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Copper-Catalyzed Coupling of *N*-Tosylhydrazones with Amines: Synthesis of Fluorene Derivatives

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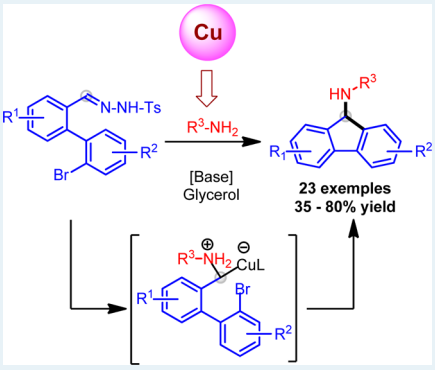
Supporting Information

ABSTRACT: An original formation of one C−N bond and one C−C bond on the same carbenic center has been developed. This approach involves a copper-catalyzed cross-coupling reaction between 2′-bromo-biaryl-*N*-tosylhydrazones and different amines leading to 9*H*-fluoren-9-amine derivatives. This reaction proceeds under mild conditions in glycerol, an inexpensive and environmentally friendly solvent, without adding any external ligand.



KEYWORDS: *N-tosylhydrazones, C−N/C−C bond formation, autotandem catalysis, carbenoid, fluoren-9H-amines*

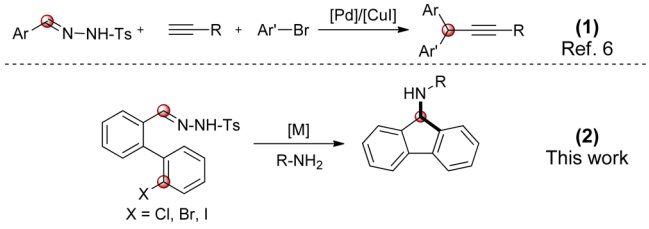
INTRODUCTION

In the past decade, *N*-tosylhydrazones have emerged as readily available and versatile partners in cross-coupling reactions, leading to the construction of C−C and C−heteroatom bonds.[1] Under basic conditions, hydrazones generate diazo compounds that are broadly used as carbene precursors, which are highly reactive intermediates.[2] Nowadays, the development of practical and inexpensive methods in synthetic chemistry is crucial because there continues to be an increasing demand for easily accessed complex structures. In fact, a growing number of cascade reactions evolved where metal carbenes (generated from *N*-tosylhydrazones) constitute a key step in the formation of two or more chemical bonds using the same catalytic system.[3] For the most part, these transformations are based on the carbene migratory insertion process that takes place during the cascade reactions.[4] More interestingly, two new bonds can occur on the same hydrazonic carbon atom.[5]

In 2010, Wang's group[6] reported a palladium/copper co-catalyzed three-component reaction between *N*-tosylhydrazones, terminal alkynes, and aryl halides leading to benzhydryl derivatives (Scheme 1, eq 1). In this work, a sequence of carbene migratory insertion, transmetalation, and reductive elimination created one C sp^3−C sp^2 bond and one C sp^3−C sp bond on the same carbenic center.[7]

Herein, we report an unprecedented sequence of copper addition leading to the formation of one C sp^3−N bond and one C sp^3−C sp^2 bond on the same carbenic center of the *N*-tosylhydrazones (Scheme 1, eq 2).

Scheme 1. Autotandem Reactions Involving *N*-Tosylhydrazones: Formation of Two New Bonds on the Same Carbenic Center



RESULTS AND DISCUSSION

In light of our interest in copper-catalyzed reactions using hydrazones, we recently developed a reductive coupling between *N*-tosylhydrazones and amines to access a wide diversity of α-branched amine derivatives (Scheme 2, eq 1).[8] As an extension, we conceived a cascade reaction using 2′-halo-biarylhydrazones

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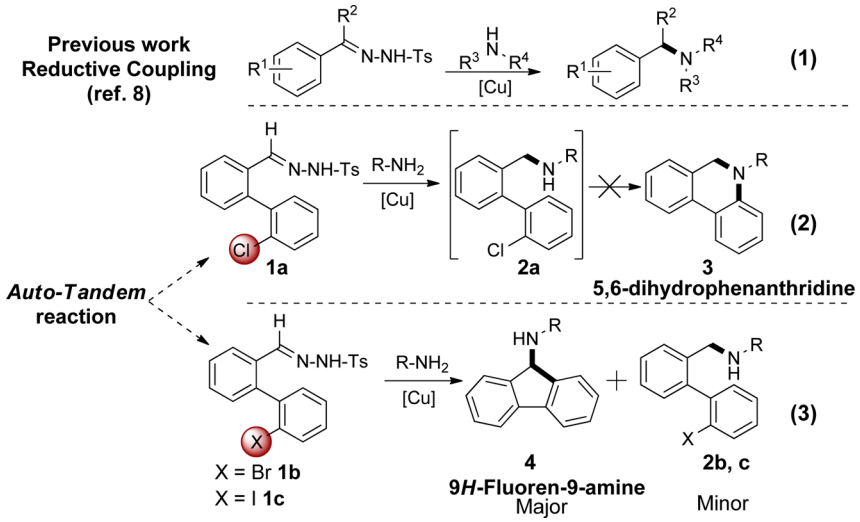
Scheme 2. Intramolecular Coupling of 2′-Halo-biarylhydrazones with Amines

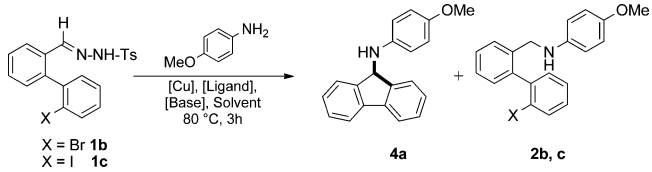


1a−c and amines to access 5,6-dihydrophenanthridines **3** through a sequence of reductive coupling and intramolecular *N*-arylation. These experiments have revealed divergent reaction pathways depending on the biarylhydrazones (**1a−c**) employed. With substrate **1a** having a chlorine atom (eq 2), the reaction furnished only reductive coupling intermediate **2a** without forming subsequent cyclization product **3**.[9] When switching from chloride derivative **1a** to more reactive substrates[10] 2′-bromo and 2′-iodo-phenylhydrazones **1b** and **1c** (eq 3), the reaction led to the unexpected formation of 9*H*-fluoren-9-amine **4** along with reductive coupling products **2b,c**. This new reactivity was far more interesting because for the first time a C−N bond and a C−C bond were created on the same carbenic center. In addition, during this process a single copper catalyst was able to initiate two mechanistically distinct reactions (autotandem catalysis). Moreover, the 9-fluorenyl amine scaffold is found in compounds showing promising biological activities (anticancer,[11] anti-tubercular,[12] and central nervous system disorders regulators[13]) and fluorescence properties for imagery.[14]

Recognizing the novelty of this process in generating 9*H*-fluoren-9-amine derivatives[15] and, more intriguingly, the origin of the unexpected intramolecular C−C bond-forming reaction, we report herein the findings of our methodological investigations. Initially, *N*-tosylhydrazones **1b** and **1c** with 4-methoxyaniline were chosen as benchmark partners to optimize the reaction conditions (Scheme 1). After evaluating different parameters (Cu salts, ligands, bases, and solvents), we found that $Cu(acac)_2$ (10 mol %) and Na_2CO_3 (2.5 equiv) in glycerol at 80 °C gave the best isolated yield of 62% of desired product *N*-(4-methoxyphenyl)-9*H*-fluoren-9-amine **4a** with hydrazone **1b**.[16] Under these optimized conditions, 97% of hydrazone **1b** was converted and not more than 7% of reductive coupling product **2b** was formed (Scheme 3). The corresponding imine and aldehyde were also formed in 12 and 5% yields, respectively, as already noticed in our previous work.[8a]

The main advantage of using glycerol lies in the fact that the addition of an external ligand can be avoided. In fact, carrying out a reaction in dioxane requires the addition of a phosphine ligand, bis[(2-diphenylphosphino)phenyl]ether (DPEPhos), to achieve the same results as observed in glycerol.[17] Glycerol is a low-cost, nontoxic, ecofriendly medium produced in large amounts as a waste product in biodiesel production. It has recently been broadly used in organic reactions.[18,19]

Scheme 3. Optimized Conditions for the Copper-Catalyzed Coupling between *N*-Tosylhydrazones 1 and 4-Methoxyaniline



	4a	2b, c
$Cu(acac)_2$ (10 mol%), DPEPhos (20 mol%) Na_2CO_3 (2.5 equiv.), Dioxane	**64%** (X = Br) **56%** (X = I)	**5%** (X = Br) **5%** (X = I)
$Cu(acac)_2$ (10 mol%), Na_2CO_3 (2.5 equiv.), Glycerol	**62%** (X = Br) **55%** (X = I)	**7%** (X = Br) **5%** (X = I)

With the optimized conditions in hand, we studied the feasibility of this coupling with different types of amines as well as 2′-bromo-biphenylhydrazones (Table 1). 9*H*-Fluoren-9-amine derivatives were obtained in moderate to good yields using electron-rich or electron-poor anilines and secondary amines. Electron-enriched anilines **4a−c** gave acceptable results with yields of up to 71% with *p*-toluidine for **4b**. *o*-Anisidine reacted with hydrazone **1b** to give corresponding fluorine **4d** in good (72%) yield; this shows that the steric hindrance has a small effect on the coupling. Aniline and 1-naphthylamine were also efficiently coupled, giving products **4e** and **4f**, respectively, in good yields.

Inactivated anilines were less reactive, and compounds **4g−j** were obtained in slightly lower yields. One can note that the reaction tolerated electrophilic functional groups (e.g., ketone, nitrile). Interestingly, fluorenes **4h**, **4k**, and **4o** revealed excellent chemical selectivity preserving the C−Cl and C−Br bonds, which could undergo further metal-catalyzed functionalization processes. Next, different substitution patterns on the hydrazones were tested, and good overall yields were obtained for fluorenes **4l−s** (47−70%) upon coupling with several amines. Extension to secondary cyclic amines was also possible under these conditions, providing 9*H*-fluoren-9-amines **4t−v** in good isolated yields. Secondary linear amine diethylamine was less reactive and afforded the desired fluorene **4w** in just 35% yield. Unfortunately, primary aliphatic amines, such as *n*-butylamine, gave only the reductive coupling product of type **2**.

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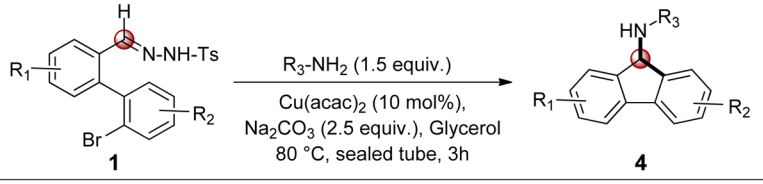
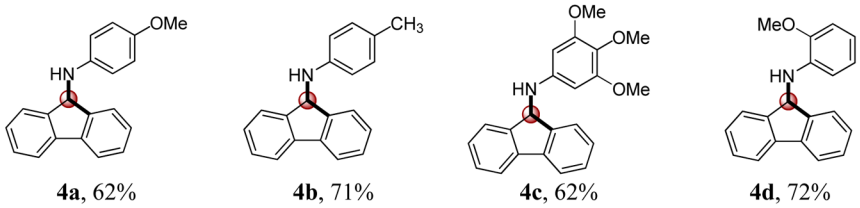
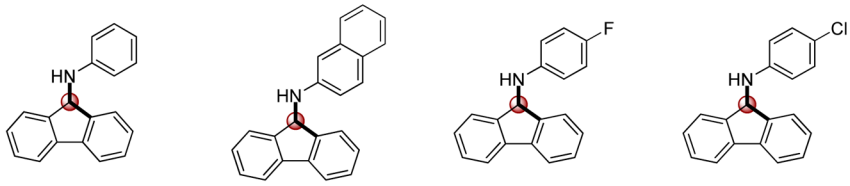
Table 1. Synthesis of 9*H*-Fluoren-9-amine Derivatives by a Copper-Catalyzed Cross-Coupling Reaction Using 2′-Bromo-biphenyl-*N*-tosylhydrazones[a]

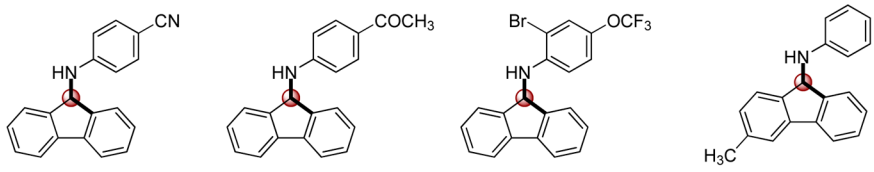




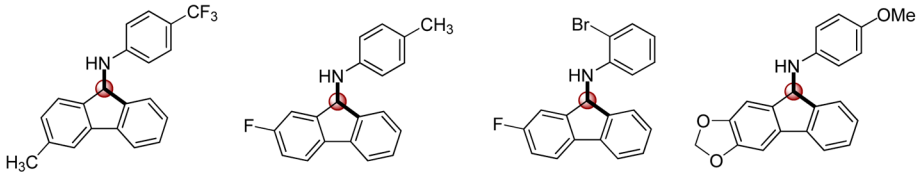
4a, 62% **4b**, 71% **4c**, 62% **4d**, 72%



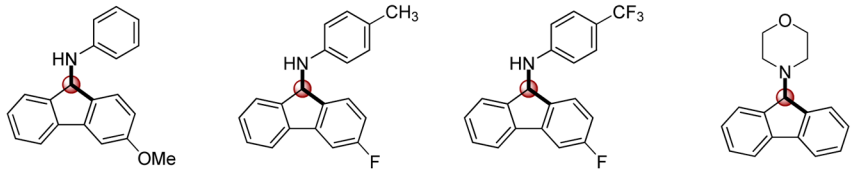
4e, 80% **4f**, 60% **4g**, 78% **4h**, 58%



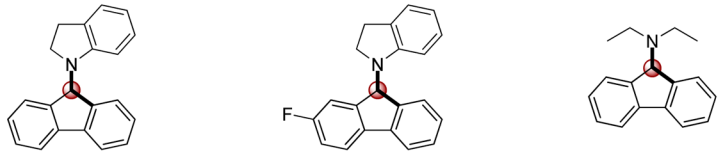
4i, 55% **4j**, 40% **4k**, 75% **4l**, 65%



4m, 61% **4n**, 70% **4o**, 52% **4p**, 47%



4q, 61% **4r**, 55% **4s**, 70% **4t**, 76%



4u, 75% **4v**, 78% **4w**, 35%

[a]Reaction conditions: *N*-tosylhydrazone (0.23 mmol), amine (1.5 equiv), $Cu(acac)_2$ (10 mol %), Na_2CO_3 (2.5 equiv), and glycerol (1 mL) in a sealed tube at 80 °C for 3 h. All of the indicated yields refer to isolated yields

MECHANISM

A plausible mechanism for the cascade formation of C−N and C−C bonds on the same carbenic center is proposed in Scheme 4.

The in situ reduction of copper(II) to catalytically active copper(I) will take place in the presence of the diazo compound[20] and/or glycerol.[18] Diazo compound **5**, obtained by *N*-tosylhydrazone decomposition under basic conditions,[2]

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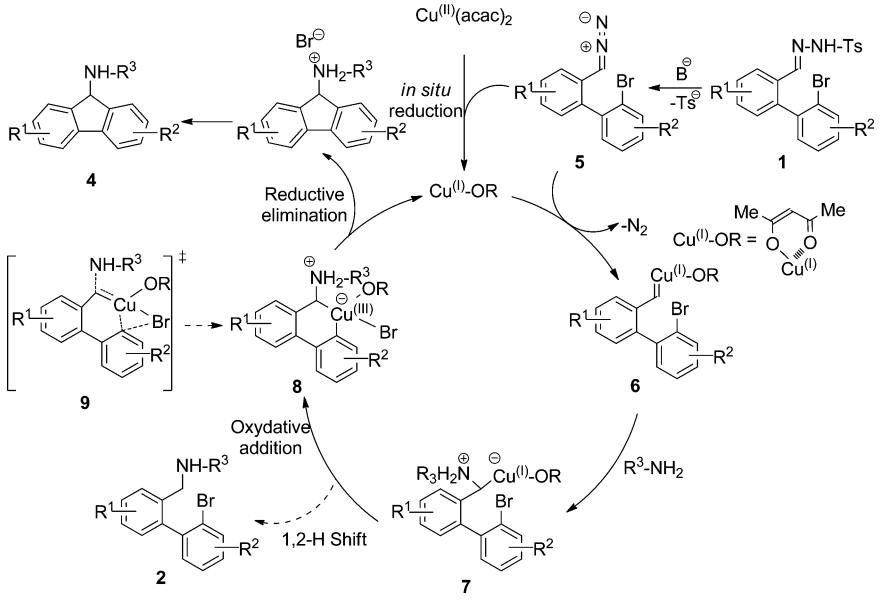
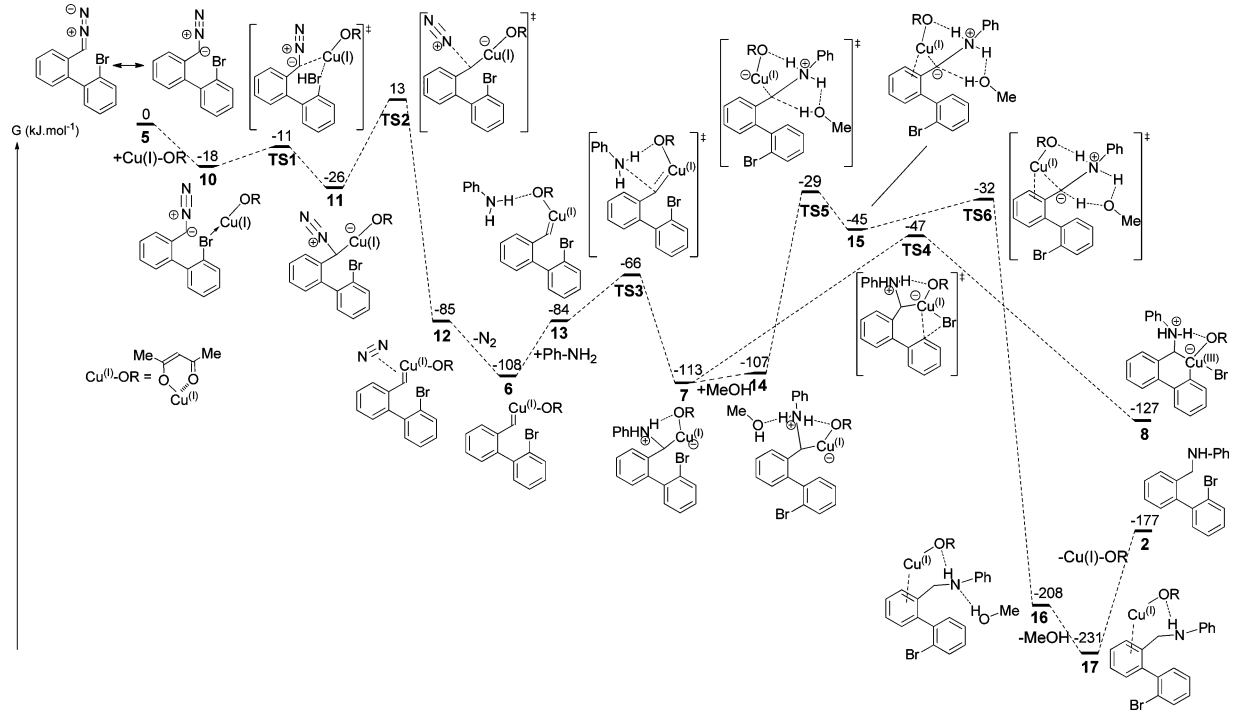
Scheme 4. Proposed Mechanism for Sequential C−N and C−C Bond Formation on the Same Carbenic Center



Scheme 5. Schematic Potential Energy Surface for the Copper-Catalyzed Coupling between Aniline and Diazo Compound 5 Obtained on the IEFPCM-B3LYP/def2-SVP Level



will react with copper(I) species to form electrophilic copper carbene species **6**. Ylide **7**, generated by the subsequent nucleophilic addition of the amine to the carbene, can undergo two competitive pathways. A 1,2 proton shift favored by the protic medium could take place, leading to N−H insertion product **2**,[8] but copper(III) intermediate **8** could be formed through an intramolecular oxidative addition of ylide **7**.[21] Then, reductive elimination followed by deprotonation under basic conditions will produce observed product **4** and regenerate the catalytic Cu(I) species. A concerted mechanism cannot be ruled out via the formation of transition state **9** where copper carbene **6** triggers an amine attack followed by an oxidative addition, directly leading to intermediate **8**.

To gain better insight into the reaction mechanism, we have carried out a computational study on the B3LYP/def2-SVP DFT level and including solvent effect (Scheme 5).[17] The calculations started from the Cu(I)(acac) catalytic complex and diazo compound **5**. Two intermediates between the metal catalyst and **5** are obtained, where the copper is coordinated either by the Br atom in **10** or by the carbenic carbon in **11**. N_2 extrusion from **11** leads to copper carbene **6** through transition state TS2 located at +13 kJ mol^{-1} relative to the reactants.

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The formation of a hydrogen bond between the amine and the acac ligand in **13** precedes the formation of ylide **7** through the low-lying TS3. Two different paths have been found from this point. Transition state TS4 corresponding to the oxidative addition is computationally located at −47 kJ mol^{-1} relative to the initial reactants, and it leads to **8**. A possible direct pathway between **6**/**13** and **8** was also investigated, but a concerted transition state could not be located by any means. Similarly, a transition state corresponding to the direct 1,2 proton shift from **7** leading to **17**/**2** could not be obtained. However, a solvent-assisted proton-shift path has been found. A molecule of methanol, which was used to model glycerol and forms a hydrogen bond to the ammonium group, induces the breaking of the Cu−C bond and the formation of intermediate **15**. Then, two concerted proton transfers corresponding to TS6 lead to **2** after the dissociation of the solvent and the catalyst. The low-energy barrier along this second path confirms its relevance. However, its highest transition state, TS5 located at −29 kJ mol^{-1} relative to the initial reactants, is slightly higher in free energy compared to that of TS4, explaining that **2** is only a minor side product.

CONCLUSIONS

9*H*-Fluoren-9-amine derivatives are obtained in a one-pot reaction from 2′-bromo-biarylhydrazones and anilines. A large number of these derivatives with different substitution patterns were easily obtained, offering a new versatile synthesis route. Furthermore, the protocol also represents an unprecedented formation of C−N and C−C bonds on the same carbenic center from 2′-bromo-biaryl-*N*-tosylhydrazones. This reaction proceeded under mild conditions, catalyzed by a ligand-free copper system in neat glycerol. This work represents a new example of the possible evolution of carbenoid moieties into complex structures via original transformations.

ASSOCIATED CONTENT

Supporting Information

The following file is available free of charge on the ACS Publications website at DOI: 10.1021/cs5014877.

Experimental details of the synthesis and characterization of starting materials and final compounds, optimization study and computational methods, and copies of ^{1}H NMR and ^{13}C NMR spectra of all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(17) For more information, please refer to the Supporting Information.
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