Tetrahedron 67 (2011) 1617–1622

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Intramolecular iminium ene reaction with Cu(I) catalysts: facile formation of 4-amino-3-methylenechromans from *O*-propargyl salicylaldehydes and dialkylamines

Noriyoshi Arai *, Takeshi Ohkuma *

Division of Chemical Process Engineering, Faculty of Engineering, Hokkaido University, Sapporo, Hokkaido 060-8628, Japan

ARTICLE INFO

Article history:
Received 2 December 2010
Accepted 5 January 2011
Available online 12 January 2011

Keywords:
Iminium
Aldehyde
Alkyne
Ene reaction
Cyclization

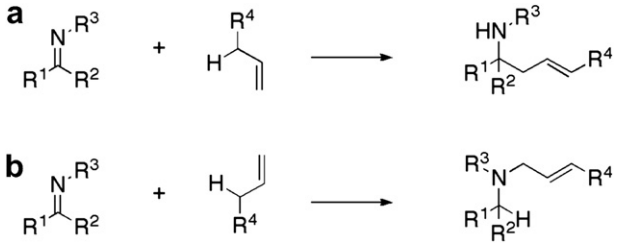
ABSTRACT

Reaction of *O*-propargyl salicylaldehyde and related compounds with dialkylamines in the presence of copper(I) iodide gave 4-(alkylamino)-3-methylenechroman derivatives in good yields through the loss of one alkyl group of the dialkylamine. The reaction also worked well by employing 2-amino benzaldehyde derivatives to afford 4-(alkylamino)-3-methylene-1,2,3,4-tetrahydroquinolines. A deuterium-labeling experiment suggested that the α-hydrogen of the dialkylamine was transferred intramolecularly into the terminal methylene. This result indicated the reaction mechanism, which involved the formation of iminium ion between the aldehyde and the dialkylamine followed by ene-type C–C bond formation with inverse electron demand and hydrolysis.

1. Introduction

The ene reaction of imines (imino ene reaction) is one of the important transformations for preparing a wide range of amine derivatives, and much effort has been devoted to its investigation so far.[1–5] In most of the imino ene reactions, the imine moiety behaves as an 'enophile.' That is, carbon–carbon bond formation occurs with hydrogen transfer from the allylic position to the nitrogen to give the homoallylic amine (Scheme 1, a), while in the other case a carbon–nitrogen bond is formed through hydrogen transfer to the imino carbon affording the allylic amine (Scheme 1, b).[6] The type (a) is often regarded as involving a stepwise Mannich-type reaction, although the intrinsic imino ene reaction should occur via a concerted pathway.[7–10]

To the best of our knowledge, the only example of the neutral imino ene reaction in which the imine moiety reacts as an 'ene' (inverse electron demand reaction) is involved in a complex series of transformations in the pyrolysis of methyl-deuterated cocaine at 600 °C.[11] An intramolecular ene reaction in which an enamine generated by tautomerization of imine acts as an ene has been reported.[12] Mayr and Ofial reported that isolated dialkylmethyleneammonium hexachloroantimonate reacted with a series of alkynes to give an ene-type adduct through an inverse electron demand reaction.[13,14] The iminium salt can be prepared in situ from dialkylmethoxymethylamine (formaldehyde *N*,*O*-acetal) and $SnCl_4$.[15] Herein, we would like to report our findings on the copper(I)-catalyzed intramolecular ene-type reaction with inverse electron demand between alkynes and iminium salts (ene), which were generated in situ from aldehydes to give the cyclized products in good yields. The reaction proceeds via a completely mechanism from that in Mayr's system.



Scheme 1. Typical ene-type reactions of imines.

2. Results and discussion

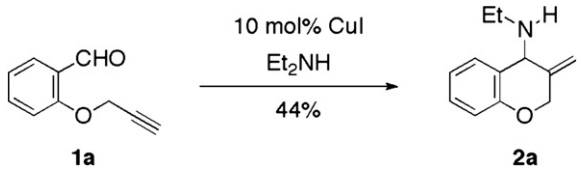
2.1. Reaction of *O*-propargyl salicylaldehyde with dialkylamines

We found that treatment of *O*-propargyl salicylaldehyde (**1a**) with neat diethylamine in the presence of catalytic amounts of CuI

* Corresponding authors. Tel.: +81 11 706 6600; fax: +81 11 706 6598 (N.A.); tel.: +81 11 706 6599; fax: +81 11 706 6598 (T.O.); e-mail addresses: n-arai@eng.hokudai.ac.jp (N. Arai), ohkuma@eng.hokudai.ac.jp (T. Ohkuma).

0040-4020/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2011.01.007

(typically 10 mol %) at room temperature gave the product **2a** in moderate yield with a loss of one ethyl group of diethylamine (Scheme 2).



Scheme 2.

Although it has been reported the oximes derived from **1a** were transformed to the dihydrochroman-4-amine derivative via radical cyclization,[16] the radical cyclization process is not plausible in the above reaction. Intramolecular cyclization of benzylic imine with prenyl moiety via carbocation intermediates has also been reported,[17] but the reaction shown in Scheme 2 proceeded in a quite distinct manner. This unusual reaction prompted us to investigate it in greater detail. The screening of solvents and the amounts of amine are summarized in Table 1.

Table 1
Screening of solvents and the amounts of amine[a]

Entry	Solvent	Amine equiv	Yield of **2a** (%)[b]	Recovery of **1a** (%)[b]
1	None	40	44	0
2	CH_2Cl_2	10	41	0
3	CH_2Cl_2	5	26	0
4	CH_2Cl_2	1.1	11	6
5	THF	10	45	2
6	THF	5	29	7
7	Toluene	10	36	trace
8	DMF	10	65	6
9	DMSO	10	44	30
10	EtOH	10	38	16

[a] All reactions were carried out with **1a** (0.20 mmol), CuI (0.02 mmol), and Et_2NH (2.0 mmol) in 0.6 mL solvent at room temperature under an argon atmosphere for 2 h.
[b] Estimated by ^1H NMR integral.

The reactions were discontinued in 2 h to compare the yield of **2a** and the recovery of **1a**. Use of dichloromethane as a solvent had little effect on the yield of **2a** (entry 2). The yield of **2a** decreased as the amounts of amine were lowered (entries 2–4). Polar solvent seemed to be suitable for this reaction (entries 2, 5, 7–10), and DMF gave the best result (entry 8). The incomplete material balances were due to the formation of unidentified brown tarry materials.

With these results in hand, we next turned our attention to the choice of the catalyst (Table 2).

Several copper(I) salts showed some catalytic activity, although they were no match for CuI (entries 1–5). Copper(II) was also employable, but gave a poor material balance (entry 6). Metal salts that are known to exhibit high affinity to the alkynes[18] turned out to be completely ineffective in this reaction (entries 7–11).

Table 2
Screening of catalysts[a]

Entry	Catalyst	Yield of **2a** (%)[b]	Recovery of **1a** (%)[b]
1	CuI	65	6
2	CuBr	39	13
3	CuCl	22	38
4	$(CuOTf)_2\cdot C_6H_6$	42	22
5	CuCN	24	73
6	$CuBr_2$	26	15
7	AgOAc	0	98
8	$AgOCOCF_3$	0	88
9	$Pd(OAc)_2$	0	99
10	$PdCl_2$	0	100
11	$PtCl_2$	0	100

[a] All reactions were carried out with **1a** (0.20 mmol), CuI (0.02 mmol), and Et_2NH (2.0 mmol) in DMF (0.6 mL) at room temperature under an argon atmosphere for 2 h.
[b] Estimated by ^1H NMR integral.

Having fixed the metal salts, we investigated the effect of ligands on the catalyst performance (Table 3).

Table 3
Screening of ligands[a]

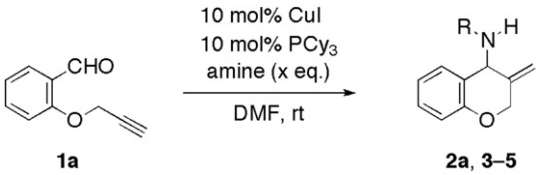
Entry	Ligand	Yield of **2a** (%)[b]	Recovery of **1a** (%)[b]
1	none	65	6
2	PPh_3	54	28
3	PPh_3[c]	38	44
4	PBu_3	38	39
5	PCy_3	67	20
6	$P(OPh)_3$	57	11
7	DPPE	40	40
8	DPPP	42	38
9	DPPB	34	47
10	DPPF	24	60
11	(±)-BINAP	20	63
12	TMEDA	56	19
13	2,2′-bipyridine	48	18

[a] All reactions were carried out with **1a** (0.20 mmol), CuI (0.02 mmol), ligand (0.02 mmol), and Et_2NH (2.0 mmol) in DMF (0.6 mL) at room temperature under an argon atmosphere for 2 h unless otherwise stated.
[b] Estimated by ^1H NMR integral.
[c] Catalyst (20 mol %).

Addition of an equimolar amount of PPh_3 to CuI was effective in inhibiting the formation of undesired tarry materials to improve the total material balance, though it slightly slowed the reaction (entry 2). Two molar amounts of PPh_3 versus copper(I) resulted in a slowdown of the reaction rate without improvement of the total recovery (entry 3). Employment of PBu_3 instead of PPh_3 did not have a desirable effect on the reaction, but the reaction with PCy_3 showed a better yield and better material balance than that with PPh_3 (entries 4 and 5). Phosphite ligand (entry 6), bidentate phosphine (entries 7–11) or amine ligands (entries 12 and 13) gave disappointing results.

Consequently, we set the standard reaction conditions to be 0.1 equiv CuI, 0.1 equiv PCy_3, 10 equiv amine, in DMF at room temperature, and then investigated the reaction by using several secondary amines other than diethylamine (Table 4). We confirmed

Table 4
Reactions with various amines[a]



Entry	Amine	x	Time (h)	Product (R)	Yield (%)[b]
1[c]	Et_2NH	10	6	**2a** (Et)	70
2[c,d]	$Allyl_2NH$	10	7	**3** (Allyl)	76
3[d]	$Allyl_2NH$	10	7	**3** (Allyl)	65
4	Bu_2NH	9	8	**4** (Bu)	78
5[e]	$[Ph(CH_2)_2]NH$	5	24	**5** ($Ph(CH_2)_2$)	59
6	$PrNH_2$	10	11	—[f]	0
7	Et_3N	10	6.5	—[g]	0

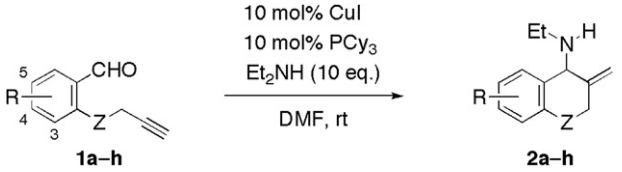
[a] All reactions were carried out with **1a** (0.20 mmol), CuI (0.02 mmol), PCy_3 (0.02 mmol), and amine (2.0 mmol) in DMF (0.6 mL) at room temperature under an argon atmosphere until the starting material had been consumed, unless otherwise stated.
[b] Isolated yield.
[c] Wet DMF (1% H_2O (v/v)) was used.
[d] Without PCy_3.
[e] Catalyst (25 mol %).
[f] Formation of imine was surmised from the ^1H NMR spectra of crude materials.
[g] Recovery (86%) of **1a**.

that dibutyl, diallyl, and di(2-phenylethyl)amine gave the corresponding products **3**–**5** in comparable yield to diethylamine (entries 2–5), whereas both propylamine (primary) and triethylamine (tertiary) were not suitable for the reaction (entries 6 and 7). In some cases, addition of a small amount of water turned out to be effective in improving the yield (entries 2 and 3).

2.2. Substrates scope

After establishing the suitable reaction conditions as described above, we turned our attention to the applicability of the reaction to various aldehydes with a propargyl moiety. The results are summarized in Table 5.

Table 5
Reactions with various substrates[a]



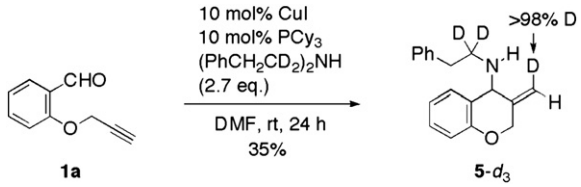
Entry	Substrate	R	Z	Time (h)	Yield of **2** (%)[b]
1[c]	**1a**	H	O	6	70
2	**1b**	3-MeO	O	8	74
3	**1c**	5-CO_2Me	O	3	81
4	**1d**	5-Br	O	7	74
5[d]	**1e**	5-NO_2	O	6	60
6	**1f**	5-Ph	O	6	65
7	**1g**	H	NBoc	11	72
8	**1h**	H	NTs	11	68
9[e]	**1a**	H	O	11	79
10[f]	**1a**	H	O	32	67

[a] All reactions were carried out with **1** (0.20 mmol), CuI (0.02 mmol), PCy_3 (0.02 mmol), and Et_2NH (2.0 mmol) in DMF (0.6 mL) at room temperature under an argon atmosphere until the starting material had been consumed, unless otherwise stated.
[b] Isolated yield.
[c] Wet DMF (1% H_2O (v/v)) was used.
[d] Without PCy_3.
[e] Catalyst (5 mol %).
[f] Catalyst (1 mol %).

The substrates with a methoxy group (**1b**) or with a methoxycarbonyl group (**1c**) on the aromatic ring gave the corresponding cyclized products in good yields (entries 2 and 3). This result shows that the electronic features of the aromatic moiety had little effect on the product yields, while the electron-donating substituent somewhat slowed the reaction. Other substituents on the aromatic ring, such as bromo, nitro, and phenyl, were well-tolerated, and afforded the corresponding products, 4-(alkylamino)-3-methylenechroman derivatives **2d**–**f**, in moderate to good yields (entries 4–6). The reaction can also be applied to the *O*-(propargylamino)benzaldehyde derivatives (**1g** and **1h**) to give 4-(alkylamino)-3-methylene-1,2,3,4-tetrahydroquinolines that are structurally related to the synthetic intermediate of martinelline, a pyrroloquinoline alkaloid (entries 7 and 8).[19] Concerning **1a**, the amounts of CuI–PCy_3 can be reduced to 1 mol % without decrease of the yield by prolonging the reaction time (entries 9 and 10).

2.3. Mechanistic considerations

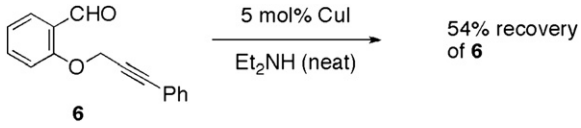
To obtain some insight into the reaction mechanism, we carried out a deuterium-labeling experiment (Scheme 3). When the reaction was carried out by using α-deuterated bis(2-phenyethyl) amine, the methylene hydrogen of **5** close to the amino group was



Scheme 3.

completely deuterated. The other methylene hydrogen was not deuterated at all. This result indicates that one of the methylene hydrogens comes from the α-hydrogen of the secondary amine via an intramolecular transfer process.

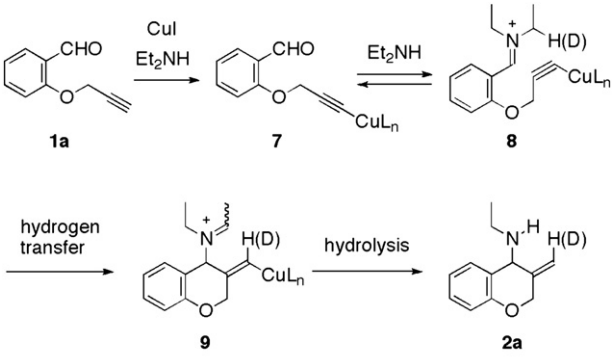
We also confirmed that the aldehyde with a phenylpropynyl group **6** did not give the cyclized product, resulting in incomplete recovery of the starting material with the formation of unidentified materials (Scheme 4). The drastic change of the substrate reactivity by substitution at the alkyne terminal suggests that the formation of copper acetylide is necessary for the cyclization reaction, though the possibility of a simple steric effect cannot be ruled out. The formation of copper acetylide under similar reaction conditions has been described in the literature.[20–23]



Scheme 4.

As shown in Table 2, this cyclization reaction was not promoted at all by Ag, Pd, or Pt, which are well known to activate alkynes by π-complexation.[24,25] These results also indicate the formation of acetylide rather than simple π-complex activation for the cyclization.

Based on these experimental results and considerations, we propose a plausible reaction mechanism as illustrated in Scheme 5. Initially, copper(I) acetylide **7** is formed by mixing a terminal alkyne, CuI, and a base.[20–23] The acetylide is considered to be in equilibrium with iminium ion **8**, which is immediately converted to a cyclized intermediate **9** through an iminium–alkyne ene-type reaction. Then, hydrolysis of **9** by quenching or water contained in the solvent gives the product **2a**. Promotion of an ene reaction through metal acetylide was reported in the Au catalytic system.[26] Hydrogen transfer from the position adjacent to the nitrogen of a propargylic amine to the carbon–carbon triple bond is known to afford an allene compound accompanied by concomitant elimination of the amine moiety.[27–30] Previous reports have shown that configuration of the



Scheme 5. Plausible reaction mechanism.

non-functionalized alkenyl copper(I) species (corresponding to **9**) does not change at ambient temperature.[31,32] This property is also consistent with our labeling experiment (Scheme 3).

3. Conclusion

We found that the treatment of *O*-propargyl salicylaldehyde and related compounds with secondary amines in the presence of CuI gave cyclized products, 3,4-dihydro-3-methylene-2*H*-chroman-4-amines, in moderate to good yields accompanied by removal of one alkyl group of the secondary amine. Addition of PCy_3 to the reaction system gave better results in some cases. A deuterium-labeling experiment revealed that the methylene hydrogen close to the amino group came from amine α-hydrogen. This reaction is considered to proceed through the intramolecular inverse electron demand ene-type reaction, in which the in situ-formed iminium moiety behaves as a hydrogen donor (ene).

4. Experimental section

4.1. General

NMR spectra were obtained on JEOL JNM-ECX400P and ECS-400 spectrometers. Carbon multiplicity was assigned by a DEPT experiment. IR spectra were recorded on a JASCO FT/IR-4100 spectrophotometer. Silica gel column chromatography was performed with Kanto Chemical Co., Inc. Silica Gel 60 N (63–210 μm) or Fuji Silisia FL60D. Preparative thin layer chromatography was carried out with Wako Gel B-5F (Wako Pure Chemical Industries, Ltd.). Solvents and reagents were used after appropriate purification, if necessary.[33] Mass spectrometry and elemental analyses were carried out at the Instrumental Analysis Division, Equipment Management Center, Creative Research Institution, Hokkaido University.

4.2. Preparation of starting materials

Compounds **1a**,[34,35] **1b**,[34] **1d**,[34,35] **1e**,[34] and **6**[36] were prepared according to the methods described in the literature. The other related compounds, **1c** and **1f**–**h**, were prepared by the same method. The physical properties of the new compounds were as follows.

*4.2.1. Methyl 3-formyl-4-(2-propynyloxy)benzoate (**1c**).* Faintly yellow crystals. Mp 92.0–92.5 °C (heptane–ethyl acetate). IR (KBr-disk) 3229, 2952, 2880, 2128, 1708, 1682, 1610, 1496, 1266, 1014, 767 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 2.61 (1H, t, *J*=2.2 Hz, C≡CH), 3.92 (3H, s, CH_3), 4.91 (2H, d, *J*=2.2 Hz, CH_2), 7.19 (1H, d, *J*=8.6 Hz, Ar–H), 8.26 (1H, dd, *J*=8.6, 2.2 Hz, Ar–H), 8.54 (1H, d, *J*=2.2 Hz, Ar–H), 10.47 (1H, s, CHO). ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.2 (CH_3), 56.5 (CH_2), 76.9 (C), 77.1 (CH), 112.9 (CH), 123.7 (C), 124.9 (C), 130.6 (CH), 135.5 (CH), 136.8 (CH), 163.5 (C), 165.8 (C), 188.5 (CH). HRMS (ESI^+) *m*/*z* 219.0653 ($M+H^+$), calcd for $C_{12}H_{11}O_4$: 219.0657. Anal. Found: C, 66.03%; H, 4.60%. Calcd for $C_{12}H_{10}O_4$: C, 66.05%; H, 4.62%.

*4.2.2. 5-Phenyl-2-(2-propynyloxy)benzaldehyde (**1f**).* Pale yellow oil. IR (KBr, neat) 3290, 3033, 2868, 2122, 1682, 1607, 1481, 1274, 1224, 1018, 762, 697 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 2.60 (1H, d, *J*=2.3 Hz, C≡CH), 4.88 (2H, d, *J*=2.3 Hz, CH_2), 7.21 (1H, d, *J*=8.7 Hz, Ar–H), 7.34–7.37 (1H, m, Ar–H), 7.42–7.46 (2H, m, Ar–H), 7.56–7.59 (2H, m, Ar–H), 7.81 (1H, dd, *J*=8.7, 2.7 Hz, Ar–H), 8.11 (1H, d, *J*=2.7 Hz, Ar–H), 10.53 (1H, s, CHO). ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.4 (CH_2), 76.6 (CH), 77.6 (C), 113.6 (CH), 125.4 (C), 126.65 (CH), 126.71 (CH), 127.4 (CH), 128.8 (CH), 134.0 (CH), 134.7 (C), 139.2 (C), 159.0 (C), 189.4 (CH). HRMS (ESI^+) *m*/*z* 237.0915 ($M+H^+$), calcd for $C_{16}H_{13}O_2$: 237.0916.

*4.2.3. tert-Butyl N-(2-formylphenyl)-N-(2-propynyl)carbamate (**1g**).* Yellow powder. Mp 85.0–87.0 °C (hexane–ethyl acetate). IR (KBr-disk) 3260, 2981, 2865, 2117, 1701, 1691, 1600, 1460, 1379, 1371, 1291, 1161, 1148, 1014, 761 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 50 °C) δ 1.37 (9H, br s, *t*-Bu), 2.23 (1H, t, *J*=2.5 Hz, C≡CH), 4.43 (2H, br s, CH_2), 7.37 (1H, br d, *J*=8.1 Hz, Ar–H), 7.41–7.45 (1H, m, Ar–H), 7.62 (1H, dt, J_d=1.4, J_t=7.7 Hz, Ar–H), 7.92 (1H, dd, *J*=7.7, 1.9 Hz, Ar–H), 10.14 (1H, s, CHO). ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.0 (CH_3), 39.7 (CH_2), 73.1 (CH), 78.5 (C), 81.9 (C), 127.9 (CH, probably overlapping), 128.4 (CH), 133.1 (C), 134.8 (CH), 143.5 (C), 153.8 (C), 190.2 (CH). HRMS (ESI^+) *m*/*z* 260.1286 ($M+H^+$), calcd for $C_{15}H_{18}NO_3$: 260.1287.

*4.2.4. N-(2-Formylphenyl)-N-(2-propynyl)-p-toluenesulfonamide (**1h**).* Colorless crystals. Mp 81.0–82.0 °C (heptane–ethyl acetate). IR (KBr-disk) 3280, 2892, 2124, 1690, 1596, 1484, 1451, 1350, 1167, 1092, 1065, 864, 822, 725, 665, 577 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 2.20 (1H, t, *J*=2.5 Hz, C≡CH), 2.45 (3H, s, CH_3), 4.48 (2H, br s, CH_2), 6.92–6.95 (1H, m, Ar–H), 7.29 (2H, d, *J*=8.0 Hz, Ar–H), 7.48–7.54 (4H, m, Ar–H), 8.00–8.03 (1H, m, Ar–H), 10.39 (1H, s, CHO). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6 (CH_3), 41.7 (CH_2), 74.7 (CH), 76.8 (C), 128.0 (CH), 128.4 (CH), 128.5 (CH), 129.2 (CH), 129.6 (CH), 134.2 (CH), 134.4 (C), 135.8 (C), 140.9 (C), 144.5 (C), 190.1 (CH). HRMS (ESI^+) *m*/*z* 314.0845 ($M+H^+$), calcd for $C_{17}H_{16}NO_3S$: 314.0851. Anal. Found: C, 65.19%; H, 4.69%; N, 4.42%. Calcd for $C_{17}H_{15}NO_3S$: C, 65.16%; H, 4.82%; N, 4.47%.

4.3. Typical procedure for the Cu(I) catalyzed cyclization

To a 30 mL two-necked flask was added CuI (3.8 mg, 0.020 mmol), PCy_3 (6.1 mg, 0.022 mmol), **1** (0.200 mmol), and DMF (0.6 mL). The mixture was stirred at room temperature under an argon atmosphere, and Et_2NH (0.21 mL, 2.0 mmol) was added. After stirring for the indicated period, all volatile materials were removed under reduced pressure. The residue was purified by silica gel column chromatography (eluent, hexane–ethyl acetate; typically 30:1 gradually to 2:1).

*4.3.1. 4-Ethylamino-3,4-dihydro-3-methylene-2H-1-benzopyran (**2a**).* Yellow oil (70%). IR (KBr, neat) 3320, 2966, 1607, 1583, 1487, 1241, 1216, 1038, 1007, 753 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.13 (3H, t, *J*=7 Hz, CH_2CH_3), 1.27 (1H, br s, NH), 2.65–2.69 (2H, br m, CH_2CH_3), 4.08 (1H, br s, CHNHEt), 4.46 (1H, d, *J*=11.8 Hz, OCH_2), 4.78 (1H, dd, *J*=11.8, 1.4 Hz, OCH_2), 5.19 (1H, br s, =CH_2), 5.24 (1H, br s, =CH_2), 6.83 (1H, dd, *J*=7.7, 0.9 Hz, Ar–H), 6.91 (1H, dt, J_d=0.9 Hz, J_t=7.7 Hz, Ar–H), 7.16 (1H, dt, J_d=1.8 Hz, J_t=7.7 Hz, Ar–H), 7.22 (1H, dd, *J*=7.7, 1.8 Hz, Ar–H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.2 (CH_3), 41.1 (CH_2), 57.9 (CH), 67.0 (CH_2), 114.0 (CH_2), 116.8 (CH), 120.6 (CH), 124.9 (C), 128.7 (CH), 129.6 (CH), 140.6 (C), 154.3 (C). HRMS (ESI^+) *m*/*z* 212.1045 ($M+Na^+$), calcd for $C_{12}H_{15}NONa$: 212.1046.

*4.3.2. 4-Ethylamino-3,4-dihydro-8-methoxy-3-methylene-2H-1-benzopyran (**2b**).* Yellow oil (74%). IR (KBr, neat) 3317, 2965, 1585, 1486, 1264, 1213, 1091, 1010, 737 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.13 (3H, t, *J*=7 Hz, CH_2CH_3), 1.34 (1H, br s, NH), 2.60–2.74 (2H, m, CH_2CH_3), 3.86 (3H, s), 4.08 (1H, br s, CHNHEt), 4.58 (1H, d, *J*=11.8 Hz, OCH_2), 4.82 (1H, dd, *J*=11.8, 1.4 Hz, OCH_2), 5.19 (1H, br s, =CH_2), 5.24 (1H, br s, =CH_2), 6.83 (1H, dd, *J*=7.7, 0.9 Hz, Ar–H), 6.76–6.89 (3H, m, Ar–H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.2 (CH_3), 41.1 (CH_2), 55.8 (CH_3), 57.7 (CH), 67.3 (CH_2), 110.2 (CH), 114.2 (CH_2), 120.3 (CH), 121.2 (CH), 125.5 (C), 140.2 (C), 143.7 (C), 148.2 (C). HRMS (ESI^+) *m*/*z* 220.1335 ($M+H^+$), calcd for $C_{13}H_{18}NO_2$: 220.1332.

*4.3.3. Methyl 4-ethylamino-3,4-dihydro-3-methylene-2H-1-benzopyran-6-carboxylate (**2c**).* Orange-yellow oil (81%). IR (KBr, neat)

3323, 2967, 1716, 1613, 1580, 1497, 1438, 1240, 1193, 1173, 1119, 1002, 917, 769 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$)[37] δ 1.14 (3H, t, J=7 Hz, CH_2CH_3), 2.61–2.74 (2H, br m, CH_2CH_3), 3.88 (3H, s), 4.11 (1H, br s, CHNHEt), 4.51 (1H, d, J=11.8 Hz, OCH_2), 4.87 (1H, d, J=11.8 Hz, OCH_2), 5.23 (1H, br s, $=CH_2$), 5.26 (1H, br s, $=CH_2$), 6.84 (1H, d, J=8.6 Hz, Ar–H), 7.84 (1H, dd, J=8.6, 1.8 Hz, Ar–H), 7.92 (1H, d, J=1.8 Hz, Ar–H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.2 (CH_3), 41.2 (CH_2), 51.8 (CH_3), 58.0 (CH), 67.4 (CH_2), 114.8 (CH_2), 116.8 (CH), 122.3 (C), 124.7 (C), 130.5 (CH), 131.7 (CH), 139.6 (C), 158.4 (C), 166.7 (C). HRMS (ESI^+) m/z 270.1098 ($M+Na^+$), calcd for $C_{14}H_{17}NO_3Na$: 270.1101.

*4.3.4. 6-Bromo-4-ethylamino-3,4-dihydro-3-methylene-2H-1-benzopyran (**2d**).* Orange oil (74%). IR (KBr, neat) 3323, 2967, 1576, 1241, 1218, 1124, 1007, 921, 816 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$)[37] δ 1.13 (3H, t, J=7.2 Hz, CH_2CH_3), 2.58–2.73 (2H, br m, CH_2CH_3), 4.04 (1H, br s, CHNHEt), 4.45 (1H, d, J=11.8 Hz, OCH_2), 4.75 (1H, d, J=11.8 Hz, OCH_2), 5.19 (1H, br s, $=CH_2$), 5.25 (1H, br s, $=CH_2$), 6.71 (1H, d, J=8.6 Hz, Ar–H), 7.24 (1H, dd, J=8.6, 2.7 Hz, Ar–H), 7.35 (1H, d, J=2.7 Hz, Ar–H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.2 (CH_3), 41.1 (CH_2), 57.6 (CH), 67.2 (CH_2), 112.4 (C), 114.7 (CH_2), 118.6 (CH), 126.9 (C), 131.6 (CH), 132.0 (CH), 139.6 (C), 153.5 (C). HRMS (ESI^+) m/z 268.0333 ($M+H^+$), calcd for $C_{12}H_{15}{}^{79}BrNO$: 268.0332.

*4.3.5. 4-Ethylamino-3,4-dihydro-3-methylene-6-nitro-2H-1-benzopyran (**2e**).* Yellow oil (60%). IR (KBr, neat) 3325, 2968, 1615, 1584, 1517, 1486, 1340, 1242, 1090, 997, 920, 832, 751 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.15 (3H, t, J=7 Hz, CH_2CH_3), 1.56 (1H, br s, NH), 2.62–2.76 (2H, br m, CH_2CH_3), 4.15 (1H, br s, CHNHEt), 4.58 (1H, d, J=11.8 Hz, OCH_2), 4.91 (1H, dd, J=11.8, 0.9 Hz, OCH_2), 5.28 (1H, br s, $=CH_2$), 5.31 (1H, br s, $=CH_2$), 6.89 (1H, d, J=9.0 Hz, Ar–H), 8.06 (1H, dd, J=9.0, 2.7 Hz, Ar–H), 8.18 (1H, d, J=7.7, 2.7 Hz, Ar–H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.2 (CH_3), 41.2 (CH_2), 57.8 (CH), 67.9 (CH_2), 115.6 (CH_2), 117.4 (CH), 124.8 (CH), 125.3 (C), 126.0 (CH), 138.5 (C), 141.1 (C), 159.9 (C). HRMS (ESI^+) m/z 235.1079 ($M+H^+$), calcd for $C_{12}H_{15}N_2O_3$: 235.1077.

*4.3.6. 4-Ethylamino-3,4-dihydro-3-methylene-6-phenyl-2H-1-benzopyran (**2f**).* Yellow oil (65%). IR (KBr, neat) 3323, 2967, 1614, 1508, 1482, 1453, 1241, 1224, 1129, 1008, 918, 826, 764, 698 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.14 (3H, t, J=7.2 Hz, CH_2CH_3), 1.36 (1H, br s, NH), 2.63–2.76 (2H, br m, CH_2CH_3), 4.15 (1H, br s, CHNHEt), 4.49 (1H, d, J=11.8 Hz, OCH_2), 4.83 (1H, dd, J=11.8, 1.4 Hz, OCH_2), 5.22 (1H, br s, $=CH_2$), 5.26 (1H, br s, $=CH_2$), 6.90 (1H, d, J=8.6 Hz, Ar–H), 7.27–7.32 (1H, m, Ar–H), 7.39–7.44 (4H, m, Ar–H), 7.53–7.56 (2H, m, Ar–H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.3 (CH_3), 41.2 (CH_2), 58.2 (CH), 67.2 (CH_2), 114.3 (CH_2), 117.2 (CH), 125.0 (C), 126.60 (CH), 126.65 (CH), 127.6 (CH), 128.2 (CH), 128.6 (CH), 133.7 (C), 140.4 (C), 140.7 (C), 153.9 (C). HRMS (ESI^+) m/z 288.1357 ($M+Na^+$), calcd for $C_{18}H_{19}NONa$: 288.1359.

*4.3.7. tert-Butyl 4-ethylamino-3,4-dihydro-3-methylene-1(2H)-quinolinecarboxylate (**2g**).* Yellow-brown oil (72%). IR (KBr, neat) 3323, 2973, 1700, 1490, 1367, 1167, 756 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$)[37] δ 1.11 (3H, t, J=7 Hz, CH_2CH_3), 1.52 (9H, s, *t*-Bu), 2.58–2.74 (2H, br m, CH_2CH_3), 4.12 (1H, br s, CHNHEt), 4.25 (1H, d, J=11.8 Hz, OCH_2), 4.42 (1H, dt, J_d=11.8 Hz, J_t=1.5 Hz, OCH_2), 4.99 (1H, br s, $=CH_2$), 5.01 (1H, br s, $=CH_2$), 7.04–7.08 (1H, m, Ar–H), 7.20–7.25 (2H, m, Ar–H), 7.60 (1H, br d, J=8.2 Hz, Ar–H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.3 (CH_3), 28.3 (CH_3), 41.4 (CH_2), 48.3 (CH_2), 61.5 (CH), 80.9 (C), 110.0 (CH_2), 124.0 (CH), 124.4 (CH), 127.1 (CH), 127.3 (CH), 132.6 (C), 137.8 (C), 143.4 (C), 153.6 (C). HRMS (ESI^+) m/z 311.1728 ($M+Na^+$), calcd for $C_{17}H_{24}N_2O_2Na$: 311.1730.

*4.3.8. 4-Ethylamino-1,2,3,4-tetrahydro-3-methylene-1-(4-methylphenylsulfonyl)quinoline (**2h**).* Orange brown oil (68%). IR (KBr, neat) 3326, 2966, 1599, 1485, 1456, 1351, 1165, 1091, 668, 578 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$)[37] δ 0.89 (3H, t, J=7 Hz, CH_2CH_3), 2.22–2.39 (5H, m including s at 2.34, CH_2CH_3 and $CH_3C_6H_4$), 3.71 (1H, br s, CHNHEt), 4.30 (1H, d, J=15 Hz, OCH_2), 4.43 (1H, d, J=15 Hz, OCH_2), 4.89 (1H, br s, $=CH_2$), 4.99 (1H, br s, $=CH_2$), 7.12–7.30 (5H, m, Ar–H), 7.42 (2H, d, J=8.1 Hz, Ar–H), 7.85 (1H, d, J=8.1 Hz, Ar–H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.0 (CH_3), 21.4 (CH_3), 40.5 (CH_2), 49.8 (CH_2), 59.5 (CH), 112.4 (CH_2), 125.2 (CH), 125.6 (CH), 127.5 (CH), 127.9 (CH), 128.3 (CH), 129.2 (CH), 133.3 (C), 135.4 (C), 136.2 (C), 140.4 (C), 143.5 (C). HRMS (ESI^+) m/z 365.1294 ($M+Na^+$), calcd for $C_{19}H_{22}N_2O_2SNa$: 365.1294.

*4.3.9. 3,4-Dihydro-3-methylene-4-(2-propenyl)amino-2H-1-benzopyran (**3**).* Yellow oil (76%). IR (KBr, neat) 3328, 3075, 2979, 1607, 1583, 1487, 1464, 1241, 1214, 1038, 1008, 918, 754 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$)[37] δ 3.24 (1H, dd, J=14.0, 6.5 Hz, CH_2), 3.32 (1H, dd, J=14.0, 5.5 Hz, $CH_2CH{=}CH_2$), 4.11 (1H, br s, CHNHallyl), 4.46 (1H, d, J=11.7 Hz, OCH_2), 4.78 (1H, d, J=11.7 Hz, OCH_2), 5.13 (1H, br d, J=9.9 Hz, $CH{=}CH_2$), 5.18 (1H, br s, $=CH_2$), 5.22 (1H, dd, J=17.2, 1.8 Hz, $CH{=}CH_2$), 5.26 (1H, br s, $=CH_2$), 5.88–5.98 (1H, m, $CH{=}CH_2$), 6.83 (1H, d, J=8.2 Hz, Ar–H), 6.89–6.93 (1H, m, Ar–H), 7.15–7.19 (1H, m, Ar–H), 7.22 (1H, d, J=7.7 Hz, Ar–H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 49.1 (CH_2), 56.8 (CH), 67.0 (CH_2), 114.5 (CH_2), 116.2 (CH_2), 116.8 (CH), 120.6 (CH), 124.6 (C), 128.8 (CH), 129.7 (CH), 136.7 (CH), 140.1 (C), 154.4 (C). HRMS (ESI^+) m/z 202.1227 ($M+H^+$), calcd for $C_{13}H_{16}NO$: 202.1226.

*4.3.10. 4-Butylamino-3,4-dihydro-3-methylene-2H-1-benzopyran (**4**).* Yellow oil (78%). IR (KBr, neat) 3326, 2957, 2927, 1607, 1583, 1487, 1465, 1241, 1219, 1039, 1008, 753 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$)[37] δ 0.91 (3H, t, J=7.3 Hz, $(CH_2)_3CH_3$), 1.29–1.54 (4H, m, $(CH_2)_2CH_3$), 2.62 (2H, br t, J=7 Hz, $NHCH_2$), 4.05 (1H, br s, CHNHBu), 4.45 (1H, d, J=11.8 Hz, OCH_2), 4.78 (1H, dd, J=11.8, 1.4 Hz, OCH_2), 5.18 (1H, br s, $=CH_2$), 5.23 (1H, br s, $=CH_2$), 6.83 (1H, dd, J=8.1, 0.9 Hz, Ar–H), 6.88–6.92 (1H, m, Ar–H), 7.14–7.18 (1H, m, Ar–H), 7.21 (1H, dd, J=7.5, 1.6 Hz, Ar–H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0 (CH_3), 20.5 (CH_2), 32.1 (CH_2), 46.5 (CH_2), 58.1 (CH), 67.0 (CH_2), 114.1 (CH_2), 116.7 (CH), 120.6 (CH), 124.9 (C), 128.7 (CH), 129.6 (CH), 140.6 (C), 154.3 (C). HRMS (ESI^+) m/z 218.1538 ($M+H^+$), calcd for $C_{14}H_{20}NO$: 218.1539.

*4.3.11. 3,4-Dihydro-3-methylene-4-(2-phenylethyl)amino-2H-1-benzopyran (**5**).* Yellow oil (59%). IR (KBr, neat) 3322, 3026, 2922, 2850, 1605, 1582, 1487, 1454, 1241, 1216, 1038, 1006, 753, 699 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.87 (1H, br s, NH), 2.78–2.97 (4H, m, $(CH_2)_2Ph$), 4.11 (1H, br s, CHNHphenethyl), 4.42 (1H, d, J=11.4 Hz, OCH_2), 4.69 (1H, dd, J=11.4, 1 Hz, OCH_2), 5.19 (1H, br s, $=CH_2$), 5.24 (1H, br s, $=CH_2$), 6.81 (1H, br d, J=8.2 Hz, Ar–H), 6.86–6.90 (1H, m, Ar–H), 7.12–7.17 (2H, m, Ar–H), 7.20–7.23 (3H, m, Ar–H), 7.28–7.32 (2H, m, Ar–H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 36.1 (CH_2), 47.9 (CH_2), 57.8 (CH), 67.0 (CH_2), 114.5 (CH_2), 116.8 (CH), 120.7 (CH), 124.4 (C), 126.2 (CH), 128.5 (CH), 128.7 (CH), 128.9 (CH), 129.6 (CH), 139.9 (C), 140.2 (C), 154.3 (C). HRMS (ESI^+) m/z 288.1357 ($M+Na^+$), calcd for $C_{18}H_{19}NONa$: 288.1359.

4.4. Deuterium-labeling experiments

4.4.1. Bis(1,1-dideuterio-2-phenylethyl)amine. This compound was prepared by $LiAlD_4/AlCl_3$ reduction of phenylacetonitrile,[38] followed by amidation with phenylacetyl chloride and $LiAlD_4$ reduction.[39]

Colorless oil. IR (KBr, neat) 3312, 3026, 2922, 2172, 2057, 1673, 1603, 1496, 1453, 1155, 744, 698 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$)[37] δ 2.77 (4H, s, CH_2Ph), 7.16–7.21 (6H, m, Ar–H), 7.26–7.29 (4H, m, Ar–H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 36.1 (CH_2), 50.1 (C, quint, $^1J_{C-D}$=20 Hz), 126.0 (CH), 128.4 (CH), 128.6 (CH), 139.9 (C). HRMS (ESI^+) m/z 230.1843 ($M+H^+$), calcd for $C_{16}H_{16}D_4N$: 230.1841.

*4.4.2. (E)-3-deuteriomethylene-4-(1,1-dideuterio-2-phenylethyl) amino-3,4-dihydro-2H-1-benzopyran (**5**-d_3).* The reaction was carried out according to the typical procedure described above (Section 4.3). The configuration of **5**-d_3 was determined by comparison of the ^{1}H NMR spectrum with that of non-deuterated **5**. The NMR signals of terminal methylene protons of **5** were assigned by NOE experiments (see Supplementary data).

Yellow oil. IR (KBr, neat) 3322, 3026, 2922, 2852, 2174, 2071, 1605, 1582, 1487, 1462, 1453, 1236, 1038, 1006, 751, 699 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.79 (1H, br s, NH), 2.80 (1H, d, J=13.6 Hz, CH_2Ph), 2.84 (1H, d, J=13.6 Hz, CH_2Ph), 4.11 (1H, br s, C*H*NHphenethyl), 4.42 (1H, d, J=11.7 Hz, OCH_2), 4.69 (1H, dd, J=11.7, 1.3 Hz, OCH_2), 5.23 (1H, br s, =CHD), 6.81 (1H, dd, J=7.5, 1.6 Hz, Ar–H), 6.86–6.90 (1H, m, Ar–H), 7.12–7.20 (2H, m, Ar–H), 7.21–7.23 (3H, m, Ar–H), 7.28–7.32 (2H, m, Ar–H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 36.0 (CH_2), 47.1 (C, quint, $^1J_{C-D}$=20 Hz), 57.7 (CH), 67.0 (CH_2), 114.1 (CH, t, $^1J_{C-D}$=24 Hz), 116.8 (CH), 120.7 (CH), 124.5 (C), 126.2 (CH), 128.5 (CH), 128.7 (CH), 128.8 (CH), 129.6 (CH), 139.9 (C), 140.2 (C), 154.3 (C). HRMS (ESI$^+$) m/z 291.1546 (M+Na$^+$), calcd for $C_{18}H_{16}D_3NONa$: 291.1547.

Acknowledgements

This work was supported by a Grant-in-Aid from the Japan Society for the Promotion of Science (JSPS) (No. 21350048).

Supplementary data

^{1}H NMR spectra of $(PhCH_2CH_2)_2NH$, $(PhCH_2CD_2)_2NH$, compound **5** and compound **5**-d_3, and the NOE experiment on **5** are included in the Supplementary data. Supplementary data related to this article can be found online at doi:10.1016/j.tet.2011.01.007.

References and notes

1. Borzilleri, R. M.; Weinreb, S. M. *Synthesis* **1995**, 347–360.
2. Mikami, K.; Shimizu, M. *Chem. Rev.* **1992**, *92*, 1021–1050.
3. Taggi, A. E.; Hafez, A. M.; Lectka, T. *Acc. Chem. Res.* **2003**, *36*, 10–19.
4. Jin, J.; Weinreb, S. M. *J. Am. Chem. Soc.* **1997**, *119*, 5773–5784.
5. Borzilleri, R. M.; Weinreb, S. M.; Parvez, M. *J. Am. Chem. Soc.* **1995**, *117*, 10905–10913.
6. Thomas, B. E., IV; Houk, K. N. *J. Am. Chem. Soc.* **1993**, *115*, 790–792.
7. Pandey, M. K.; Bisai, A.; Pandey, A.; Singh, V. K. *Tetrahedron Lett.* **2005**, *46*, 5039–5041.
8. Tanner, D.; Hagberg, L. *Tetrahedron* **1998**, *54*, 7907–7918.
9. Sakane, S.; Maruoka, K.; Yamamoto, H. *Tetrahedron* **1986**, *42*, 2203–2209.
10. Yamanaka, M.; Nishida, A.; Nakagawa, M. *J. Org. Chem.* **2003**, *68*, 3112–3120.
11. Novák, M.; Novák, J.; Salemink, C. A. *Tetrahedron Lett.* **1991**, *32*, 4405–4408.
12. Cossy, J.; Bouzide, A.; Pfau, M. *Tetrahedron Lett.* **1992**, *33*, 4883–4884.
13. Ofial, A. R.; Mayr, H. *J. Org. Chem.* **1996**, *61*, 5823–5830.
14. Ofial, A. R.; Mayr, H. *Angew. Chem., Int. Ed.* **1997**, *36*, 143–145.
15. Rehn, S.; Ofial, A. R.; Mayr, H. *Synthesis* **2003**, 1790–1796.
16. Booth, S. E.; Jenkins, P. R.; Swain, C. J.; Sweeney, J. B. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3499–3508.
17. Laschat, S.; Grehl, M. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 458–461.
18. Yamamoto, Y. *J. Org. Chem.* **2007**, *72*, 7817–7831.
19. Yoshitomi, Y.; Arai, H.; Makino, K.; Hamada, Y. *Tetrahedron* **2008**, *64*, 11568–11579.
20. Chinchilla, R.; Nájera, C. *Chem. Rev.* **2007**, *107*, 874–922.
21. Okuro, K.; Furuune, M.; Enna, M.; Miura, M.; Nomura, M. *J. Org. Chem.* **1993**, *58*, 4716–4721.
22. Miura, M.; Enna, M.; Okuro, K.; Nomura, M. *J. Org. Chem.* **1995**, *60*, 4999–5004.
23. Hattori, G.; Sakata, K.; Matsuzawa, H.; Tanabe, Y.; Miyake, Y.; Nishibayashi, Y. *J. Am. Chem. Soc.* **2010**, *132*, 10592–10608.
24. Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2004**, *104*, 3079–3159.
25. Formation of amino benzofurans via π-complex between Cu(I) and in situ-generated propargyl amine followed by nucleophilic addition of oxygen: Nguyen, R.-V.; Li, C.-J. *Synlett* **2008**, 1897–1901.
26. Cheong, PH.-Y.; Morganelli, P.; Luzung, M. R.; Houk, K. N.; Toste, F. D. *J. Am. Chem. Soc.* **2008**, *130*, 4517–4526.
27. Nakamura, H.; Sugiishi, T.; Tanaka, Y. *Tetrahedron Lett.* **2008**, *49*, 7230–7233.
28. Kuang, J.; Ma, S. *J. Org. Chem.* **2009**, *74*, 1763–1765.
29. Kuang, J.; Ma, S. *J. Am. Chem. Soc.* **2010**, *132*, 1786–1787.
30. Lo, VK.-Y.; Zhou, C.-Y.; Wong, M.-K.; Che, C.-M. *Chem. Commun.* **2010**, *46*, 213–215.
31. Normant, J. F.; Alexakis, A. *Synthesis* **1981**, 841–870.
32. Whitesides, G. M.; Casey, C. P. *J. Am. Chem. Soc.* **1966**, *88*, 4541–4543.
33. Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*, 3rd ed.; Pergamon: Oxford, 1988.
34. Khoshkholgh, M. J.; Balalaie, S.; Gleiter, R.; Rominger, F. *Tetrahedron* **2008**, *64*, 10924–10929.
35. Janietz, D.; Rudorf, W.-D. *Tetrahedron* **1989**, *45*, 1661–1666.
36. Lingam, V. S. P. R.; Vinodkumar, R.; Mukkanti, K.; Thomas, A.; Gopalan, B. *Tetrahedron Lett.* **2008**, *49*, 4260–4264.
37. The signal of the NH proton was not clearly observed.
38. Frejd, T.; Klingstedt, T. *Synthesis* **1987**, 40–42.
39. Trost, B. M.; Yeh, V. S. C.; Ito, H.; Bremeyer, N. *Org. Lett.* **2002**, *4*, 2621–2623.