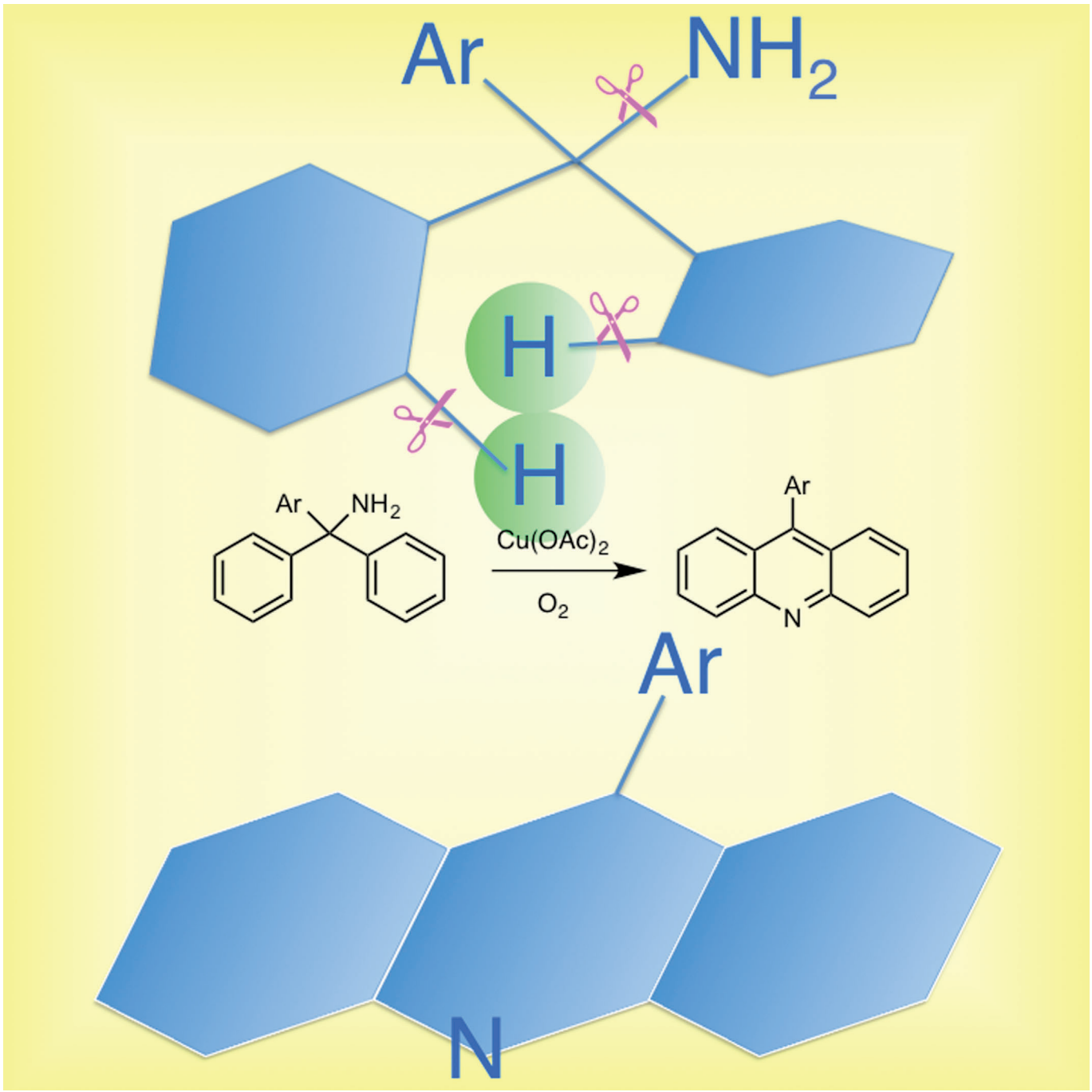
Synthetic Methods

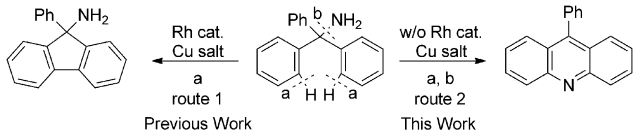
Unexpected Cyclization of Tritylamines Promoted by Copper Salt through C–H and C–N Bond Cleavages to Produce Acridine Derivatives

Ryosuke Morioka,[a] Koji Hirano,[a] Tetsuya Satoh,*[a, b] and Masahiro Miura*[a]



Abstract: Herein, we demonstrate that tritylamines undergo an unprecedented copper-mediated cyclization involving the cleavages of two C–H bonds and one C–N bond to give 9-arylacridine derivatives. This kind of acridines is of interest due to their biological properties and their unique optical and electro- and photochemical properties. Some of obtained acridine derivatives exhibit intense fluorescence in the solid state.

The transition-metal-catalyzed C–H bond-functionalization reactions have attracted much attention in organic-synthesis field, because they enable to simplify synthetic routes to various complex molecules.[1] Among a variety of potential C–H transformation reactions is the intramolecular dehydrogenative cyclizations involving twofold C–H bond cleavages. They are highly useful for constructing fused polycyclic frameworks, which are of interest for their application to various fine chemicals.[2,3] As such an example, we recently reported that tritylamine undergoes dehydrogenative cyclization in the presence of $[RhCl(cod)]_2$ and $Cu(OAc)_2{\cdot}H_2O$ as catalyst and oxidant, respectively, accompanied by amino-directed C–H bond cleavage to produce 9-phenyl-9*H*-fluoren-9-amine in high yield (route 1 in Scheme 1).[2b] In the course of our further study of

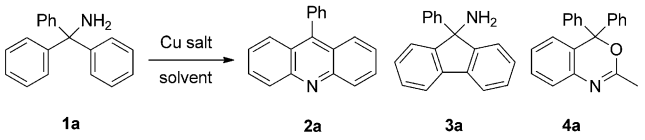


Scheme 1. Dehydrogenative cyclization of tritylamine.

the cyclizative coupling, we have discovered that treatment of the same substrate in the absence of any rhodium catalyst gives rise to an unexpected cyclization product, 9-phenylacrydine, accompanied by the cleavages of two C–H bonds and one C–N bond (route 2 in Scheme 1). In this case, fluorene formation was not detected at all. This new cyclization appears to involve a mechanistically fascinating copper series of reactions. 9-Phenylacrydine derivatives are also an important class of molecules because of their biological properties, such as DNA intercalation and antitumor activities,[4] as well as their unique optical and electro- and photochemical properties.[5] Although various synthetic methods for acrydines through transition-metal-catalyzed coupling reactions have been recently developed,[6] the present cyclization provides a more simple, straightforward route from readily available substrates.

Similar to our previous work,[2b] treatment of tritylamine (**1a**; 0.5 mmol) in the presence of $[RhCl(cod)]_2$ (0.01 mmol) and $Cu(OAc)_2{\cdot}H_2O$ (1 mmol) in *o*-xylene (3 mL) at 160 °C for 8 h under N_2 gave 9-phenyl-9*H*-fluoren-9-amine (**3a**) in 90% yield (entry 1 in Table 1). Eliminating the rhodium catalyst dramatically changed the cyclization mode. Thus, in the absence of $[RhCl(cod)]_2$, a mixture of 9-phenylacrydine (**2a**) and 2-methyl-4,4-diphenyl-4*H*-3,1-benzoxazine (**4a**) was obtained with no formation of **3a** (entry 2).[7,8] Further elimination of the copper salt resulted in the complete recovery of **1a** (entry 3). Other copper salts, such as $CuCO_3$ (entry 4), Cu_2O (entry 5), $CuCl_2$ (entry 6), and $Cu(acac)_2$ (acac = acetylacetonate, entry 7), were ineffective or far less effective. $Cu(OCOCF_3)_2$ was as effective as the acetate (entry 8). The use of anhydrous $Cu(OAc)_2$ was found to improve the yield of **2a** up to 56% (entry 9). In this case, formation of **4a** was effectively suppressed (entry 9 vs. 2), although the reason is obscure at the present stage. Moreover, when the reaction was conducted under air upon gentle heating at reflux in mesitylene (bath temperature 170 °C), **2a** was obtained in 70% yield along with a minuscule amount of **4a** (entry 10). In other solvents, such as *N*,*N*-dimethylacetamide (DMA), diglyme, *o*-$C_6H_4Cl_2$, and dodecane, the **2a** yield de-

Table 1. Reaction of tritylamine (**1a**).[a]



1a **2a** **3a** **4a**

Entry	Cu salt [mmol]	Solvent	*T* [°C]	Yield [%][b]		
				2a	**3a**	**4a**
1[c]	$Cu(OAc)_2{\cdot}H_2O$ [1]	*o*-xylene	160	0	90	0
2	$Cu(OAc)_2{\cdot}H_2O$ [2]	*o*-xylene	160	34	0	22
3	–	*o*-xylene	160	0	0	0
4	$CuCO_3$ [2]	*o*-xylene	160	0	0	0
5	Cu_2O [2]	*o*-xylene	160	0	0	0
6	$CuCl_2$ [2]	*o*-xylene	160	0	0	0
7	$Cu(acac)_2$ [2]	*o*-xylene	160	12	0	0
8	$Cu(OCOCF_3)_2$ [2]	*o*-xylene	160	32	0	0
9	$Cu(OAc)_2$ [2]	*o*-xylene	160	56	0	8
10[d]	$Cu(OAc)_2$ [2]	mesitylene	170	70 (62)	0	1
11[d]	$Cu(OAc)_2$ [2]	DMA	170	22	0	tr
12[d]	$Cu(OAc)_2$ [2]	diglyme	170	36	0	7
13[d]	$Cu(OAc)_2$ [2]	*o*-$C_6H_4Cl_2$	170	46	0	0
14[d]	$Cu(OAc)_2$ [2]	dodecane	170	62	0	tr
15[d]	$Cu(OAc)_2$ [3]	mesitylene	170	62	0	tr
16[d]	$Cu(OAc)_2$ [0.5]	mesitylene	170	60	0	1
17[d]	$Cu(OAc)_2$ [0.1]	mesitylene	170	28	0	tr
18[e]	$Cu(OAc)_2$ [0.5]	mesitylene	170	72 (72)	0	tr

[a] Reaction conditions: **1a** (0.5 mmol) and Cu salt in solvent (3 mL) under N_2 for 6–8 h, unless otherwise noted. [b] GC yield is based on the amount of **1a** used. Value in parentheses indicates yield after purification. [c] With $[RhCl(cod)]_2$ (0.01 mmol). [d] Under air (1 atm). [e] Under O_2 (1 atm). tr = traces.

[a] *R. Morioka, Dr. K. Hirano, Prof. Dr. T. Satoh, Prof. Dr. M. Miura*
Department of Applied Chemistry
Faculty of Engineering, Osaka University
Suita, Osaka 565-0871 (Japan)
E-mail: satoh@chem.eng.osaka-u.ac.jp
miura@chem.eng.osaka-u.ac.jp

[b] *Prof. Dr. T. Satoh*
JST, ACT-C, 4-1-8 Honcho, Kawaguchi, Saitama 332-0012 (Japan)

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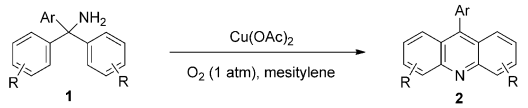
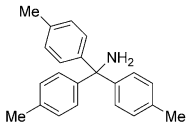
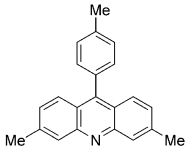
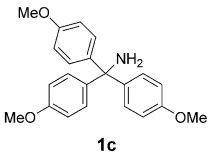
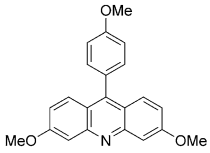
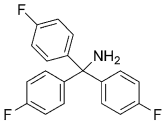
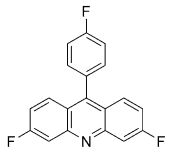
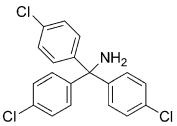
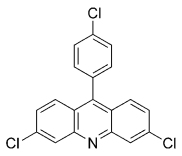
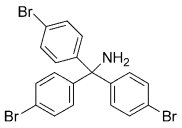
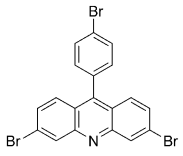
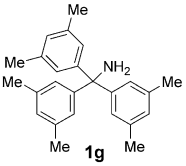
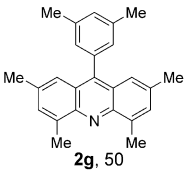
creased (entries 11–14). Although increasing and decreasing the amount of $Cu(OAc)_2$ to 3 and 0.5 mmol did not affect the result severely (entries 15 and 16), its further decrease to 0.1 mmol reduced the **2a** yield to 28% (entry 17). Fortunately, even with 0.5 mmol of copper salt, **2a** was obtained in good isolated yield by conducting the reaction under O_2 (1 atm; entry 18).

Under the optimized conditions, the cyclization of variously substituted triarylmethylamines **1b**–**g** was examined (Table 2). Treatment of tris(4-methylphenyl)methylamine (**1b**) and tris(4-methoxylphenyl)methylamine (**1c**) gave the corresponding 3,6-disubstituted 9-arylacridines **2b** and **c** in 72 and 68% yield, respectively (entries 1 and 2). Halogenated tritylamines **1d**–**f** also underwent the cyclization to give acridines **2d**–**f**, although prolonged reaction times were needed (entries 3–5). Even in the reaction of **1f**, no other product could be detected by GC and GC-MS, although the substrate was completely consumed. Interestingly, the cyclization of a highly substituted substrate, tris(3,5-dimethylphenyl)methylamine (**1g**), proceeded smoothly under standard conditions to give 9-(3,5-dimethylphenyl)-2,4,5,7-tetramethylacridine (**2g**) selectively (entry 6).

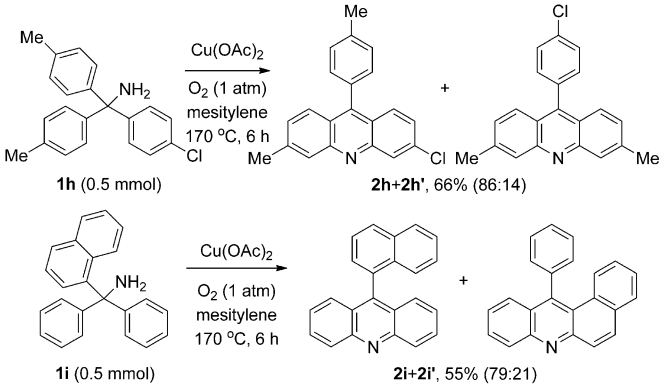
Table 2. Reaction of triarylmethylamine **1**.[a]



Entry	1	t [h]	Product, yield [%][b]
1	 **1b**	6	 **2b**, 72
2	 **1c**	6	 **2c**, 68
3[c]	 **1d**	20	 **2d**, 53
4[c]	 **1e**	18	 **2e**, 66
5[c]	 **1f**	20	 **2f**, 13
6	 **1g**	6	 **2g**, 50

[a] Reaction conditions: **1a** (0.5 mmol), $Cu(OAc)_2$ (0.5 mmol) in mesitylene (3 mL) at 170 °C under O_2. [b] Isolated yield. [c] By using $Cu(OAc)_2$ (2 mmol).

Next, the reactions of unsymmetrically substituted triarylmethylamines were examined (Scheme 2). Treatment of (4-chlorophenyl)bis(4-methylphenyl)methylamine (**1h**) under

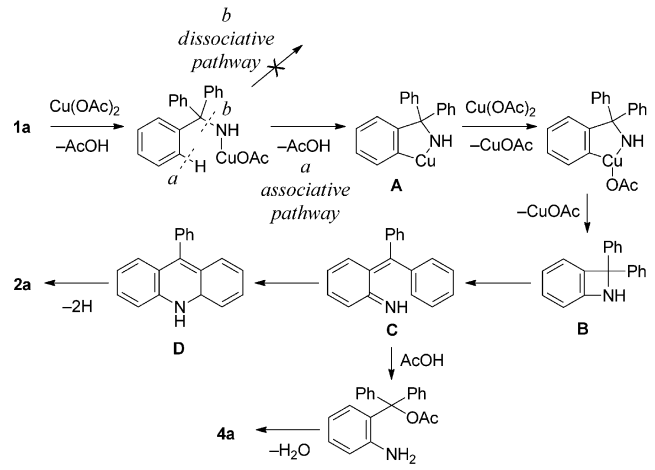


Scheme 2. Reactions of **1h** and **i**.

standard conditions gave a mixture of cyclization products, **2h** and **h′** (86:14, 66% total yield). This indicates that the C–H cleavage on the chloro-substituted phenyl ring preferably takes place compared to the methyl-substituted rings, and thus, some electronic control can intervene. In the reaction of (1-naphthyl)diphenylmethylamine (**1i**), the phenyl groups were involved in the cyclization in preference to the naphthyl moiety (**2i**/**2i′** 79:21), probably due to steric reasons. In contrast to triarylmethylamines, diphenyl(3-thienyl)methylamine and 1,1-diphenylethylamine did not undergo the cyclization at all. In these cases, these amines were completely consumed by unidentified side reactions.

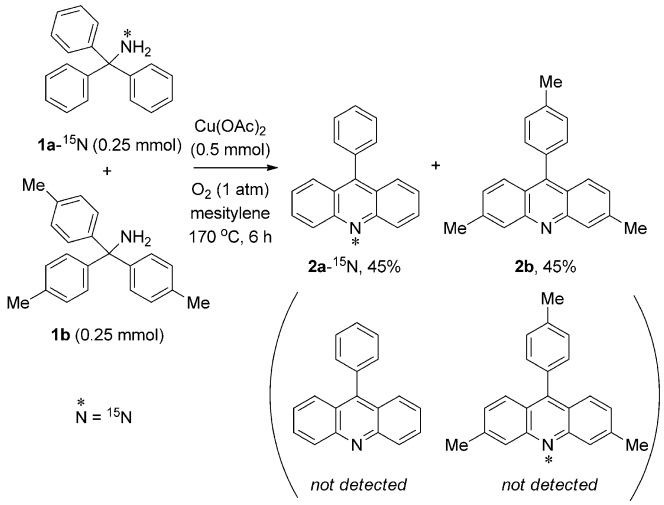
A plausible mechanism for the cyclization of **1a** is illustrated in Scheme 3. Coordination of the amino function of **1a** to $Cu(OAc)_2$ and subsequent cyclometalation take place to form a five-membered intermediate **A**.[9] Thus formed **A** undergoes oxidation of its copper center leading to reductive elimination[10] to give a four-membered intermediate **B**.[11] Then, two-fold electrocyclic reactions **B** to **C** and **C** to **D** and successive dehydrogenation in **D** take place to generate **2a**.[12] Meanwhile, **4a** may be formed through addition of AcOH toward the common intermediate **C** and subsequent dehydrative cyclization.

Besides such an associative pathway (path a in Scheme 3) involving C–N bond formation step prior to C–N bond cleavage, it is possible that the reaction proceeds through a dissociative pathway (path b in Scheme 3) through a C–N bond cleavage/



Scheme 3. Possible pathways from **1a** to **2a** and **4a**.

formation sequence. However, this latter could be excluded by a crossover experiment. Thus, treatment of a mixture of ^{15}N-labeled tritylamine (**1a**-^{15}N) and unlabeled **1b** under standard conditions did not give any crossover products (Scheme 4).



Scheme 4. Crossover experiment between **1a**-^{15}N and **1b**.

Most 9-arylacrydines **2** described above showed solid-state fluorescence, as was expected (see the Supporting Information). Notably, compound **2d** exhibited a relatively strong emission compared with a typical emitter, such as tris(8-hydroxyquinolino)aluminium (Alq_3), by a factor of 2.6 (λ_{emis} 495 nm). The quantum efficiency (Φ) of the solid-state fluorescence of **2d** was measured at an absolute value of 0.30.

In summary, we have demonstrated that the unprecedented cyclization of tritylamines involving cleavages of two C–H bonds and one C–N bond takes place in the presence of copper acetate under a normal pressure of molecular oxygen to give 9-phenylacridine derivatives. The new reaction may involve an associative pathway with respect to C–N bond formation/cleavage after the first C–H cleavage. Notably, some of the resulting products exhibit intense fluorescence in the solid state.

Experimental Section

General procedure for the reaction of tritylamines **1**: A mixture of tritylamine **1** (0.5 mmol), $Cu(OAc)_2$ (0.5 mmol, 91 mg), and dibenzyl (ca. 40 mg) as internal standard was stirred in mesitylene (3.0 mL) under O_2 at 170 °C for 6–20 h. GC and GC-MS analyses of the mixtures confirmed consumption of **1**. After cooling, the reaction mixture was extracted with ethyl acetate (40 mL) and ethylenediamine (1 mL). The organic layer was washed with water three times (40 mL), dried over Na_2SO_4, and concentrated in vacuo. The desired product **2** was isolated by column chromatography on silica gel by using *n*-hexane/ethyl acetate (10:1) as eluent. Further purification by using preparative GPC was conducted, if necessary. Characterization data of products are summarized in the Supporting Information.

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Keywords: C–H activation · copper · cyclization · dehydrogenation · nitrogen heterocycles

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