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Metal-Free Geminal Difunctionalization of Diazocarbonyl Compounds: A One-Pot Multicomponent Strategy for the Construction of α,β-Diamino Carbonyl Derivatives

Dan Zhu, Yuan Yao, Rong Zhao, Yang Liu, and Lei Shi*

Abstract: An unprecedented three-component domino oxidative coupling of diazocompounds for the efficient synthesis of α-azido-β-amino esters with non-activated dimethylamino compounds and simple $TMSN_3$ was achieved. The highlighted features of this method are in terms of metal-free catalysis, satisfactory functional group tolerance, general applicability in complex molecule architectures, and excellent diastereoselectivity in the presence of chiral auxiliaries. Besides, several related control experiments have been conducted reasonably to investigate the reaction mechanism.

α,β-Diamino acid derivatives as important functional moieties are present in a number of biologically relevant molecules and natural products (Figure 1), which have been widely applied in the field of medicinal chemistry. In addition, they can also be used as highly privileged synthetic building blocks in the bioactive and stability modifications of polypeptides.[1] Due to the considerable interest to the scientific community, dozens of methods have been developed for the synthesis of α,β-diamino carbonyl derivatives (Scheme S-1 in the supporting information).[2]

Diazo groups and azido groups have been used extensively as versatile synthetic intermediates and critical synthons[3] in the synthesis of diverse nitrogen-rich natural products, and have also been successfully employed as the excellent reporters to the rapid incorporation of nitrogenous groups in chemical biology.[4] In contrast to azido groups, diazo groups, which are smaller than analogous azido groups, are found in many natural products (Figure S-1 in the supporting information)[5] and display a broader range of reactivity and selectivity.[6]

In recent years, much attention has been paid to diazocompounds bearing electron-withdrawing substituents such as α-diazocarbonyl compounds due to their greater stabilities as compared to the alkyl diazo compounds. Through the thermal or photochemical cleavage of the carbon-nitrogen bond releasing thermodynamically stable dinitrogen as a leaving group, α-diazocarbonyl compounds generate carbenes carrying a carbonyl

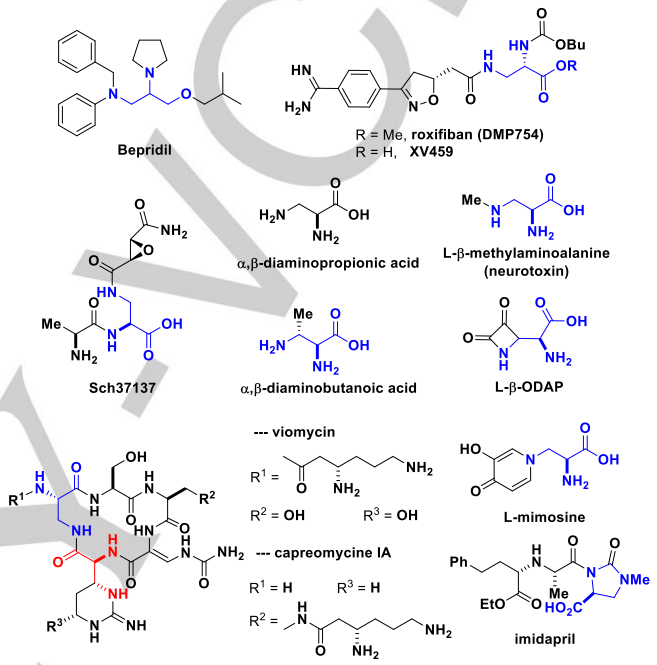

Figure 1. Selected natural products containing an α,β-diamino acid moiety.

substituent which is highly reactive, and in case of transition metal-carbenes also highly chemo-, regio-, and stereoselective. Their versatility in chemical transformations[6c] (Scheme S-2 in the supporting information) including cycloadditions, insertion reactions, ylide formations, and the Wolff rearrangements, makes them important reagents and precursors for organic synthesis. On the other hand, α-diazocarbonyl compounds are also served as the significant radical acceptors, and can be trapped by the *in situ* generated radical toward crucial chemical bond formation.[7]

Among various strategies for the reported diazo-based transformations, the introduction of dual functionality to the α-diazo carbonyl compounds in a geminal fashion has received increasing attention due to the simultaneous formation of two geminal chemical bonds.[6]

However, despite enormous progress in this field, the geminal difunctionalization of α-diazo carbonyl compounds through a multicomponent process, especially when done in a stereocontrolled manner, still remains less explored and challenging. In this regard, an array of transition-metal-catalyzed multicomponent reactions of diazo carbonyl compounds have been investigated extensively since the pioneering work of Hu and Gong, by virtue of electrophilic trapping of a wide variety of active oxonium ylides, ammonium ylides or zwitterionic intermediates.[8] In 2015, Liu and Tan reported an enantioselective

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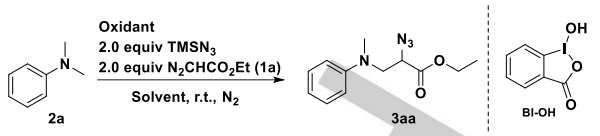
multicomponent reaction of diazooxindoles, nitrosoarenes, and nitroalkenes using a newly developed bis(thiourea) hydrogen-bond catalyst.[9] Recently, Wan successfully developed a Co-catalyzed three-component tandem reaction of α-diazo esters with styrenes and tertiary amines using *tert*-butyl hydroperoxide (TBHP) as the only oxidant, which involved the oxidative multi-component coupling between cobalt-based carbene radicals and α-amino alkyl radicals to yield β-ester-γ-amino ketones.[10] Shortly thereafter, Li, Tu and Jiang jointly demonstrated two domino oxidative three-component couplings of α-diazo ketones in moderate to good yields to construct functionalized α-oxy-β-amino ketones and α,β-diamino ketones.[11] Meanwhile, Szabó disclosed two examples of rhodium-catalyzed three-component coupling sequences of α-diazo ketones to access a broad range of gem-oxyfluoride or gem-oxytrifluoride products.[12] More recently, Zhou invented silver-catalyzed three-component reaction of diazoketones, anilines and *N*-fluorobenzenesulfonimide (NFSI), providing an interesting gem-aminofluorination approach in moderate to good yields.[13]

Herein, we report metal-free oxidative geminal carboazidation of α-diazo carbonyl compounds with readily accessible tertiary amines and commercially available $TMSN_3$ to afford the valuable α,β-diamino acids derivatives with high structural diversity and complexity. The versatile, operationally simple and highly efficient one-pot three-component approach for the synthesis of α-azido-β-amino carbonyl derivatives results in the concomitant construction of C–C and C–N bonds, providing carboazidation products in moderate to excellent yields. In contrast to traditional approaches towards α,β-diamino acids, the attractive feature of this method is that the construction of the carbon skeleton and the introduction of nitrogen atoms take place in one-pot multicomponent procedure, thus providing an easy access for highly efficient construction of α-azido-β-amino carbonyl derivatives from simple substrates under mild reaction conditions. To the best of our knowledge, this represents the first example of an effective multicomponent sequence that rapidly affords α-azido-β-amino carbonyl derivatives.

We initiated our studies by investigating the three-component reaction between *N,N*-dimethylaniline (**2a**), ethyl diazoacetate (**1a**) and $TMSN_3$ under a nitrogen atmosphere using kinds of hypervalent iodine reagents as the only oxidant in DCM at room temperature. The experiment results show that when use the BI-OH as the oxidant, the reaction can give the desired product in a 7% isolated yield (Table 1, entry 3). Encouraged by this result, various solvents have been screened immediately to optimize the reaction conditions. In stark contrast to toluene, DCM, and THF, using acetonitrile as the solvent can significantly increase the yield of the reaction to 42% (Table 1, entry 4). Further improvement in the yield was achieved carefully by decreasing the stoichiometric ratio of the oxidant to 1.2 (Table 1, entry 7). However, replacing the $TMSN_3$ to NaN_3 is proved to be useless in the transformation (Table 1, entry 10). Consequently, the reaction condition described in entry 7 was selected as the standard condition. It is worth noting that the corresponding α-azido-β-amino carbonyl derivatives as simple but polyfunctional molecules represent a significant synthetic challenge owing to the presence of contiguous stereocenters in a flexible acyclic molecule. The ester and the azido group can serve as versatile handles for further transformations. Interestingly, before our investigation, the same carboazidation product **3aa** could be

Table 1. Optimization of the reaction conditions.[a]



Entry	Oxidant (equiv)	Solvent	Yield[b] (%)
1	PIDA (2.0)	DCM	Trace
2	PIFA (2.0)	DCM	None
3	BI-OH (2.0)	DCM	7
4	BI-OH (2.0)	MeCN	42
5	BI-OH (2.0)	THF	Trace
6	BI-OH (2.0)	Toluene	None
7	**BI-OH (1.2)**	**MeCN**	72
8	BI-OH (1.2)	MeCN	64[c]
9	BI-OH (1.2)	MeCN	37[d]
10	BI-OH (1.2)	MeCN	None[e]

[a] The reaction condition: *N,N*-dimethyl aniline (**2a**, 0.3 mmol), $TMSN_3$ (2.0 equiv, 0.6 mmol), N_2CHCO_2Et (2.0 equiv, 0.6 mmol), oxidant, solvent (2 mL), under N_2 condition. [b] Isolated yield. [c] N_2CHCO_2Et (3.0 equiv, 0.9 mmol). [d] $TMSN_3$ (3.0 equiv, 0.9 mmol). [e] Choose NaN_3 as the reaction reagent.

obtained only through three successive reactions in a 38% overall yield (76% x 68% x 74%).[14]

With the optimized reaction condition in hand (Table 1, entry 7), we then set out to evaluate the substrate scope of this reaction with respect to the applied tertiary amines. As shown in Scheme 1, various functional groups including halides, methyl, azo, ketone, aldehyde, and alcohol were well tolerated, furnishing the corresponding α-azido-β-amino carbonyl compounds without difficulty. It's worth mentioning that *N*-methylene of the tetrahydroisoquinoline (**2l**) was also well achieved the expectant result under the standard reaction condition and get the corresponding product (**3al**) with a single diastereomer based on the ^1H NMR and ^{13}C NMR analysis. As far as we know, tetrahydroisoquinolines (0.55 V vs. SCE)[15] have lower oxidation potentials than similar *N,N*-dimethylanilines (0.84 V vs. SCE).[16] Even so, the tetrahydroquinoline moiety is present in various natural products, and exhibit a broad range of biological activities, which magnified its value perfectly.[17] Notably, the challenging late-stage application of complex biologically important compounds and architectures, such as steroid (**3am**), mifepristone (**3an**) and dihydroartemisinin derivatives (**3ao** and **3ap**) is all right. Moreover, the introduction of the azide group into such compounds maybe conductive to their drug or biological activity at some level. Modification of steroidal and sesquiterpene drugs provides an efficient route for the fine-tuning of their biological activity. Therefore, our method was applied to the late-stage carboazidation to afford the desired products in 17-54% yields. Meanwhile, this transformation highlights the chemoselectivity of the method in the presence of carbon−hydrogen bonds, olefins, alkynes, and carbonyls, which can react with α-diazocarbonyl compounds. The utility of the transformation is demonstrated in the late-stage site-selective

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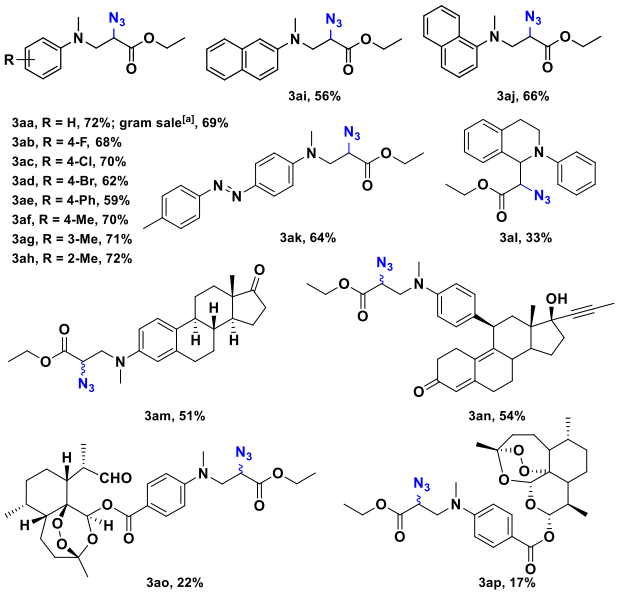
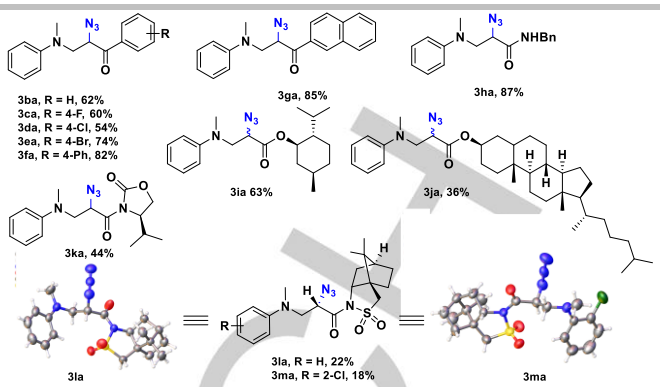
functionalization of natural products and pharmaceuticals, allowing rapid derivatization for investigation of structure−activity relationships.



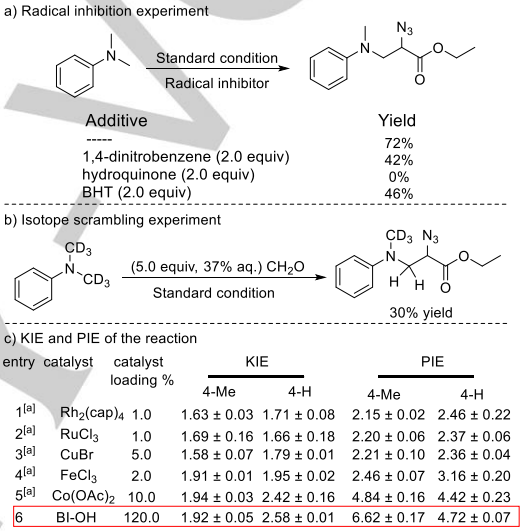
Scheme 1. Scope of this reaction with respect to the applied tertiary amines. [a] **2a**: 30 mmol.

We then turned our attention to examining the applicability of various diazocompounds. As shown in Scheme 2, the attached substituent groups on the phenyl ring not only electron-donating but also electron-withdrawing were compatible, and gave the expectant products in satisfactory yields (**3ba**-**3ga**). Besides the above-mentioned diazoesters and α-diazo carbonyls, diazoamides can also carry out the reaction well (**3ha**).

Next, we focused on the development of an asymmetric variant of this unprecedented three-component reaction. As a large number of chiral auxiliaries can be introduced at the ester moiety of α-diazo compounds, asymmetric induction of central chirality during our multicomponent reactions of α-diazocarbonyl compounds might be also anticipated.[18] Kinds of chiral auxiliary of α-diazocarbonyl compounds have been detected in our system. It is desirable that both oxazolidinone (**3ka**) and camphorsultam can get the objective product as an essentially single stereoisomer in 44% and 22% yield respectively. We think the possible reason for the low yield of the desired products (such as **1k**, **1l** and **1m**) is the existence of the relatively bulky ester. Gratifyingly, a noteworthy observation is that the absolute and relative configuration of **3la** and **3ma** by X-ray single crystal diffraction analysis was unambiguously confirmed, a further reminder of the feasibility of the method to generate high selectivity induced by chiral auxiliaries.[19] The successful incorporation of the azide group with high selectivity will be potential and of high value in their bioactivity and other properties. Compare to the above, using the piperitol and steroid (**3ia** and **3ja**) as the chiral auxiliary can nearly not induce the stereoselectivity with a diasteromeric ratio of 1:1 base on the ^{1}H NMR and ^{13}C NMR analysis.



Scheme 2. Scope of various diazocompounds.

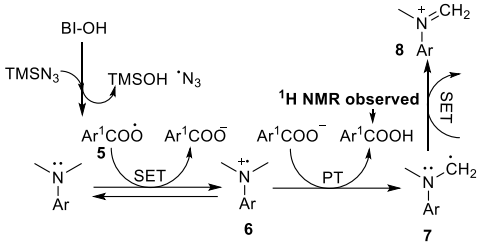


entry	catalyst	catalyst loading %	KIE 4-Me	KIE 4-H	PIE 4-Me	PIE 4-H
1[a]	$Rh_2(cap)_4$	1.0	1.63 ± 0.03	1.71 ± 0.08	2.15 ± 0.02	2.46 ± 0.22
2[a]	$RuCl_3$	1.0	1.69 ± 0.16	1.66 ± 0.18	2.20 ± 0.06	2.37 ± 0.06
3[a]	CuBr	5.0	1.58 ± 0.07	1.79 ± 0.01	2.21 ± 0.10	2.36 ± 0.04
4[a]	$FeCl_3$	2.0	1.91 ± 0.01	1.95 ± 0.02	2.46 ± 0.07	3.16 ± 0.20
5[a]	$Co(OAc)_2$	10.0	1.94 ± 0.03	2.42 ± 0.16	4.84 ± 0.16	4.42 ± 0.23
6	BI-OH	120.0	1.92 ± 0.05	2.58 ± 0.01	6.62 ± 0.17	4.72 ± 0.07

Scheme 3. Control experiments and mechanistic studies. [a] Doyle's work.

Several control experiments (Scheme 3) were conducted to reveal the reaction mechanism. The radical inhibition experiments were firstly carried out with the use of diverse radical inhibitors. Compared to the partial inhibition of 1,4-dinitrobenzene and BHT(2,6-di-*tert*-butyl-4-methylphenol), the hydroquinone can totally inhibit, suggesting a radical pathway largely. Kinetic and product isotope effects were then calculated to investigate the process of the C–H cleavage at the α-position to nitrogen. We found that the obtained KIE and PIE values were closely related with those for the reaction reported in the Doyle's work,[20] suggesting that they could share the reaction mechanism as shown in Scheme 4. The radical **5** was formed in a general oxidant way, followed by the SET which is accompanied by a competing backward SET to generate the critical intermediate amine radical cation **6**. It will clearly reduce the bond dissociation energy (BDE) and the pKa of α-C–H bond to the nitrogen,[21] making it certainly practicable in the next deprotonation of the amine radical cation to form α-aminoalkyl radical **7**. In our reaction, we always find a demethylation phenomenon. We speculated that it was maybe derived from immonium ion. Then we used the HCHO to capture the immonium ion to prove the hypothesis through an isotopic scrambling experiment. The isolated product lacked any deuterium labeling in methylene group explicitly

indicates that a competing second SET followed by the rate determining SET step consist in the reaction from α-aminoalkyl radical to an iminium ion, which is confirmed by ^{1}H NMR. As for the subsequent process, unfortunately, according to the existing experimental results, we still can't give strong evidence to confirm radical or ionic mechanism. Further investigations will continue to explore in our laboratory.



Scheme 4. Proposed reaction mechanism.

In conclusion, we have described an unprecedented three-component domino oxidative coupling of dimethylamino compounds with diazocompounds and simple $TMSN_3$ for the synthesis of α-azido-β-amino esters under a mild and efficient condition. This novel method realized the direct α-C(sp^3)–H azidation of tertiary amines without any metal catalysis and offers a facile and flexible access to privileged amino acid precursors. The mild reaction conditions, cheap reaction reagents, excellent functional group compatibility, and high levels of substrate-directed diastereocontrol provide an opportunity for late-stage azidation of complex molecules. More importantly, the introduction of the oxazolidinone and camphorsultam as the auxiliary attached to the diazocarbonyl compounds can successfully impart its chirality, leading the corresponding products with an essentially single stereoisomer. Further investigations on related reactions to expand the utility of the hypervalent iodine reagents, and catalytic enantioselective version of the transformation are currently underway in our laboratory.

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Keywords: metal-free • C–H functionalization • geminal carboazidation • three-component coupling • hypervalent iodine reagents

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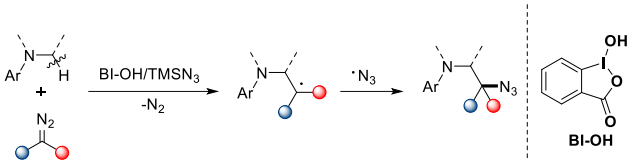

An unprecedented three-component domino oxidative coupling of diazocompounds for the efficient synthesis of α-azido-β-amino esters with non-activated dimethylamino compounds and simple $TMSN_3$ was achieved. Meanwhile, this reaction offers a straightforward approach for the asymmetric synthesis of α-azido-β-amino esters in the presence of chiral auxiliaries.

*Dan Zhu, Yuan Yao, Rong Zhao, Yang Liu, and Lei Shi**

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Metal-Free Geminal difunctionalization of Diazocarbonyl Compounds: A One-Pot Multicomponent Strategy for the Construction of α,β-Diamino Carbonyl Derivatives