# Catalytic Oxidative Carbene Coupling of α-Diazo Carbonyls for the Synthesis of β-Amino Ketones via C(sp³)−H Functionalization

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S *Supporting Information*

ABSTRACT: A catalytic domino oxidative carbene coupling (OCC) of α-diazo carbonyls has been established by treatment with *N,N*-dimethylanilines and carboxylic acids (or *N*-methylaniline) via direct C(sp³)−H functionalization under convenient conditions. The reaction pathway is proposed to proceed through the sequence of carbene formation, enolization, and nucleophilic addition. The reaction enables de-diazotized carbo-oxygenation and carbo-amination of α-diazo carbonyls and provides practical access to α-(acyloxy)-β-amino ketones and α,β-diamino ketones.
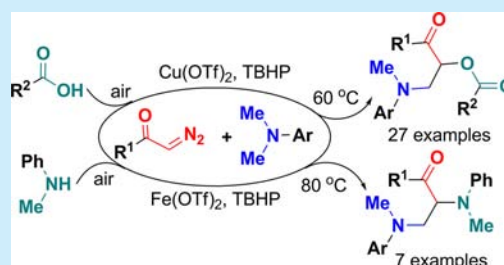
Diazo compounds are privileged building blocks and have been extensively utilized for numerous challenging syntheses due to the adequate reactivity of their diazo functionality.[1] Meanwhile, the study of transition-metal-catalyzed reactions of diazo compounds has been among the most active topics in chemical science,[2] as these compounds are represented by the formation of metal carbene species via de-diazotization to enable the insertion of metal carbenes into X−H (X = B, N, O, S, Si et al.) bonds[3] and cyclopropanations.[4] The most recent attractive work involves the de-diazotized bifunctionalization of diazo compounds including C−H bond activation/cyclization,[5] three-component coupling,[6] and insertion of metal carbenes into X−Y[7] (Scheme 1a). Additionally, Hu and co-workers developed transition-metal-catalyzed multi-component reactions of a diazo compound with a nucleophile (Nu) and an electrophile (E), enabling a continuous ylide formation, enolization, and nucleophilic addition sequence to form functional molecules, but the enolization step is difficult to control as soft nucleophiles like carboxylic acid were trapped (Scheme 1b).[8] Recently, Hu and co-workers have achieved the coupling of oxonium yields, generated from carboxylic acids and Rh carbenoids with *N*-Boc-imines as electrophiles.[9] To further expand the synthetic utility of carboxylic acids in metal carbene coupling reactions, we reasoned that the use of suitable oxidants could eliminate hydrogen migration involved in reaction process, thereby achieving carbene coupling to access important molecular structures. To the best of our knowledge, this metal-catalyzed oxidative carbene coupling (OCC) of α-diazo carbonyls and in situ generated electrophiles using carboxylic acid as a nucleophile via C(sp³)−H functionalization has not yet been documented (Scheme 1c).

The oxidative C(sp³)−H bond functionalization that allows the direct conversion of C−H bonds to C−X bonds is a highly attractive strategy regarding its versatility and atom-economic synthesis.[10] Very recently, we have established a three-component reaction of α-diazo carbonyls with *N,N*-dimethylanilines and *N*-hydroxyphthalimide in the presence of PhI(OAc)₂, in which in situ generated phthalimide *N*-oxyl radical-triggered de-diazotization/radical coupling to synthesize α-aminooxy-β-amino ketones through radical C(sp³)−H functionalization.[11] During our continuous study on C−H activation projects,[12] we commenced exploration of a new metal-catalyzed oxidative

**Scheme 1. Reactivity Fashions of Metal Carbenes**
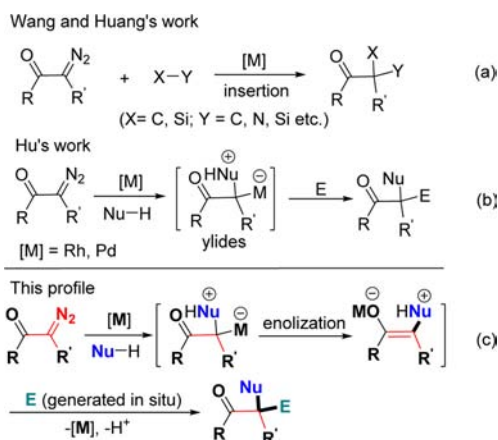
carbene coupling (OCC) of α-diazo carbonyls with *N,N*-dimethylanilines and carboxylic acids based on the facts that (i) carboxylic acid cannot be considered as a radical donor, but as a coupling precursor for O−H insertion with α-diazo carbonyls in metal catalysis (Scheme 2a),[13] which tolerates oxidative

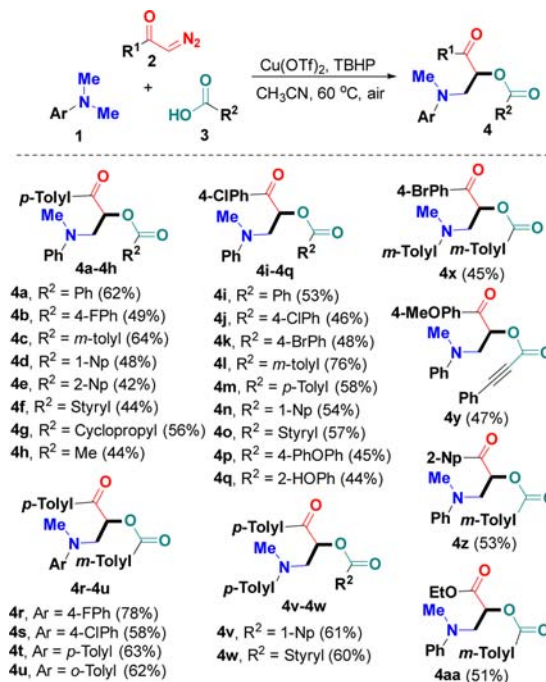## Scheme 2. Domino Synthesis of β-Amino Ketones 4 and 6
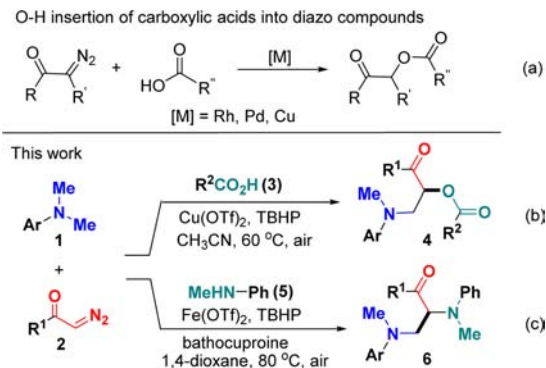
conditions and generates nucleophilic enol intermediate through dehydrogenation,[8] and (ii) under oxidative conditions, *N,N*-dimethylanilines were oxidized to yield electrophilic iminium salt, intercepted by suitable nucleophiles to realize C(sp³)−H functionalization.[14] Herein, we disclose a new catalytic C−O insertion reaction resulting from this analysis. The reaction was achieved by the treatment of in situ generated metal carbene species with substituted *N,N*-dimethylanilines **1** and carboxylic acids **3** (Scheme 2b), affording a wide range of α-acyloxy-β-amino ketones **4** through Cu-catalyzed de-diazotized bifunctionalization. Using *N*-methylaniline **5** as a nucleophile to expand the synthetic utility of this protocol, the reaction catalyzed by Fe(OTf)₂ proceeded smoothly through a similar oxidative carbene-coupling process, giving access to a series of new functionalized α,β-diamino ketones **6** with acceptable yields (Scheme 2c). It should be noticed that in the former, copper-catalyzed oxidative carbene coupling using carboxylic acid as a soft nucleophile via C(sp³)−H functionalization is very rare in organic and organometallic chemistry, particularly when it is performed in a functionally compatible fashion under one-pot catalytic conditions. The present protocol allowed the domino introduction of two different functional groups into a carbon center making the metal catalysis a useful tool for easy access to a wide range of challenging ketone-derived vicinal amino alcohols.[15]

Our initial investigation began with the three-component reaction of *N,N*-dimethylaniline (**1a**) with 2-diazo-1-(*p*-tolyl)-ethan-1-one (**2a**) and benzoic acid (**3a**). The reaction did not proceed at all under our previous conditions (Table S1, entry S1; see the Supporting Information). Using 5 mol % Cu(OTf)₂ as a catalyst, the above reaction at 60 °C gave a complex mixture (entry S2). We then considered adjusting the oxidants for this transformation. Exchanging PhI(OAc)₂ for *tert*-butyl hydroperoxide (TBHP, 70% in water) resulted in the desired β-amino ketone **4a**, albeit in poor yield (32%, entry S3). Other oxidants such as di-*tert*-butyl peroxide (DTBP) and benzoquinone (BQ) were found to be inefficient for this reaction (entries S4 and S5). Taking the combination of 5 mol % of Cu(OTf)₂ with TBHP, we then utilized other aprotic solvents, such as 1,4-dioxane, acetonitrile (CH₃CN), and tetrahydrofuran (THF), to explore the solvent effect on the reaction outcomes (entries S6−S8), and we found that CH₃CN exhibited the best performance, affording

the desired product **4a** in 50% yield (entry S8). Encouraged by these results, several metal salts like CuI, CuCl₂, Fe(OTf)₂, and FeCl₃ were examined for this system. Unfortunately, all of these metal catalysts did not show higher catalytic activity than Cu(OTf)₂ (entries S9−S12). Increasing the loading of Cu(OTf)₂ catalyst to 10 mol % was not beneficial for the reaction rate and gave a slightly lower yield (45%, entry S13). Subsequent optimizations were focused on adjusting the molar ratio of the three reactants in the presence of 5 mol % of Cu(OTf)₂ (entry S8 vs entries S14 and S15). To our delight, when the stoichiometric ratio of reactants was adjusted to 1.5:1.5:1, the yield of **4a** was improved to 62% (entry S14). However, further increasing the stoichiometric ratio of substrate **2a** delivered a slightly reduced yield (57%, entry S15). Afterward, changing the dosage of TBHP (1.0 or 3.0 equiv) led to lower conversion (entries S16 and S17). Control experiments confirmed that there was no reaction observed at all in the absence of either Cu(OTf)₂ or TBHP (entries S18 and S19).

Having the optimized conditions in hand (Table S1, entry 14), we then set out to investigate the substrate generality of this copper-catalyzed de-diazotized carbo-oxygenation by using a variety of *N,N*-dimethylanilines, α-diazo carbonyls, and carboxylic acids. We found that the reaction led to the formation of a wide range of α-acyloxy-β-amino ketones **4a−aa** with structural diversity in a highly selective and functional-group-compatible manner (Scheme 3). At first, *N,N*-dimethylaniline (**1a**) and α-diazoketones **2a** and **2b** were selected as model substrates to evaluate the scope of carboxylic acids. It was found that substrates **3** bearing either electronically neutral, poor, or rich substituents on the phenyl ring can be efficiently converted into the corresponding poly functionalized products **4a−f** and **4i−q** with yields ranging from 42% to 76%. A variety of functional

Scheme 3. Substrate Scope for Synthesis of 4[a,b]

4a−4h
4a, R² = Ph (62%)
4b, R² = 4-FPh (49%)
4c, R² = *m*-tolyl (64%)
4d, R² = 1-Np (48%)
4e, R² = 2-Np (42%)
4f, R² = Styryl (44%)
4g, R² = Cyclopropyl (56%)
4h, R² = Me (44%)

4i−4q
4i, R² = Ph (53%)
4j, R² = 4-ClPh (46%)
4k, R² = 4-BrPh (48%)
4l, R² = *m*-tolyl (76%)
4m, R² = *p*-Tolyl (58%)
4n, R² = 1-Np (54%)
4o, R² = Styryl (57%)
4p, R² = 4-PhOPh (45%)
4q, R² = 2-HOPh (44%)

4x (45%)

4y (47%)

4z (53%)

4r−4u
4r, Ar = 4-FPh (78%)
4s, Ar = 4-ClPh (58%)
4t, Ar = *p*-Tolyl (63%)
4u, Ar = *o*-Tolyl (62%)

4v−4w
4v, R² = 1-Np (61%)
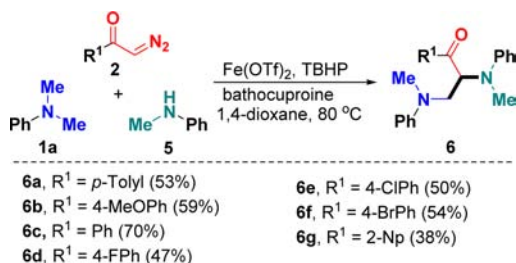**4w**, R² = Styryl (60%)

4aa (51%)

[a]Reaction conditions: *N,N*-dimethylanilines (**1**, 1.5 mmol), α-diazo carbonyls (**2**, 1.5 mmol), carboxylic acids (**3**, 1.0 mmol), Cu(OTf)₂ (5 mol %), TBHP (70% in water, 2.0 mmol), CH₃CN (3.0 mL), 60 °C, 12 h. [b]Isolated yields based on **3**.

groups including methyl, fluoro, chloro, and bromo can tolerate the catalytic conditions very well. The electronic effect of substituents of aryl acids showed an obvious influence on the reaction efficiency. For instance, aryl carboxylic acids **3** bearing electron-withdrawing groups showed the lower capability in reactivity than those with electron-donating counterparts (**4b** vs **4c**; **4j**–**4k** vs **4l**–**4m**). Similarly, 1- and 2-naphthalenyl (1- and 2-Np) analogues were successfully engaged in these three-component transformations, providing the corresponding functionalized α-acyloxy-β-amino ketones **4d**–**e** and **4n** in moderate yields. Furthermore, the reaction can be extended to different α,β-unsaturated and aliphatic acids, and the corresponding prodcuts were afforded in decent to fair yields for α,β-unsaturated (**4f**), cyclic (**4g**), and linear (**4h**) substrates. In addition, the sterically more demanding 2-hydroxyphenyl substituent showed a higher reactivity, giving access to the corresponding coupling product **4q** in a 44% yield. Next, the scope with respect to the N,N-dimethylaniline coupling partner was explored. The reaction can tolerate various N,N-dimethylanilines possessing both electron-deficient and electron-rich substituents at different positions of aromatic rings, leading to the formation of structurally diverse α-acyloxy-β-amino ketones **4r**–**w** in synthetically useful yields (Scheme 3). The presence of fluoro functionality at the *para*-position of N,N-dimethylanilines led to a higher yield (78%) for product **4r**. Alternatively, α-diazoketones bearing 4-methoxyphenyl (**4y**) and 2-naphthalenyl groups (**4z**) were compatible in this oxidative carbene coupling. Notably, the commercial ethyl diazoacetate (EDA) was also found to be a suitable substrate and can be converted into α-acyloxy-β-amino esters **4aa** in 51% yield under the standard conditions. Among them, the structure of **4j** was determined by X-ray diffraction analysis.

After our success with α-acyloxy-β-amino ketones **4**, we evaluated the feasibility of the synthesis of α,β-diamino ketones **6** by using N-methylaniline **5** as replacement for carboxylic acid component. The coupling of **1a** with **2a** and **5** was conducted under the conditions described above, and the expected α,β-diamino ketone **6a** was obtained in a low 21% yield. After systematical optimizations with respect to catalyst, ligands, and solvents as well as the mole ratio of substrates (Supporting Information, Table S2), we found that using 5 mol % of Fe(OTf)$_2$ and 10 mol % of bathocuproine ligand in the presence of TBHP in 1,4-dioxane solvent at 80 °C was the most suitable condition for this coupling reaction, affording the expected α,β-diamino ketone **6a** in an optimal 53% yield. As shown in Scheme 4, this protocol can tolerate differently substituted α-

Scheme 4. Substrate Scope for Synthesis of 6[a,b]

6a, R^1 = p-Tolyl (53%)   6e, R^1 = 4-ClPh (50%)
6b, R^1 = 4-MeOPh (59%)   6f, R^1 = 4-BrPh (54%)
6c, R^1 = Ph (70%)   6g, R^1 = 2-Np (38%)
6d, R^1 = 4-FPh (47%)

[a]Reaction conditions: N,N-dimethylaniline (**1a**, 1.2 mmol), α-diazo carbonyls (**2**, 1.5 mmol), N-methylaniline (**5**, 1.0 mmol), Fe(OTf)$_2$ (5 mol %), bathocuproine (10 mol %), TBHP (70% in water, 2.0 mmol), 1,4-dioxane (3.0 mL), 80 °C, 10 h. [b]Isolated yields based on **5**.

diazoketones **2** carrying either electronically poor, neutral, or rich groups, leading to the formation of structurally diverse α,β-diamino ketones **6b**–**f** in overall acceptable yields (up to 70%).

To gain mechanistic insight into this reaction, several control experiments were conducted. When 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO)[16] was subjected to the reaction system under the standard conditions, a 62% yield of product **4l** was obtained (Scheme S1a, Supporting Information), indicating that the mechanism may not be involved a radical process. Subsequent investigation on an intermolecular deuterium-labeling competing reaction of **1a** and **1a**-d_6 (kinetic isotope effect, KIE = 1.08, Scheme S1b) confirmed that the C−H bond cleavage is not the rate-limiting step, and N,N-dimethylanilines were preferentially oxidized to form iminium salt. Both hydrogen−deuterium exchange experiments (Scheme S1c) suggested that the proton at the α-position of α-diazo carbonyls would be involved an intermolecular proton-transfer equilibrium by enol−keto tautomerization but not participate in the reaction process under oxidative conditions. Next, the preformed 2-oxo-2-(p-tolyl)ethyl acetate **7** was reacted with **1a** under the standard conditions, but no expected product **4h** was observed with the starting material **7** remaining (Scheme S1d), which showed that the reaction process did not involve α-acyloxy ketone intermediate formation.

Based on the above analysis and information found in the literature,[8] we proposed a mechanism for this de-diazotized carbo-oxygenation reaction (Scheme 5). In the first stage, in the

Scheme 5. Proposed Mechanism for Forming 3
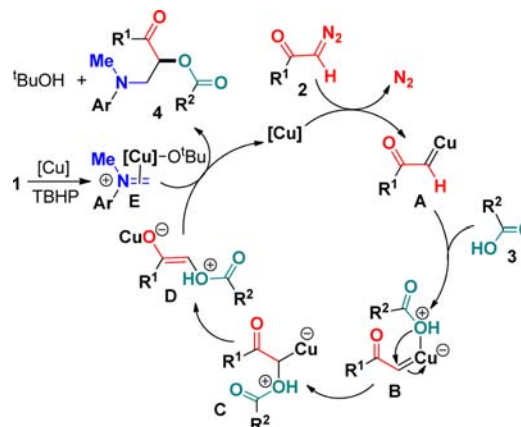
presence of Cu catalyst, α-diazo carbonyls are converted into Cu carbene species **A**, followed by the reaction with carboxylic acids **3** to copper ylides **B**,[17] which undergo migration insertion (**B** to **C**) and enolization (**C** to **D**) to yield intermediate **D** with nucleophilicity. Next, nucleophilic addition of **D** into iminium cations **E** (detected by GC−MS, see the Supporting Information), derived from copper-catalyzed oxidation of N,N-dimethylanilines **1** in the presence of peroxides,[14b] results in the final products **4** and completes the catalytic cycle to regenerate Cu catalyst. The mechanism for the formation of α,β-diamino ketones **6** is similar to this proposed one.

In conclusion, we have discovered a new oxidative carbene coupling of α-diazo carbonyls through a metal-catalyzed de-diazotized process. In the former, the reaction can be readily performed by coupling α-diazo carbonyls with N,N-dimethylanilines and carboxylic acids via direct C(sp^3)−H activation in a one-pot catalytic operation and under mild conditions in which a series of structurally diverse α-acyloxy-β-amino ketones of

chemical and biomedical importance were obtained. The latter generated new functionalized α,β-diamino ketones via de-diazotized carbo-animation of α-diazo carbonyls. The reaction shows attractive advantages in terms of the commercial accessibility, inexpensiveness, and stability of the starting materials, common peroxides, and copper(II) and iron(II) catalysts. Further investigation on new reactivity modes for these metal carbene intermediates and an asymmetric version of this reaction is currently underway in our laboratories.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01189.

> Experimental procedures and spectroscopic data for all new compounds **4a−4aa** and **6a−g** (PDF)
> X-ray crystal data for **4j** (CIF)

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Author Contributions

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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