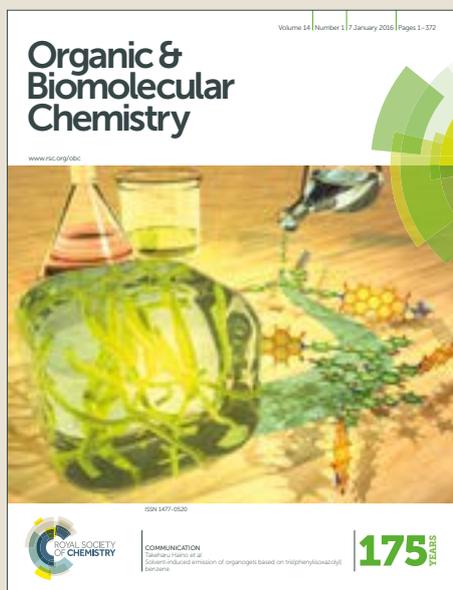


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Silver-Catalyzed [3+2] Domino Reaction: An Efficient Strategy to Synthesize Imidazole-5-carbaldehydes

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An unprecedented regioselective silver-catalyzed [3+2] domino reaction of amidines and ynals for the formation of C-N bonds has been developed. The reaction provided a new route to prepare imidazole-5-carbaldehydes which are important intermediate for the construction of fine chemicals. The reaction proceeds smoothly with a broad range of substrates to give imidazoles in good yields.

Transition metal-catalyzed organic synthetic reactions¹ are powerful tools for the formation of new carbon-carbon and carbon-hetero bonds in both industrial applications and academic research. A lot of great and successful methods, such as Heck reaction,² Suzuki reaction,³ Negishi coupling,⁴ Sonogashira coupling⁵ and Buchwald-Hartwig reaction,⁶ have been developed for the synthesis of complex molecules from readily accessible starting materials under mild conditions. On the basis of these classical transformations, new and facile routes have been developed to prepare fine chemicals. These advancements have encouraged chemists to design an inexpensive, environmentally friendly and nontoxic catalytic system. With the development of green chemistry and increased concern over environmental issues,⁷ one of the current challenges in organic synthesis is to develop green methods. As the biggest

pollution problem in most of organic transformation is caused by organic solvents, the development of efficient synthetic methods for organic transformation with non-toxic solvents is an important goal. It is well known that water is a non-toxic, non-hazardous, non-flammable, uniquely redoxstable, inexpensive green solvent, therefore, using water as the reaction solvents⁸ has attracted considerable attention.

Imidazole derivatives recognized as a significant class of skeleton in many natural products, pharmaceuticals, and biologically active molecules.⁹ The commercially available drugs, for instance, Ketoconazole, Clotrimazole, Miconazole and Tinidazole, are derived from imidazole scaffolds. One of the most important reaction is the Debus-Radziszewski method¹⁰ for the construction of imidazole derivatives. As far as transition metal-catalyzed strategies to access imidazoles are concerned, significant advances based on Pd-, Cu-, and Fe-catalyzed reactions have been achieved in the field.¹¹ Although many efforts have been devoted to prepare imidazole derivatives,¹² the search for the development of more environmentally friendly reaction is still highly desirable.

Combined with our previous work on the synthesis of furans¹³ and imidazo[1,2-a]pyridines¹⁴, herein, we report an efficient Ag-catalyzed [3+2] domino process to synthesize imidazole-5-carbaldehydes from amidines and ynals.

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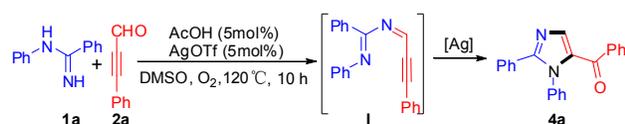
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Table 1. Optimization of the Reaction Conditions^a

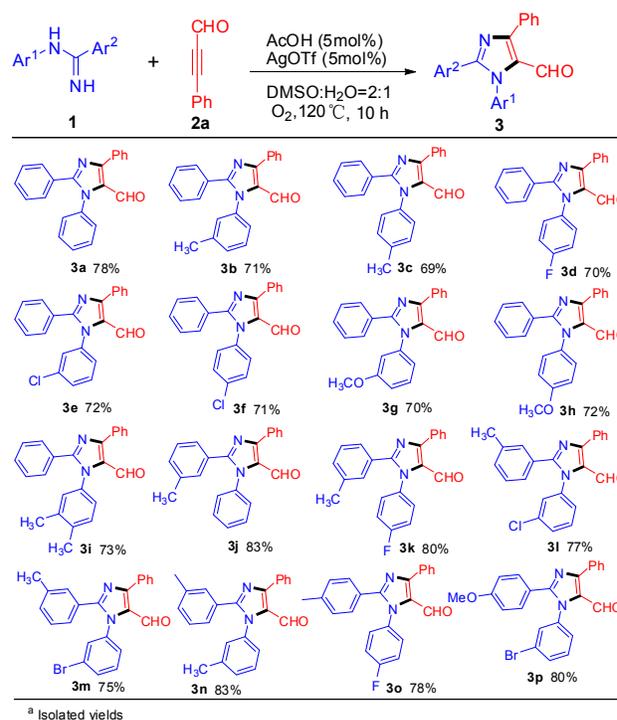
entry	catalyst	additive	solvent	oxidant	yield ^b (%)
1	AgOTf	AcOH	DMSO	O ₂	63
2	AgNO ₃	AcOH	DMSO	O ₂	39
3	AgOAc	AcOH	DMSO	O ₂	22
4	Ag ₂ O	AcOH	DMSO	O ₂	25
5	AgSbF ₆	AcOH	DMSO	O ₂	trace
6	AgBF ₄	AcOH	DMSO	O ₂	trace
7	Cu(OAc) ₂	AcOH	DMSO	O ₂	n.d.
8	CuI	AcOH	DMSO	O ₂	12
9	AuCl	AcOH	DMSO	O ₂	trace
10	AuCl ₃	AcOH	DMSO	O ₂	trace
11	AgOTf	TFA	DMSO	O ₂	13
12	AgOTf	TsOH	DMSO	O ₂	trace
13	AgOTf	AcOH	DMA	O ₂	41
14	AgOTf	AcOH	DMF	O ₂	33
15	AgOTf	AcOH	toluene	O ₂	<5
16	AgOTf	AcOH	DMSO/H ₂ O=5:1	O ₂	78
17	AgOTf	AcOH	DMSO/H ₂ O=2:1	O ₂	80
18	AgOTf	AcOH	DMSO/H ₂ O=1:1	O ₂	77
19	AgOTf	AcOH	H ₂ O	O ₂	trace
20	AgOTf	AcOH	DMSO/H ₂ O=2:1	DDQ	trace
21	AgOTf	AcOH	DMSO/H ₂ O=2:1	K ₂ S ₂ O ₈	trace
22	AgOTf	AcOH	DMSO/H ₂ O=2:1	TBHP	trace
23 ^c	AgOTf	AcOH	DMSO/H ₂ O=2:1	-	n.d.
24 ^d	AgOTf	AcOH	DMSO/H ₂ O=2:1	-	n.d.

^aReaction conditions: **1a** (0.25 mmol), **2a** (0.3 mmol), catalyst (5 mol %), additive (5 mol %), and oxidant (2.0 equiv) in solvent (2 mL) at 120 °C for 8 h. ^bDetermined by GC analysis. ^cReaction conducted at N₂ atmosphere. ^dReaction conducted at Ar atmosphere.

Scheme 1. The formation of byproduct **4a**.

Initially, N-phenylbenzamidinium (**1a**) and phenylpropynal (**2a**) were chosen as model substrates, and the results are described in Table 1. The transformation was carried out in the presence of AgOTf (5 mol %) and AcOH (5 mol %) in DMSO (2 mL) under O₂ as the oxidant at 120 °C (Table 1, entry 1). After 12 h, we were pleased to find that the product **3a** was generated in 63% yield with a little byproduct **4a** in 12% yields (Scheme 1). According to the preliminary result in entry 1, we next evaluated the influence of other silver,

including AgNO₃, Ag₂O, AgOAc, AgSbF₆, and AgBF₄ (Table 1, entries 2-6). It was found that a decreased yield was obtained in the reaction. The poor yields were observed when copper- (Cu(OAc)₂, CuI) and gold (AuCl, AuCl₃) salts were employed (Table 1, entries 7-10). Furthermore, Unsatisfactory yields were formed when TsOH or TFA was used as additive (Table 1, entries 11-12). The effect of solvents were next tested. Other solvents, such as DMA, DMF, or toluene, did not lead to any improved result (Table 1, entries 13-15). We then attempted to improve the yield of product **3a** by adding water that restrained dehydration of **1a** and **2a** to produce intermediate **I** and later form **4a**. As we expected, the desired product **3a** was generated in 77-80% yields when the reaction carried out by using DMSO and H₂O as the co-solvent (Table 1, entries 16-18). However, no imidazoles formation was observed by using H₂O as the solvent (Table 1, entry 19). Then, different oxidants (DDQ, K₂S₂O₈) were also employed and only trace amount of **3a** was formed (Table 1, entries 20-22).

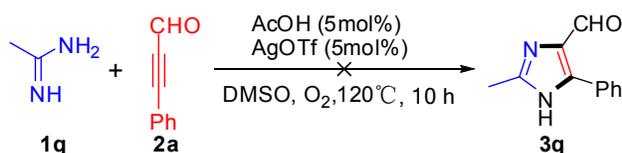


^a Isolated yields

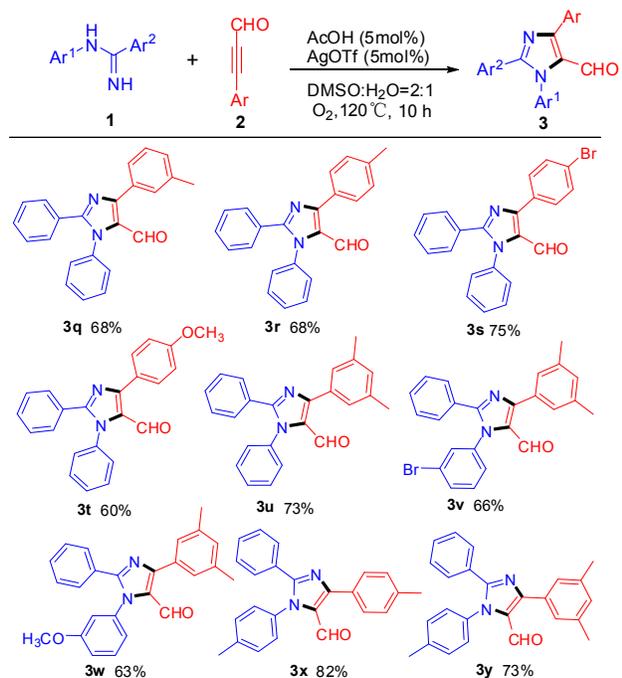
Scheme 2. Scope of the AgOTf-Catalyzed Reaction.

With the optimized catalytic system in hand, we then explored the substrate scope of amidiniums with diverse substituents. The results are shown in Scheme 2.

The reaction was successfully extended to various N-substituted amidines (Ar^1). All of the reactions proceeded smoothly under the optimized conditions and gave the substituted imidazole aldehydes (**3a-3i**). This transformation tolerated different substituents, such as electron-rich (CH_3 , OCH_3) and electron-poor (F , Cl), on the benzene ring of N-substituted amidines (Ar^1). The effect of Ar^2 was then investigated for this Ag-catalyzed strategy. The substituted groups on the arene (Ar^2) such as CH_3 and OCH_3 remained unaffected and were also well-tolerated under optimized conditions (**3j-3p**). All those reactions afforded the corresponding products in moderate to good yields. To further investigate useful substrate, we use acetimidamide. But unfortunately, the desired product was not detected in this reaction (Scheme 3).

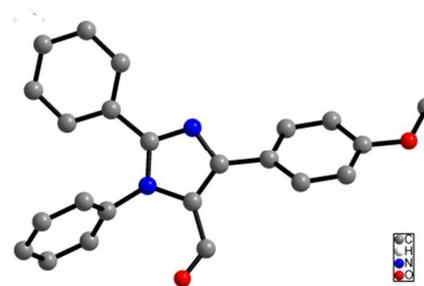
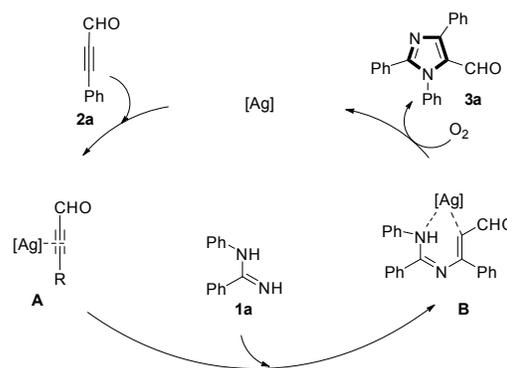


Scheme 3. Synthesis of imidazole by using acetimidamide

^a Isolated yields

Scheme 4. AgOAc-Catalyzed Synthesis of Imidazoles

We were also pleased to find that this Ag-catalyzed process could be successfully applied to different ynals and the results are described in Scheme 4. A variety of ynals, bearing either electron-donating groups (4-CH_3 , 4-OMe , $3,4\text{-dimethyl}$) or electronwithdrawing groups (Br) on the phenyl ring, reacted smoothly with various amidines, affording the corresponding products (**3q-3y**) in 60–82% yields. Notably, the bromo substituent products could be subjected to further transformations to prepare diverse molecules. The molecular structure of product **3t** was determined by X-ray crystallography (**Figure 1**).

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

Scheme 5. Proposal Mechanism

On the basis of above results, a plausible mechanism for this reaction is illustrated in Scheme 5. For the synthesis of **3a**, the carbon-carbon triple bond of **2a** is activated by coordination with Ag-salt to give the intermediate **A**,¹⁵ followed **1a** attack the Ag-coordinated triple bond to give the intermediate **B**. The intermediate **B** then undergoes dehydrogenation oxidation¹⁶ in the presence of oxygen to give the final product **3a** and releases the Ag catalyst.

Conclusions

In summary, we have successfully developed a facile regioselective silver-catalyzed [3+2] domino reaction of amidines and ynals for the formation of C-N bonds. This strategy has provided a new route for the synthesis of imidazole-5-carbaldehydes that are important materials and intermediates for the construction of complex organic compounds. This reaction has several advantages: 1) the reaction has employed O₂ as a clean oxidant instead of other chemical oxidants; 2) the employment of H₂O and DMSO as the co-solvents is cheaper; 3) this reaction has showed good selectivity and susceptible aldehyde products have been formed without further oxidation.

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