DOI: 10.1002/adsc.200800249

Sequential Copper(I)-Catalyzed Reaction of Amines with *o*-Acetylenyl-Substituted Phenyldiazoacetates

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Received: April 26, 2008; Published online: September 9, 2008

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.200800249.

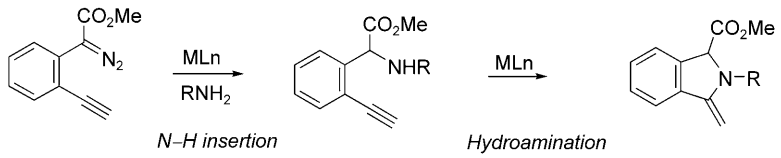
Abstract: A highly efficient, tetrakis(acetonitrile)-copper(I) hexafluorophosphate [$Cu(MeCN)_4PF_6$]-catalyzed tandem Cu(I)-carbene N–H insertion/Cu(I)-catalyzed hydroamination of alkynes, which leads to sequential formation of two C–N bonds to yield isoindole derivatives, has been developed.

Keywords: alkynes; carbenoids; copper; diazo compounds; homogeneous catalysis; insertion

Introduction

Transition metal catalysis has become indispensable in modern organic synthesis. While efficiency and selectivity are the major concerns in these metal-catalyzed reactions, an emerging area of research in this field is to develop reaction systems in which a single catalyst mediates two or more different reactions in a selective manner.[1–4] Such a kind of sequential or concurrent catalysis is particularly attractive in organic synthesis in view of ecological and economical concerns in the fine chemical industries. Because there are many different reactions that can be catalyzed by the same or similar transition metal catalysts, a great potential exists to link these reactions in sequence. Recently, a number of efficient sequential catalytic processes, such as Ru-catalyzed RCM/hydrogenation,[2] Rh-catalyzed allylic alkylation/Pauson–Khand reaction,[3] Pd-catalyzed aryl alkylation/cyanation reaction,[4] have been developed.

C–N bond formation is important in organic synthesis, and there have been many reports on transition metal-catalyzed C–N bond formations. Among these catalytic C–N bond formations, metal carbene N–H bond insertion[5,6] and hydroamination of alkynes[7] are particularly attractive due to their high efficiency. For metal carbene N–H insertions, α-diazocarbonyl compounds normally serve as metal carbene precursors, and Cu(I) and Rh(II) complexes are the most widely used catalysts. While for hydroamination of alkynes, transition metal complexes of Ti,[8] Pd,[9] Pt,[10] Ru,[11] Au,[12] Rh,[13] Ir,[14] La,[7f,15] Zn and Cd,[16] Hg,[17] Zr[18] and Ac[19] have been widely utilized. Although it is less common, copper-catalyzed hydroamination of alkynes has also been reported.[20] Significant progress has been made in both intra- and intermolecular hydroaminations of alkynes by utilizing these catalytic systems. We thought that it might be possible to combine the metal carbene N–H insertion and hydroamination of alkynes into a sequential catalytic process with only one catalyst. Here we report our study based on this concept (Scheme 1).



Scheme 1. Two C–N bond formations catalyzed by single catalyst.

Results and Discussion

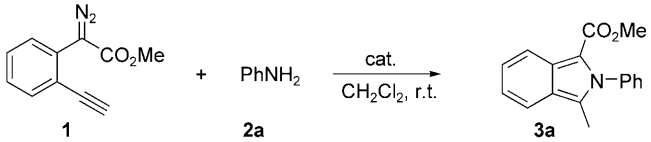
o-Acetylenyl-substituted phenyldiazoacetate **1** was selected as the substrate and it was subjected to copper catalysts in the presence of aniline (Table 1). $Cu(MeCN)_4PF_6$ was found to effectively catalyze diazo decomposition, and the subsequent N–H insertion and alkyne hydroamination (entry 1). The reaction gave isoindole **3a** through 5-*exo-dig* cyclization. No products from 6-*endo-dig* cyclization could be detected. Other copper catalysts were also examined. $Cu(acac)_2$, CuI and $(CuOTf)_2{\cdot}C_6H_6$ were all found to be effective for the reaction, but with lower yields as compared with the $Cu(MeCN)_4PF_6$-catalyzed reaction (entries 2–4). Catalyst loading and reaction temperature had only maginal effects on the reaction (entries 5 and 6).

A series of substituted anilines was then subjected to this sequential catalytic reaction with diazoacetate substrate **1**. As shown in Table 2, the reactions with substituted anilines all gave the corresponding isoindole derivatives in high yields. The electronic nature of the substituent on the amine seems to have no effect on the reaction. Both *p*-NO_2- and *p*-MeO-substituted anilines gave the corresponding isoindole products in high yields (entries 3 and 4). However, for the reactions with benzylamine and the aliphatic amine *t*-$BuNH_2$ as substrates, only low yields or trace amounts of isoindole products could be identified (entries 7 and 8). The reaction with tosylamide gave only the carbene dimerization product (entry 9). The structure of isoindole **3d** was unambiguously confirmed by single crystal X-ray analysis (Figure 1).[21]

Next, a series of substituted diazo compounds **4a–h** was prepared and their reactions with *p*-$MeC_6H_4NH_2$ were investigated (Table 3). The reactions all gave isoindole derivatives as major products. In contrast to the reaction of **1**, various amounts of dihydroquinoline derivatives **6a–h** were also isolated in these cases. It was noted that the reactions with **4a–h** all took longer time as compared to the reaction with **1**.

A proposed mechanism is shown in Scheme 2. Cu(I) carbene **7** is generated upon treatment of **1a** with $Cu(MeCN)_4PF_6$. Intermolecular N–H insertion

Table 1. Reaction of **1** and aniline **2a** with various Cu catalysts.

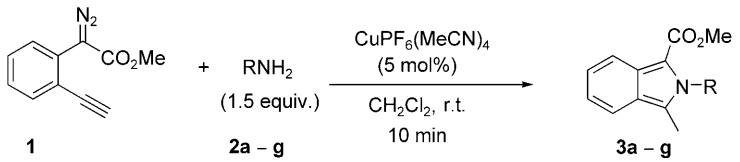


1 **2a** **3a**

Entry	Catalyst (mol%)	**2** (mol%)	Temperature [°C]	Time	Yield [%][a]
1	$CuPF_6(MeCN)_4$ (10)	120	35	10 min	87
2	$Cu(acac)_2$ (5)	150	35	10 h	56
3	CuI (5)	150	35	24 h	74
4	$(CuOTf)_2{\cdot}C_6H_6$ (2.5)	150	35	30 min	89
5	Cu $(MeCN)_4PF_6$ (10)	150	35	10 min	91
6	Cu $(MeCN)_4PF_6$ (5)	150	60	10 min	90

[a] Isolated yield after separation with column chromatography.

Table 2. Reaction of substrate **1** with substituted anilines.

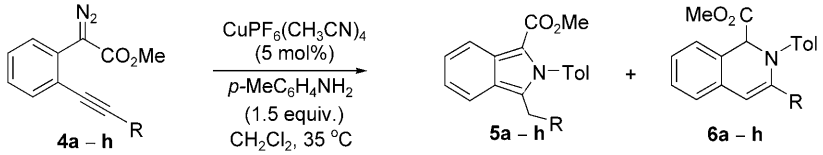


1 **2a – g** **3a – g**

Entry	**2**, R	**3**, Yield [%][a]	Entry	**2**, R	**3**, Yield [%][a]
1	**2a**, C_6H_5	**3a**, 90	6	**2f**, *p*-BrC_6H_4	**3f**, 92
2	**2b**, *p*-MeC_6H_4	**3b**, 95	7	**2g**, $C_6H_5CH_2$	**3g**, 28
3	**2c**, *p*-MeO-C_6H_4	**3c**, 93	8	**2h**, *t*Bu	**3h**, *trace*
4	**2d**, *p*-$NO_2C_6H_4$	**3d**, 90	9	**2i**, *p*-$MeC_6H_4SO_2$	**3i**, –[b]
5	**2e**, *m,p*-$Cl_2C_6H_3$	**3e**, 97			

[a] Isolated yield after separation with column chromatography.
[b] The reaction gave the dimerization product.

Table 3. Cu(I)-catalyzed reaction of **4a–h** with p-$MeC_6H_4NH_2$.



Entry	**4**, R	Time [h]	**5**, Yield [%][a]	**6**, Yield [%][a]
1	**4a**, C_6H_5	23	**5a**, 85	**6a**, 11
2	**4b**, p-BrC_6H_4	6	**5b**, 94	**6b**, 4
3	**4c**, p-MeC_6H_4	6	**5c**, 78	**6c**, 16
4	**4d**, o-ClC_6H_4	5	**5d**, 87	**6d**, <1
5	**4e**, o-BrC_6H_4	5	**5e**, 87	**6e**, <1
6	**4f**, m-MeC_6H_4	6	**5f**, 93	**6f**, 7
7	**4g**, p-$MeOC_6H_4$	24	**5g**, 57	**6g**, 33
8	**4h**, Me	23	**5h**, 66	**6h**, 17

[a] Isolated yield after separation with column chromatography.

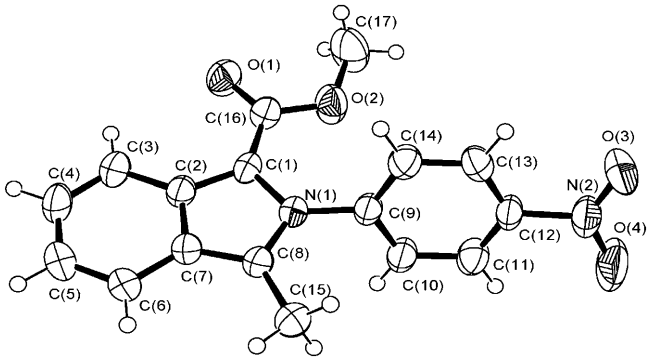
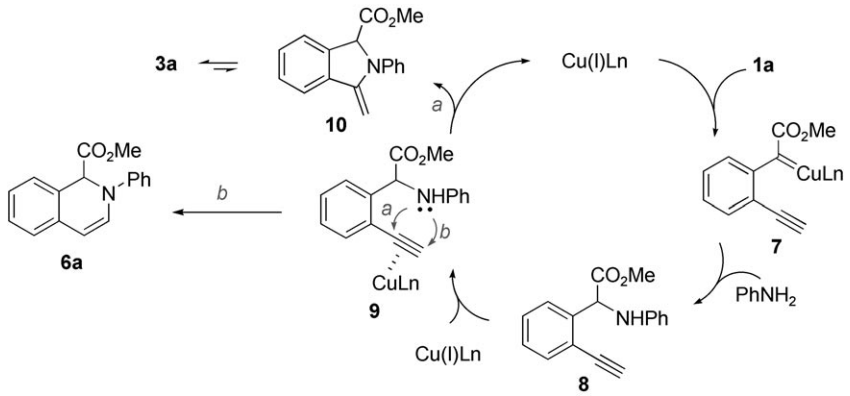


Figure 1. X-ray structure of **3d**.

with aniline leads to amine **8**. Subsequently, the amino nitrogen attacks the activated triple bond, which is coordinated with Cu(I) complex, in a 5-*exo-dig* manner, to give intermediate **10**. Compound **10** quickly isomerizes to isoindole **3a** (*path a*). If 6-*endo-dig* cyclization from **9** occurs, dihydroisoquinoline **6a** is generated (*path b*).

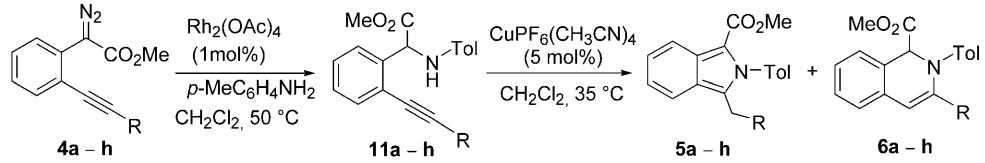
To substantiate the proposed mechanism, we tried to isolate the N–H insertion intermediate such as **8**. The reaction of **1** with amine was so fast that isolation of the N–H insertion intermediate proved to be difficult. Gratifyingly, the reaction of **4a** with p-$MeC_6H_4NH_2$ catalyzed by $Rh_2(OAc)_4$ could afford the N–H insertion product **11a** (Table 4, entry 1). Product **11a** was then subjected to further catalysis with $Cu(MeCN)_4PF_6$. However, contrary to our expectation isoindole **5a** was isolated in only 6% yield. The major product was dihydroisoquinoline derivative **6a**, which was isolated in 76% yield (entry 1). The formation of **6a** is due to 6-*endo-dig* attack of the amino group to the Cu(I)-activated triple bond.

A series of substituted N–H insertion products **11b–h** was then prepared by similar reactions catalyzed by $Rh_2(OAc)_4$. The N–H insertion products were subsequently subjected to catalysis by $Cu(MeCN)_4PF_6$. The reactions with the substrates **11b**, **c**, **f** and **g**, which bear *para*- and *meta*-aryl substituents in the triple bond moiety, all afforded the dihydroisoquinoline derivative as the major products



Scheme 2. Mechanistic proposal.

Table 4. Stepwise reaction of **4a–h** and *p*-$MeC_6H_4NH_2$ with two catalysts.[a]



4a – h 11a – h 5a – h 6a – h

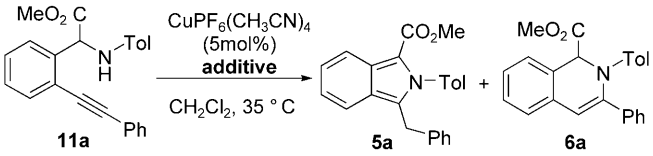
Entry	**4**, R	Time [h]	**11**, Yield [%][b]	Time [h]	**5**, Yield [%][b]	**6**, Yield [%][b]
1	**4a**, C_6H_5	8	**11a**, 92	12	**5a**, 6	**6a**, 76
2	**4b**, *p*-BrC_6H_4	7	**11b**, 99	5	**5b**, 19	**6b**, 81
3	**4c**, *p*-MeC_6H_4	20	**11c**, 90	5	**5c**, 4	**6c**, 95
4	**4d**, *o*-ClC_6H_4	6	**11d**, 70	4	**5d**, 85	**6d**, 9
5	**4e**, *o*-BrC_6H_4	25	**11e**, 85	5	**5e**, >99	**6e**, <1
6	**4f**, *m*-MeC_6H_4	11	**11f**, 72	6	**5f**, 8	**6f**, 89
7	**4g**, *p*-$MeOC_6H_4$	5	**11g**, 84	4	**5g**, 1	**6g**, 91
8	**4h**, Me	23	**11h**, 90	4	**5h**, 3	**6h**, 85

[a] The two reactions were carried out separately with two different catalysts.
[b] Isolated yield after separation with column chromatography.

(entries 2, 3, 6, 7). The corresponding substrates **11d** and **11e**, which bear *ortho*-substituents, gave isoindoles as the major products (entries 4 and 5). This selectivity might be due to the steric effect of the *ortho*-substituent, which raise the energy of the transition state of 6-*endo-dig* cyclizaiton. The aliphatic substituent also gave the dihydroisoquinoline derivative **6h** as the major product (entry 8).

Compared with the one-catalyst reactions summarized in Table 3, the regioselective hydroamination observed in the stepwise reaction was unexpected. The conditions of $Cu(MeCN)_4PF_6$-catalyzed reaction were essentially identical, except that in one-catalyst reactions an excess amount of amine (1.5 equiv.) was applied. Was the excess amine responsible for the observed selective formation of isoindole derivatives in the case of one-catalyst reactions? With this hypothesis in mind, we investigated the effect of organic bases on the Cu(I)-catalyzed reaction of **11a** (Table 5). Adding 10 mol% of *p*-tolylamine indeed reversed the selectivity of the reaction, leading to **5a** as the major product. Other bases, such as pyridine, morpholine and 1*H*-pyrrole also enchanced the selectivity for **5a**, albeit with less efficiency as compared to *p*-tolylamine. When 2,2′-bipyridine or 1*H*-imidazole was used as additive, the reaction was completely shut down. Although further study is needed to fully understand this remarkable additive effect, we consider that the steric effect of the additive, which coordinates with Cu(I) catalyst, is responsible for the observed change of reaction pathway.[22]

Table 5. Cu(I)-catalyzed reaction of **11a** with additives.



11a 5a 6a

Entry	Additive (mol%)	Time [h]	**5**, Yield [%][a]	**6**, Yield [%][a]
1	none	12	6	76
2	*p*-$MeC_6H_4NH_2$ (10)[b]	4	90	9
3	pyridine (50)	4	56	4
4	pyridine (20)	4	68	2
5	pyridine (10)	4	86	4
6	1*H*-pyrrole (10)	4	64	34
7	morpholine (10)	4	74	12
8	2,2′-bipyridine (10)	12	N.R.[c]	N.R.[c]
9	1*H*-imidazole (10)	24	N.R.[c]	N.R.[c]

[a] Isolated yield after separation with column chromatography.
[b] The number in paranthesis refers to the molar ratio of the amine additive relative to **11a**.
[c] N.R.: no reaction. Starting material was recovered.

Conclusions

In summary, we have developed a highly efficient tandem N–H insertion/hydroamination of alkyne catalyzed by a single Cu(I) catalyst. This tandem process provides a novel and straightforward way to synthesize isoindole and dihydroisoquinoline derivatives.[23] Moreover, a mechanistic study reveals a remarkable effect of amine in directing the regioselectivity of Cu(I)-catalyzed intramolecular hydroamination of alkynes. This discovery opens a possibility to control the regioselectivity of the hydroamination by additives to the catalysts.

Experimental Section

General Information

For chromatography, 200–300 mesh silica gel (Qingdao, China) was employed. ^{1}H and ^{13}C NMR spectra were recorded at 200 and 50 MHz with a Varian Mercury 200 spectrometer, or 300 and 75 MHz with a Varian Mercury 300 spectrometer. Chemical shifts are reported in ppm using tetramethylsilane as internal standard. Mass spectra were obtained on a VG ZAB-HS mass spectrometer.

For the preparation of the diazo substrates and the characterization data of all new compounds, see the Supporting Information.

Typical Procedure for $Rh_2(OAc)_4$-Catalyzed N−H Insertion Reaction

To a solution of **4a** (138 mg, 0.5 mmol) and $Rh_2(OAc)_4$ (2 mg, 0.005 mmol) was added *p*-$MeC_6H_4NH_2$ (0.75 mmol, 80 mg) at 50 °C. After the reaction has finished, the solvent was evaporated under vacuum. Then purification by column chromatography of the mixture gave the pure **11a** as a pale yellow solid; yield: 163 mg (92%).

General Procedure for the Cu(I)-Catalyzed Tandem Reaction

To a solution of **1** (100 mg, 0.5 mmol) and $CuPF_6(MeCN)_4$ (9 mg, 0.025 mmol) was added $PhNH_2$ **2a** (70 mg, 0.75 mmol) at room temperature. After completion of the reaction as monitored by TLC, the solvent was evaporated under vacuum. Then purification by column chromatography of the mixture gave the pure **3a** as a pale yellow oil; yield: 119 mg (90%).

The procedure of the reaction of **11a** catalyzed by Cu(I) is the same as that for the Cu(I)-catalyzed tandem reaction.

Acknowledgements

The project is generously supported by Natural Science Foundation of China (Grant No. 20572002, 20521202, 20772003) and the Ministry of Education of China (Cheung Kong Scholars Program).

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