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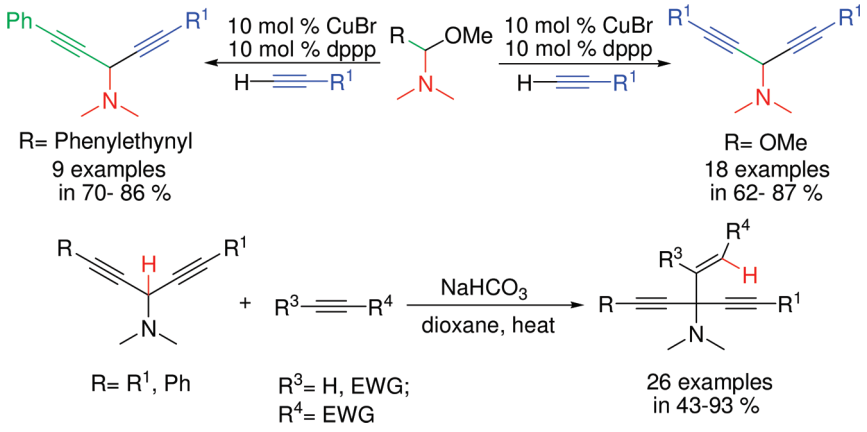
Copper-Catalyzed Coupling Reaction of C−OMe Bonds Adjacent to a Nitrogen Atom with Terminal Alkynes

Bangben Yao, Yuhong Zhang,* and Yong Li

Department of Chemistry, Zhejiang University, Hangzhou 310027, People's Republic of China

yhzhang@zju.edu.cn

Received April 21, 2010



The cross coupling of the C−OMe bond adjacent to a nitrogen atom in dialkoxy-*N*,*N*-dialkylmethanamines with terminal alkynes was efficiently approached in the presence of copper catalyst under mild conditions to give 3-amino-1,4-diynes in good yields. The reaction is promoted by phosphine ligands and the chemistry provides a simple and efficient route to 3-amino-1,4-diynes. Importantly, the Michael addition occurred with as-prepared 3-amino-1,4-diynes to give the useful Michael-adducts containing *tert*-alkylamines in a very convenient way. Further studies revealed that (*E*)-1,5-diarylpent-1-en-4-yn-3-one was formed through the rearrangement by using the neutral alumina column, and the corresponding imine 2-(1,5-diphenylpent-2-en-4-ynylideneamino)ethanol was obtained in the presence of AgOTf.

Inrtoduction

Propargylamines are important structural elements in natural products and drug molecules[1] and also versatile synthetic intermediates in organic chemistry.[2] Methods for their preparation by transition metal catalysis have been investigated intensely over the past decades.[3] However, the general solutions for 3-amino-1,4-diynes from direct catalytic couplings of terminal alkynes have not been presented. All published methods for 3-amino-1,4-diynes rely on stoichiometric quantities of alkyne anions that are prepared from

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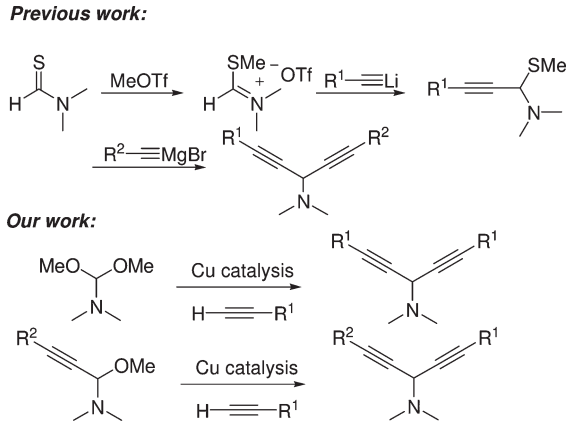
(3) For recent works on metal-promoted coupling of alkynes, aldehydes, and amines (A^3 coupling) leading to propargylic amines see: (a) Li, C.-J.; Wei, C.-M. *Chem. Commun.* **2002**, 268. (b) Gommermann, N.; Koradin, C.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 5763. (c) Wei, C.-M.; Li, C.-J. *J. Am. Chem. Soc.* **2003**, *125*, 9584. (d) Wei, C.-M.; Li, Z.-P.; Li, C.-J. *Synlett* **2004**, 1472. (e) Shi, L.; Tu, Y.-Q.; Wang, M.; Zhang, F.-M.; Fan, C.-A. *Org. Lett.* **2004**, *6*, 1001. (f) Lo, V. K.-Y.; Liu, Y.-G.; Wong, M.-K.; Che, C.-M. *Org. Lett.* **2006**, *8*, 1529. (g) Li, P.-H.; Zhang, Y.-C.; Wang, L. *Chem.—Eur. J.* **2009**, *15*, 2045. (h) Zhang, Y.-C.; Li, P.-H.; Wang, M.; Wang, L. *J. Org. Chem.* **2009**, *74*, 4364.

Published on Web 06/10/2010 DOI: 10.1021/jo1007898

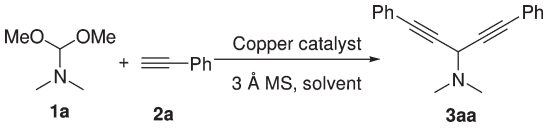
SCHEME 1



terminal alkynes and organometal bases (Scheme 1).[4] Direct alkynylation with terminal alkynes would constitute a more efficient approach because it eliminates the need for the stoichiometric preparation of alkyne anions. Over the past ten years, the direct coupling of terminal alkynes with acetals have been studied.[5] For instance, copper-mediated coupling of alkynes with *N*-acylimine was reported by Li and co-workers,[6] which provides an attractive alternative to traditional method through alkyne anions. Sakai and co-workers reported the use of the $InBr_3-Et_3N$ system to promote the alkynylation of *N*,*O*- or *N*,*S*-acetals.[7] However, the application of those methods is limited owing to the lack of a general and mild method for their generation and the need for stoichiometric amounts of metal in their reactions.

The development in transition metal-catalyzed transformations involving C−OMe coupling reactions has attracted much interest due to being a highly attractive research area in organic chemistry.[8] We have recently studied the coupling of the C−H bond adjacent to nitrogen and oxygen atoms,[9,10] and the direct coupling of terminal alkynes with the C−H bond adjacent to a nitrogen atom has been achieved under oxidative conditions through a copper-catalyzed cross-dehydrogenative coupling process by Li and co-workers.[11] In light of these advances, our interest in new catalytic reactions inspired us to explore the reactivity of C−OMe adjacent to a nitrogen atom. Herein, we describe a method for the direct alkynylation of *N*,*N*-dimethylformamide dialkyl acetals with terminal alkynes by the use of copper catalyst and phosphine ligand. The transformation involves the coupling of C−OMe adjacent to a nitrogen atom with terminal alkynes under mild reaction conditions to give 3-amino-1,4-diynes (Scheme 1).

TABLE 1. Optimization of Reaction Conditions [a]



entry	catalyst	ligand[b]	solvent	temp (°C)	yield[c] (%)
1	CuBr	none	toluene	80	45
2	none	none	toluene	80	0[d]
3	CuBr	PPh_3	toluene	80	68
4	CuBr	dppb	toluene	80	65
5	CuBr	dppe	toluene	80	72
6	CuBr	dppp	toluene	80	85
7	CuBr	bipyridine	toluene	80	36
8	CuBr	L-proline	toluene	80	52
9	CuBr	dppp	toluene	70	68
10	CuCl	dppp	toluene	80	58
11	CuI	dppp	toluene	80	83
12	$CuBr_2$	dppp	toluene	80	43
13	CuBr	dppp	dioxane	80	62
14	CuBr	dppp	THF	80	75
15	CuBr	dppp	DMF	80	0
16[e]	CuBr	dppp	toluene	80	75
17[f]	CuBr	dppp	toluene	80	84

[a]Reaction conditions: **1a** (0.5 mmol), **2a** (1.5 mmol), copper catalyst (0.05 mmol), ligand (0.05 mmol), 3 Å MS (100 mg), solvent (3 mL), N_2, 10 h. [b]dppe = 1,2-bis(diphenylphosphino)ethane; dppp = 1,2-bis(diphenylphosphino)propane; dppb = 1,2-bis(diphenylphosphino)butane. [c]Isolated yields. [d]1-Methoxy-*N*,*N*-dimethyl-3-phenylprop-2-yn-1-amine **4a** was obtained in 32% yield. [e]No 3 Å MS added. [f]**1a** scaled up to 10 mmol.

Results and Discussion

Our initial studies focused on the coupling reaction of cheap and commercially available *N*,*N*-dimethylformamide dimethyl acetal **1a** with phenyl acetylene **2a**. The reaction was carried out in toluene at 80 °C for 10 h with the aid of 3 Å molecular sieve. Copper catalyst was absolutely required for the production of **3aa** and CuBr alone gave low yield (Table 1, entries 1 and 2). However, the addition of phosphine ligand led to the rapid increase in activity, and an 85% yield was obtained when 1,3-bis(diphenylphosphino)propane (dppp) was used as the ligand (Table 1, entries 3−6). L-Proline and bipyridine showed a poor effect on the reaction (Table 1, entries 7 and 8). The yield dropped to 68% when the reaction temperature was decreased to 70 °C (Table 1, entry 9). A number of Cu sources tested revealed that certain species including CuCl, CuBr, and CuI were active in the coupling, while $CuBr_2$ showed low reactivity (Table 1, entries

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(9) (a) Cheng, K.; Huang, L.-H.; Zhang, Y.-H. *Org. Lett.* **2009**, *11*, 2908. (b) Huang, L.-H.; Zhang, X.-B.; Zhang, Y.-H. *Org. Lett.* **2009**, *11*, 3730. (c) Huang, L.-H.; Cheng, K.; Yao, B.-B.; Zhao, J.-L.; Zhang, Y.-H. *Synthesis* **2009**, 3504.

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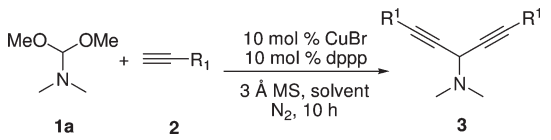
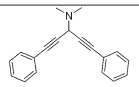
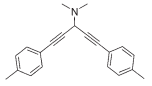
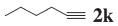
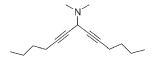
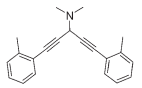
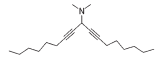
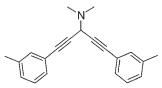
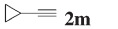
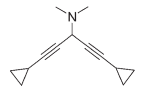
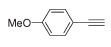
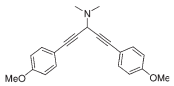
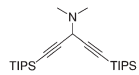
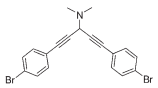
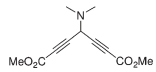
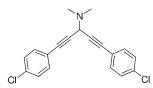
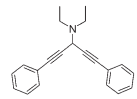
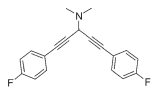
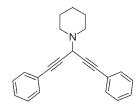
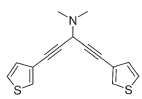
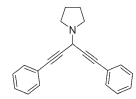
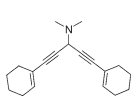
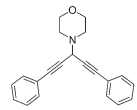
TABLE 2. Cu-Catalyzed Cross-Coupling of Acetals with Terminal Alkynes[a]



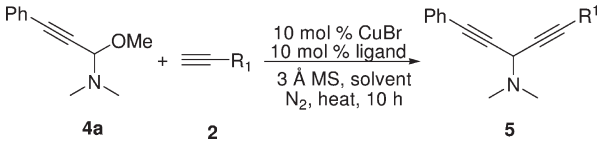
1a **2** **3**

entry	alkynes	temp (°C)	3	yield[b] (%)	entry	alkynes	temp (°C)	3	yield[b] (%)
1	 **2a**	80	 **3aa**	85				**3aj**	
2	 **2b**	85	 **3ab**	85	11	 **2k**	110	 **3ak**	76 [c]
3	 **2c**	85	 **3ac**	73	12	**2l**	110	 **3al**	75 [c]
4	 **2d**	85	 **3ad**	76	13	 **2m**	110	 **3am**	79 [c]
5	 **2e**	110	 **3ae**	87	14	**2n**	110	 **3an**	65 [c]
6	 **2f**	110	 **3af**	62	15	**2p**	85	 **3ap**	0 [a, c]
7	 **2g**	110	 **3ag**	66	16	**2a**	80	 **3ba**	76 [d]
8	 **2h**	85	 **3ah**	77	17	**2a**	100	 **3ca**	71 [e]
9	 **2i**	85	 **3ai**	85	18	**2a**	100	 **3da**	85 [f]
10	 **2j**	110		80 [c]	19	**2a**	90	 **3ea**	72 [g]

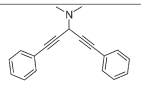
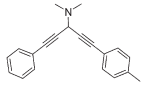
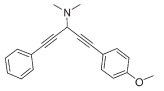
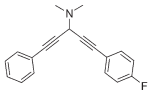
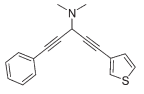
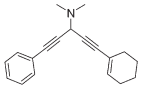
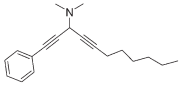
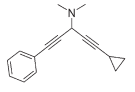
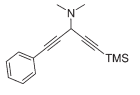
[a]Reaction conditions: **1a** (0.5 mmol), terminal alkynes (1.5 mmol), CuBr (0.05 mmol), dppp (0.05 mmol), 3 Å MS (100 mg), toluene (3 mL). [b]Isolated yields. [c]Reaction run with $(n\text{-Bu})_3P$ (0.05 mmol) in THF (3 mL) for 8 h. [d]*N*,*N*-Diethylformamide dimethyl acetal (**1b**) was used. [e]*N*-Formylpiperidine dimethyl acetal (**1c**) was used. [f]*N*-Formylpyrrolidine dimethyl acetal (**1d**) was used. [g]*N*-Formylmorpholine dimethyl acetal (**1e**) was used.

10−12). Other solvents such as dioxane and THF furnished the coupling product in lower yields (Table 1, entries 13 and 14). It should be noted that *N*,*N*-dimethylformamide (DMF) was totally inactive, even used as solvent (Table 1, entry 15). The addition of 3 Å molecular sieve facilitated the coupling reaction and the yield decreased without the use of 3 Å MS (Table 1,

TABLE 3. Cross-Coupling of Terminal Alkynes with 4a[a]



4a **2** **5**

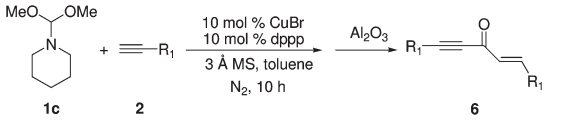
entry	alkynes	product	yield (%)[b]
1	**2a**	 **3aa**	86
2	**2b**	 **5ab**	84
3	**2e**	 **5ae**	83
4	**2h**	 **5ah**	76
5	**2i**	 **5ai**	85
6[c]	**2j**	 **5aj**	81
7[c]	**2l**	 **5al**	71
8[c]	**2m**	 **5am**	71
9[c]	TMS—≡ **2o**	 **5ao**	70

[a]Reaction conditions: **4a** (0.5 mmol), terminal alkynes (0.6 mmol), CuBr (0.05 mmol), dppp (0.05 mmol), 3 Å MS (100 mg), toluene (3 mL). [b]Isolated yields. [c]Reaction run with $(n\text{-Bu})_3P$ (0.05 mmol) in THF (3 mL).

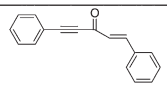
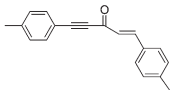
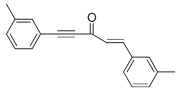
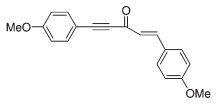
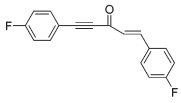
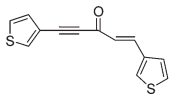
entry 16). The reaction could be scaled up to 10 mmol to give an 84% isolated yield (Table 1, entry 17).

This new cross-coupling reaction displayed good functional group tolerance toward terminal alkynes **2**. Terminal alkynes possessing aryl, thiophenyl, alkenyl, alkyl, cyclopropyl, and TIPS were nearly equally efficient in the alkynylation. It is important to note that fluoride, chloride, and bromide groups are tolerated in the reaction (Table 2, entries 6−8). These valuable functional groups should enable further elaboration of the alkynylation products. In the case of methyl propiolate, no desired product could be obtained (Table2, entry 15). The substrate scope in *N*,*N*-dialkylformamide dimethyl acetal was evaluated with phenyl acetylene

TABLE 4. Synthesis of 1,5-Diarylpent-1-en-4-yn-3-one[a]

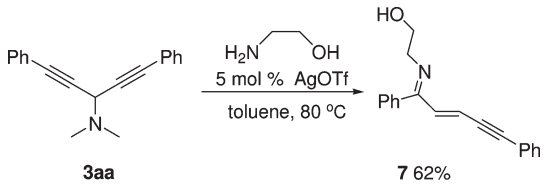


1c **2** **6**

entry	alkynes	product	yield (%)[b]
1	**2a**	 **6a**	62
2	**2b**	 **6b**	73
3	**2d**	 **6d**	54
4	**2e**	 **6e**	51
5	**2h**	 **6h**	52
6[c]	**2g**		68

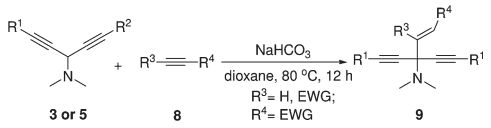
[a]Reaction conditions: **1c** (0.5 mmol), terminal alkynes (1.5 mmol), CuBr (0.05 mmol), dppp (0.05 mmol), 3 Å MS (100 mg), toluene (3 mL), 110 °C, N_2, 10 h. Treatment in neutral alumina column results in the products. [b]Isolated yields.

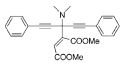
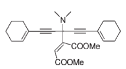
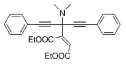
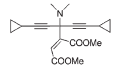
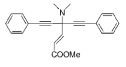
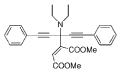
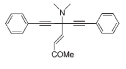
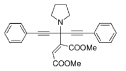
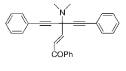
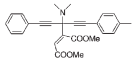
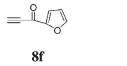
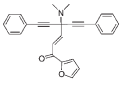
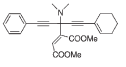
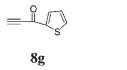
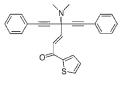
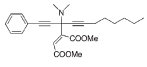
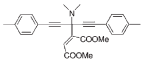
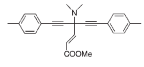
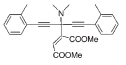
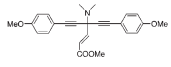
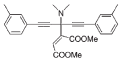
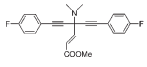
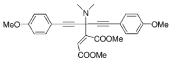
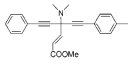
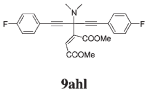
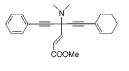
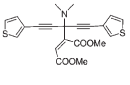
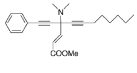
SCHEME 2



3aa **7** 62%

TABLE 5. Michael-Type Addition Reaction of 3-Amino-1,4-diynes[a]



entry	3	8	product	yield[b] (%)	entry	3	8	product	yield[b] (%
1	**3aa**	**8a**	 **9aaa**	82	14	**3aj**	**8a**	 **9ajn**	77
2	**3aa**	**8b**	 **9aab**	84	15	**3am**	**8a**	 **9amo**	68
3	**3aa**	**8c**	 **9aac**	69[c]	16	**3ba**	**8a**	 **9bap**	65
4	**3aa**	**8d**	 **9aad**	43[d]	17	**3da**	**8a**	 **9daq**	77
5	**3aa**	**8e**	 **9aae**	56	18	**5ab**	**8a**	 **9abr**	93
6	**3aa**	 **8f**	 **9aaf**	59	19	**5aj**	**8a**	 **9ajs**	81
7	**3aa**	 **8g**	 **9aag**	53	20	**5al**	**8a**	 **9alt**	82
8	**3ab**	**8a**	 **9abh**	88	21	**3ab**	**8c**	 **9abu**	70[c]
9	**3ac**	**8a**	 **9aci**	83	22	**3ae**	**8c**	 **9aev**	68[c]
10	**3ad**	**8a**	 **9adj**	84	23	**3ah**	**8c**	 **9ahw**	75[c]
11	**3ae**	**8a**	 **9aek**	75	24	**5ab**	**8c**	 **9abx**	78[c]
12	**3ah**	**8a**	 **9ahl**	85	25	**5aj**	**8c**	 **9ajy**	70[c]
13	**3ai**	**8a**	 **9aim**	80	26	**5al**	**8c**	 **9alz**	72[c]

[a]Reaction conditions: 3-amino-1,4-diynes (1 equiv), **8** (1.5 equiv), $NaHCO_3$ (2 equiv), 12 h. [b]Isolated yields. [c]The amount of **8c** was 2 equiv. [d]Reaction temperature was 80 °C, and the amount of **8d** was 2.5 equiv.

as the coupling partner. Both acyclic and cyclic formamide dimethyl acetals are accommodated with good efficiency (Table 2, entries 16−19). Attempted cross-coupling with 1,1-dimethoxy-*N*,*N*-dimethylethanamine failed to afford the desired product, with only unreacted starting material recovered.

We next conceived to extend the coupling reaction with 1-methoxy-*N*,*N*-dimethyl-3-phenylprop-2-yn-1-amine **4a** to prepare unsymmetrical 3-amino-1,4-diynes. We are pleased to find that the optimized conditions also could be successfully applied to the coupling reaction of **4a** to give the corresponding asymmetric 3-amino-1,4-diynes **5** (Table 3). Good alkynylation yields were obtained for various terminal alkynes. This method would provide avenues for the development of asymmetric processes leading to C−C bond formation.

The plausible mechanism for this copper-catalyzed coupling reaction of the C−OMe bond adjacent to a nitrogen atom might take place through the elimination of MeOH from *N*,*N*-dimethylformamide dialkyl acetals to form iminium salt.[3] The subsequent nucleophilic addition of copper acetylide gives the final product. The phosphine ligands significantly improve the reaction and the absorption of produced MeOH by 3 Å molecular sieve facilitates the generation of products.

Table 4 highlights the utilization of as-prepared 3-amino-1,4-diynes as useful building blocks. The treatment of crude products of **3ca**−**3cg** in neutral alumina column led to the easy rearrangement by the use of petroleum ether/ethyl acetate as eluant to give the mono configuration of (*E*)-1,5-diarylpent-1-en-4-yn-3-one (Table 4), which are important intermediates in organic synthesis.[12] Arylalkynes with both electron-withdrawing (−F) or electron-donating (−OMe) groups in the aromatic ring worked well under the reaction conditions to afford the products of rearrangement smoothly (Table 4, entries 1−5). Notably, heterocyclealkyne (**2g**) could also give its corresponding rearrangement product **6g** in 68% yield. In addition, the treatment of *N*,*N*-dimethyl-1,5-diphenylpenta-1,4-diyn-3-amine **3aa** with 2-aminoethanol in the presence of 5 mol % AgOTf led to the formation of imine **7**, 2-(1,5-diphenylpent-2-en-4-ynylideneamino)ethanol, in 62% yield (Scheme 2).

It should be noted that as-prepared 3-amino-1,4-diynes reacted with both terminal and internal electron-deficient alkynes to deliver the corresponding Michael adducts 4-amino-2-en-5-ynoates containing *tert*-alkylamines[13] in the presence of 2 equiv of $NaHCO_3$ (Table 5). In general, dialkyl but-2-ynedioate showed higher reactivity than alkyl propiolate and prop-2-yn-1-one (Table 5, entries 1−7). It was found that dimethyl but-2-ynedioate and diethyl but-2-ynedioate provided the Michael adducts in high yields (Table 5, entries 1 and 2), while methyl propiolate, but-3-yn-2-one, 1-phenylprop-2-yn-1-one, 1-(furan-2-yl)prop-2-yn-1-one, and 1-(thiophen-2-yl)prop-2-yn-1-one were less active to give the corresponding addition products in relatively lower yields (Table 5, entries 3−7). In all cases, the Michael addition reaction took place cleanly, without any competitive formation of second Michael addition products. The reaction tolerated a wide range of 3-amino-1,4-diynes, including symmetric and asymmetric 3-amino-1,4-diynes (**3** and **5,** Table 5, entries 8−26). The analogous addition to an electron-deficient double bond failed possibly due to the lower reactivity.

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Conclusion

In summary, we have developed a copper-catalyzed process for the cross-coupling of the C−OMe bond adjacent to a nitrogen atom with terminal alkynes. The simple and efficient catalytic system worked well with a broad range of terminal alkynes and allowed the facile synthesis of 3-amino-1,4-diynes under mild reaction conditions. It was found that 3-amino-1,4-diynes were interesting building blocks in the straightforward synthesis of various useful molecules. The easy rearrangement by the use of petroleum ether/ethyl acetate as eluant gives the mono configuration of (*E*)-1,5-diarylpent-1-en-4-yn-3-ones, and the treatment of *N*,*N*-dimethyl-1,5-diphenylpenta-1,4-diyn-3-amine with 2-aminoethanol in the presence of 5 mol % AgOTf led to the formation of the corresponding imine. Notably, the as-prepared 3-amino-1,4-diynes can be used as a Michael donor to addition toward the electron-deficient triple bonds to give the Michael adducts containing *tert*-alkylamines. The exploration of other new coupling reactions of *N*,*N*-dialkylformamide dimethyl acetals is in progress in our laboratories.

Experimental Section

A Typical Procedure for the Preparation of 3aa−3ai and 3ba−3ea (Method A). Under nitrogen atmosphere, an oven-dried Schlenk tube equipped with a magnetic stir bar was charged with terminal alkynes **2a**−**2i** (1.5 mmol), *N*,*N*-dialkyllformamide dimethyl acetals **1a**−**1e** (0.5 mmol), CuBr (0.05 mmol), dppp (0.05 mmol), 3 Å molecular sieves (100 mg), and toluene (3.0 mL). The resulting mixture was stirred at 80−110 °C for 10 h. After cooling to room temperature, the mixture was filtered through a pad of Cellite and the solvent was removed under reduced pressure. The residue was subjected to flash column chromatography on a silica gel column to afford the desired products **3aa**−**3ai** and **3ba**−**3ea**.

A Typical Procedure for the Preparation of 3aj−3an (Method B). Under nitrogen atmosphere, an oven-dried sealed tube equipped with a magnetic stir bar was charged with terminal alkynes **2j**−**2n** (1.5 mmol), *N*,*N*-dimethylformamide dimethyl acetal **1a** (0.5 mmol), CuBr (0.05 mmol), $(n\text{-Bu})_3P$ (0.05 mmol), 3 Å molecular sieves (100 mg), and THF (3.0 mL). The resulting mixture was stirred at 110 °C for 8 h. After cooling to room temperature, the mixture was filtered through a pad of Cellite and the solvent was removed under reduced pressure. The residue was subjected to flash column chromatography on a silica gel column to afford the desired product **3aj**−**3an**.

A Typical Procedure for the Preparation of 5ab−5ai (Method C). Under nitrogen atmosphere, an oven-dried Schlenk tube equipped with a magnetic stir bar was charged with terminal alkynes **2a**−**2i** (0.6 mmol), 1-methoxy-*N*,*N*-dimethyl-3-phenylprop-2-yn-1-amine **4a** (0.5 mmol), CuBr (0.05 mmol), dppp (0.05 mmol), 3 Å molecular sieves (100 mg), and toluene (3.0 mL). The resulting mixture was stirred at 110 °C for 10 h. After cooling to room temperature, the mixture was filtered through a pad of Cellite and the solvent was removed under

reduced pressure. The residue was subjected to flash column chromatography on a silica gel column to afford the desired product **5ab**−**5ai**.

A Typical Procedure for the Preparation of 5aj−**5ao (Method D).** Under nitrogen atmosphere, an oven-dried sealed tube equipped with a magnetic stir bar was charged with terminal alkynes **2j**−**2o** (1.0 mmol), 1-methoxy-*N*,*N*-dimethyl-3-phenylprop-2-yn-1-amine **4a** (0.5 mmol), CuBr (0.05 mmol), $(n\text{-Bu})_3P$ (0.05 mmol), 3 Å molecular sieves (100 mg), and THF (3.0 mL). The resulting mixture was stirred at 110 °C for 8 h. After cooling to room temperature, the mixture was filtered through a pad of Cellite and the solvent was removed under reduced pressure. The residue was subjected to flash column chromatography on a silica gel column to afford the desired product **5aj**−**5ao**.

A Typical Procedure for the Preparation of 6a−**6g (Method E).** Under nitrogen atmosphere, an oven-dried Schlenk tube equipped with a magnetic stir bar was charged with terminal alkynes **2a** (1.5 mmol), *N*-formylpiperidine dimethyl acetal **1c** (0.5 mmol), CuBr (0.05 mmol), dppp (0.05 mmol), 3 Å molecular sieves (100 mg), and toluene (3.0 mL). The resulting mixture was stirred at 110 °C for 10 h. After cooling to room temperature, the mixture was filtered through a pad of Cellite and the solvent was removed under reduced pressure. The residue was subjected to flash column chromatography on neutral Al_2O_3 (ethyl acetate/petroleum ether = 1:10, v/v) at 25 °C to afford the desired product **6a**−**6g**.

A Typical Procedure for the Preparation of 7 (Method F). Under nitrogen atmosphere, an oven-dried Schlenk tube equipped with a magnetic stir bar was charged with *N*,*N*-dimethyl-1,5-diphenylpenta-1,4-diyn-3-amine **3aa** (0.5 mmol), 2-aminoethanol (1.0 mmol), AgOTf (6 mg, 0.025 mmol), and toluene (3.0 mL). The resulting mixture was stirred at 80 °C for 12 h. After cooling to room temperature, the mixture was filtered through a pad of Cellite and the solvent was removed under reduced pressure. The residue was subjected to flash column chromatography on a silica gel column to afford the desired product **7**.

A Typical Procedure for the Preparation of 9aaa−**9alz (Method G).** Under nitrogen atmosphere, an oven-dried Schlenk tube equipped with a magnetic stir bar was charged with 3-amino-1,4-diynes **3** or **5** (1 equiv), **8** (1.5−2.5 equiv), $NaHCO_3$ (2 equiv), and dioxane (3 mL). The resulting mixture was stirred at 80−100 °C for 12 h. After cooling to room temperature, the mixture was filtered through a pad of Cellite and the solvent was removed under reduced pressure. The residue was subjected to flash column chromatography on a silica gel column to afford the desired product **9aaa**−**9alz**.

***N*,*N*-Dimethyl-(1,5-di-*p*-tolylpenta)-1,4-diyn-3-amine (3ab).** Preparation according to method A with *N*,*N*-dimethylformamide dimethyl acetal **1a** (64 mg, 0.5 mmol), 1-ethynyl-4-methylbenzene (174 mg, 1.5 mmol) at 85 °C provided **3ab** (122 mg; 85% yield) after flash chromatography with a solution of EA/Pet = 1/6 as eluent. Gray solid, mp 68−69 °C; ^{1}H NMR ($CDCl_3$, 400 MHz, TMS) δ 7.37−7.39 (d, J = 8.0 Hz, 4 H), 7.10−7.12 (d, J = 7.6 Hz, 4 H), 4.76 (s, 1 H), 2.47 (s, 6 H), 2.34 (s, 6 H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ 138.2, 131.5, 128.4, 119.3, 84.3, 82.7, 49.8, 41.1, 21.2 ppm; IR (neat) ν 3208, 2976, 2944, 2860, 2823, 2780, 2244, 1509, 1293, 1035, 816 cm^{-1}; MS (ESI) m/z 288.2 ([M + H]$^+$); HRMS (ESI) calcd for $C_{21}H_{22}N$ ([M + H]$^+$) 288.1752, found 288.1747.

***N*,*N*-Dimethyl-1,5-dicyclohexenyl-1,4-diyn-3-amine (3aj).** Preparation according to method B using *N*,*N*-dimethylformamide dimethyl acetal **1a** (64 mg, 0.5 mmol) and 1-ethynylcyclohex-1-ene (159 mg, 1.5 mmol) at 110 °C provided **3aj** (107 mg; 80% yield) after flash chromatography with a solution of EA/Pet = 1/20 as eluent. Yellow liquid; ^{1}H NMR ($CDCl_3$, 400 MHz, TMS) δ 6.13 (m, 2 H), 4.53 (s, 1 H), 2.34 (s, 6 H), 2.07−2.13 (m, 8 H), 1.54−1.65 (m, 8 H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ 135.1, 120.1, 85.9, 81.0, 49.8, 41.1, 29.2, 25.5, 22.2, 21.4 ppm; IR (neat) ν 3026, 2933, 2858, 2823, 2778, 2219, 1451, 1284, 1024, 918, 841 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{26}N$ ([M + H]$^+$) 268.2065, found 268.2064.

***N*,*N*-Dimethyl-1-phenyl-5-*p*-tolylpenta-1,4-diyn-3-amine (5ab).** Preparation according to method C with 1-methoxy-*N*,*N*-dimethyl-3-phenylprop-2-yn-1-amine **4a** (95 mg, 0.5 mmol) and 1-ethynyl-4-methylbenzene (70 mg, 0.6 mmol) provided **5ab** (114 mg; 84% yield) after flash chromatography with a solution of EA/Pet = 1/6 as eluent. Yellow liquid; ^{1}H NMR ($CDCl_3$, 400 MHz, TMS) δ 7.48−7.49 (m, 2 H), 7.37−7.39 (d, J = 7.6 Hz, 2 H), 7.30 (m, 3 H), 7.10−7.11 (d, J = 7.6 Hz, 2 H), 4.77 (s, 1 H), 2.47 (s, 6 H), 2.33 (s, 3 H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ 138.5, 131.9, 131.8, 129.0, 128.4, 128.2, 122.6, 119.5, 84.6, 84.4, 83.7, 82.8, 50.1, 41.4, 21.5 ppm; IR (neat) ν 3073, 3056, 2977, 2944, 2861, 2824, 2780, 2227, 1594, 1509, 1489, 1489, 1453, 1324, 1292, 1037, 817, 756, 691 cm^{-1}; HRMS (EI) calcd for $C_{20}H_{19}N$ (M$^+$) 273.1517, found 273.1516.

1-Cyclohexenyl-*N*,*N*-dimethyl-5-phenylpenta-1,4-diyn-3-amine (5aj). Preparation according to method D with 1-methoxy-*N*,*N*-dimethyl-3-phenylprop-2-yn-1-amine **4a** (95 mg, 0.5 mmol) and 1-ethynylcyclohex-1-ene (66 mg, 0.6 mmol) provided **5aj** (106 mg; 81% yield) after flash chromatography with a solution of EA/Pet = 1/6 as eluent. Yellow liquid; ^{1}H NMR ($CDCl_3$, 400 MHz, TMS) δ 7.46−7.48 (m, 2 H), 7.28−7.32 (m, 3 H), 6.16−6.18 (m, 1 H), 4.66 (s, 1 H), 2.41 (s, 6 H), 2.07−2.18 (m, 4 H), 1.56−1.65 (m, 4 H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ 135.4, 131.8, 128.3, 122.7, 120.1, 86.3, 84.1, 83.9, 80.6, 49.9, 41.3, 29.2, 25.6, 22.2, 21.4 ppm; IR (neat) ν 3055, 3025, 2975, 2936, 2859, 2824, 2779, 2222, 1599, 1489, 1452, 1443, 1323, 1288, 1026, 918, 756, 691 cm^{-1}; HRMS (EI) calcd for $C_{19}H_{21}N$ (M$^+$) 263.1674, found 263.1682.

(*E*)-1,5-Di(*p*-tolyl)pent-1-en-4-yn-3-one (6b). Preparation according to method E with as-prepared *N*-formylpiperidine dimethyl acetal **1c** (90 mg, 0.5 mmol) and 1-ethynyl-4-methylbenzene (174 mg, 1.5 mmol) provided **6b** (95 mg; 73% yield) after flash chromatography at 25 °C on neutral Al_2O_3 with a solution of EA/Pet = 1/10 as eluent. White solid, mp 147−148 °C; ^{1}H NMR ($CDCl_3$, 400 MHz, TMS) δ 7.86−7.90 (d, J = 16.4 Hz, 1 H), 7.54−7.55 (d, J = 7.6 Hz, 2 H), 7.49−7.51 (d, J = 8.0 Hz, 2 H), 7.21−7.26 (m, 4 H), 6.81−6.85 (d, J = 15.6 Hz, 1 H), 2.40 (s, 6 H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ 178.3, 148.2, 141.8, 141.2, 132.9, 131.4, 129.8, 129.4, 128.7, 127.7, 117.1, 92.0, 86.5, 21.7, 21.6 ppm; IR (KBr) ν 2916, 2211, 2161, 1622, 1598, 1504, 1380, 1307, 1288, 1169, 816 cm^{-1}; HRMS (EI) calcd for $C_{19}H_{16}O$ (M$^+$) 260.1201, found 260.1196.

(2*Z*)-2-((*E*)-1,5-Diphenylpent-2-en-4-ynylideneamino)ethanol (7). Preparation according to method F with as-prepared *N*,*N*-dimethyl-1,5-diphenylpenta-1,4-diyn-3-amine **3aa** (129 mg, 0.5 mmol) and 2-aminoethanol (61 mg, 1.0 mmol) provided **7** (85 mg; 62% yield) after flash chromatography with a solution of EA/Pet = 1/2 as eluent. Yellow solid, mp 106−107 °C; ^{1}H NMR (d_6-DMSO, 400 MHz, TMS) δ 7.70−7.74 (t, J = 8.2 Hz, 4 H), 7.35−7.56 (m, 7 H), 7.05−7.09 (d, J = 16.8 Hz, 1 H), 4.70−4.73 (t, J = 5.6 Hz, 1 H), 3.87−3.90 (t, J = 6.2 Hz, 2 H), 3.71−3.76 (q, J = 6.1 Hz, 2 H) ppm; ^{13}C NMR (d_6-DMSO, 100 MHz, TMS) δ 151.7, 139.0, 135.8, 132.7, 130.6, 129.9, 129.65, 129.4, 129.3, 128.0, 121.0, 98.0, 80.5, 61.5, 59.4 ppm; IR (KBr) ν 3422, 3214, 291, 2221, 1631, 1565, 1489, 1446, 1384, 1321, 1056, 964, 762, 689 m^{-1}; MS (ESI) m/z 276.1 ([M + H]$^+$); HRMS (ESI) calcd for $C_{19}H_{17}NO$ (M)$^+$ 275.1310, found 275.1308.

(*Z*)-Dimethyl-2-(3-(dimethylamino)-1,5-diphenylpenta-1,4-diyn-3-yl)maleate (9aaa). Preparation according to method G with *N*,*N*-dimethyl-1,5-diphenylpenta-1,4-diyn-3-amine **3aa** (129 mg, 0.5 mmol) and dimethyl but-2-ynedioate (106 mg, 0.75 mmol) at 85 °C provided **9aaa** (166 mg; 83% yield) after flash

chromatography with a solution of EA/Pet = 1/6 as eluent. Yellow solid, mp 87−88 °C; ^{1}H NMR ($CDCl_3$, 400 MHz, TMS) δ 7.51−7.53 (m, 4 H), 7.33−7.35 (m, 6 H), 6.69 (s, 1 H), 3.91 (s, 3 H), 3.76 (s, 3 H), 2.49 (s, 6 H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz, TMS) δ 166.1, 164.9, 150.3, 132.0, 128.8, 128.3, 122.0, 121.97, 87.7, 83.1, 62.5, 52.7, 52.1, 40.1 ppm; IR (neat) ν 3057, 2994, 2952, 2866, 2829, 2785, 2231, 1743, 1649, 1597, 1490, 1434, 1350, 1252, 1198, 1168, 1069, 1007, 985, 889, 757, 691 cm^{-1}; HRMS (EI) calcd for $C_{25}H_{23}NO_4$ (M^+) 401.1627, found 401.1634.

Acknowledgment. Funding from Natural Science Foundation of China (No. 20872126) and Zhejiang Provincial Natural Science Foundation of China (R407106) is acknowledged.

Supporting Information Available: Experimental procedure, crystallographic information files (CIF) for **9aaa** and **9aac**, and spectroscopic data (^{1}H NMR, ^{13}C NMR, MS, and HRMS) for the products. This material is available free of charge via the Internet at http://pubs.acs.org.