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Silver triflate and triphenylphosphine co-catalyzed reactions of 2-alkynylbenzaldehyde, amine, and α,β-unsaturated ketone

Shengqing Ye[a], Jie Wu[a,b,*]

[a] Department of Chemistry, Fudan University, 220 Handan Road, Shanghai 200433, China
[b] State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, China

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This Letter is dedicated to Professor Li-Xin Dai on the occasion of his 85th birthday

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ABSTRACT

A two-component activation system that combines metal catalysis (AgOTf) and the employment of catalytic amount of organocatalyst (PPh_3) has been successfully employed in the three-component reaction of 2-alkynylbenzaldehyde, amine, and α,β-unsaturated ketone. This reaction proceeds smoothly in THF under mild conditions leading to the functionalized 1,2-dihydroisoquinolines in moderate to good yields.

Recently, a combination of metal catalysis and organocatalyst[1] as two-component activation system has been successfully employed in organic synthesis.[2,3] For example, Córdova[2a] developed direct catalytic α-allylic alkylation of aldehydes and cyclic ketones via a combination of palladium and enamine catalysis. We also realized that one-pot combination of silver triflate and proline catalysis was highly effective for the synthesis of 1,2-dihydroisoquinoline derivatives via multicomponent reaction of 2-alkynylbenzaldehyde, amine, and ketones.[2i] Prompted by these results and our interests for accessing privileged scaffolds, we became interested in exploring new two-component activation system (co-catalyzed by metal and organocatalyst) to facilitate the natural product-like compounds generation.

The significance of Baylis–Hillman reaction[4–6] in organic synthesis has been recognized. Usually, a Lewis base, such as phosphine, tertiary amine, or sulfide is utilized as catalyst or promoter to initiate the reaction. Recently, 2-alkynylbenzaldehyde was identified as a versatile building block for the construction of N-heterocycles.[7,8] We also involved in this field and developed efficient methods for the synthesis of diverse 1,2-dihydroisoquinolines via tandem reactions starting from 2-alkynylbenzaldehyde and related compounds.[2i,9] For instance, we realized that copper(I), silver(I), or palladium(II) salts were effective catalysts in the three-component reactions of 2-alkynylbenzaldehyde, amine, and diethyl phosphite.[9j,k] In the reaction process, an isoquinolinium intermediate might be involved. Encouraged by these results and the advancement of Baylis–Hillman reaction, we conceived that under suitable catalytic conditions, three-component reactions of 2-alkynylbenzaldehyde, amine, and α,β-unsaturated ketone might occur. Herein, we disclosed our recent efforts for the three-component reaction of 2-alkynylbenzaldehyde, amine, and α,β-unsaturated ketone co-catalyzed by AgOTf and PPh_3, which afforded the expected 1,2-dihydroisoquinoline derivatives in moderate to good yields.

Our studies commenced with the reaction of 2-alkynylbenzaldehyde **1a**, *p*-anisidine **2a**, and but-3-en-2-one **3a** (Table 1). In our previous report,[9] we have demonstrated silver triflate as an effective catalyst for the isoquinolinium intermediate generation. Thus, initial efforts were performed in the presence of AgOTf and PBu_3 as catalysts in THF at 70 °C (Table 1, entry 1). However, only trace amount of the product was detected after 24 h under the above-mentioned conditions. Similar results were observed when TFP or P(*o*-Tol)$_3$ was employed as a replacement (Table 1, entries 2 and 3). Gratifyingly, the result was dramatically improved when

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* Corresponding author. Address: Department of Chemistry, Fudan University, 220 Handan Road, Shanghai 200433, China. Tel.: +86 21 5566 4619; fax: +86 21 6510 2412.
E-mail address: jie_wu@fudan.edu.cn (J. Wu).

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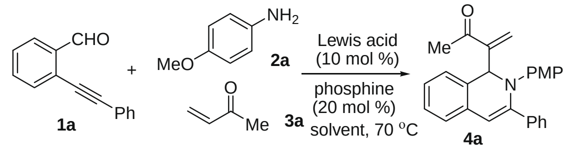
Table 1
Conditions optimization for the reaction of 2-alkynylbenzaldehyde, *p*-anisidine, and but-3-en-2-one



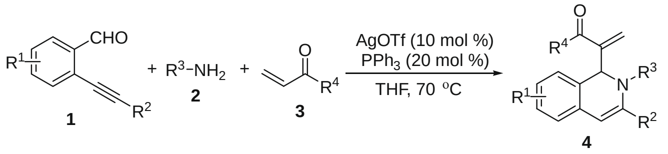
Entry	Lewis acid	Phosphine	Solvent	Yield[a] (%)
1	AgOTf	PBu_3	THF	Trace
2	AgOTf	TFP	THF	Trace
3	AgOTf	P(*o*-Tol)$_3$	THF	Trace
4	AgOTf	PPh_3	THF	70
5	AgOTf	PCy_3	THF	24
6	AgOTf	PPh_3	MeCN	54
7	AgOTf	PPh_3	DCE	49
8	AgOTf	PPh_3	DMF	53
9	AgOTf	PPh_3	Toluene	41
10	AgOTf	PPh_3	DME	33
11	AgOTf	PPh_3	EtOH	Trace
12[b]	AgOTf	PPh_3	THF	54
13[c]	AgOTf	PPh_3	THF	52
14[d]	AgOTf	PPh_3	THF	70
15	CuI	PPh_3	THF	11
16	Cu(OTf)$_2$	PPh_3	THF	13
17	Dy(OTf)$_3$	PPh_3	THF	NR
18	AgOAc	PPh_3	THF	Trace
19[e]	AgOTf	PPh_3	THF	47

[a] Isolated yield based on 2-alkynylbenzaldehyde.
[b] In the presence of 10 mol % of PPh_3.
[c] In the presence of 5 mol % of PPh_3.
[d] In the presence of 50 mol % of PPh_3.
[e] In the presence of 4 Å molecular sieves.

PPh_3 was used as an organocatalyst in the reaction, and the desired product **4a** was isolated in 70% yield (Table 1, entry 4). Inferior yield was displayed when PCy_3 was utilized (24% yield, Table 1, entry 5). Blank experiment indicated that no desired product was detected in the absence of phosphine (data not shown in Table 1). Further screening of the solvents revealed that THF was the best choice for this transformation (Table 1, entries 6–11). Decreasing the amount of PPh_3 diminished the product yield (Table 1, entries 12 and 13). A similar result was obtained when the amount of PPh_3 was increased to 50 mol % (70% yield, Table 1, entry 14). We also examined other Lewis acids in the reaction. Thus, copper salts or Dy(OTf)$_3$ was tested, however, no better results were displayed (Table 1, entries 15–17). Addition of molecular sieves could not improve the final outcome as well (Table 1, entry 19). Moreover, we tried to add additive [proline, Zn(OTf)$_2$, Mg(ClO$_4$)$_2$, and urea] in the reaction based on the advancement of Baylis–Hillman reaction[4] (data not shown in Table 1). Again, low yields of product **4a** were isolated.

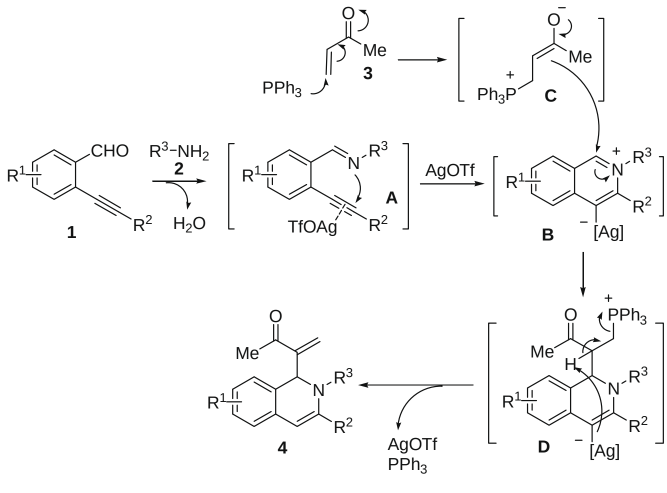
With this preliminary optimized conditions in hand, the scope of this reaction was then investigated [AgOTf (10 mol %), PPh_3 (20 mol %), THF, 70 °C], and the results are summarized in Table 2. From Table 2, we noticed that, for most cases, the silver triflate and triphenylphosphine co-catalyzed reactions of 2-alkynylbenzaldehyde **1**, amine **2**, and α,β-unsaturated ketone **3** proceeded smoothly leading to the corresponding products **4** in moderate to good yields. Usually, 12–24 h was needed for the completion of the reaction. We found that the conditions have proven to be useful for various aromatic amines. As expected, both electron-rich and electron-poor anilines are suitable partners in the reaction of 2-alkynylbenzaldehyde **1a** and but-3-en-2-one **3a**. However, no reactions occurred when aliphatic amines were employed in the above reactions (data not shown in Table 2). We reasoned that it might be due to the stability issue of the imine generated. With respect to the R^2 group attached on the triple bond in substrate **1**, it seemed that the *n*-butyl group was not suitable in this process. We observed the product formation during the reaction process, however, the product obtained was not stable and easy to be decomposed (Table 2, entry 7). Product **4h** was generated with 40% yield when cyclopropyl group was used as a replacement (Table 2, entry 8). Fluoro-substituted 2-alkynylbenzaldehyde **1** also worked well, which afforded the desired product **4i** or **4j** in 60% or 40% yields, respectively (Table 2, entries 9–10). However, only trace amount of product **4k** was detected when 2-alkynylbenzal-

Table 2
Silver triflate and triphenylphosphine co-catalyzed reactions of 2-alkynylbenzaldehyde **1**, amine **2**, and α,β-unsaturated ketone **3**[10]



Entry	R^1	R^2	R^3	R^4	Product	Yield[a] (%)
1	H	Ph	4-MeOC$_6$H$_4$ (**2a**)	Me (**3a**)	**4a**	70
2	H	Ph	4-MeC$_6$H$_4$ (**2b**)	Me (**3a**)	**4b**	63
3	H	Ph	3-NO$_2$C$_6$H$_4$ (**2c**)	Me (**3a**)	**4c**	60
4	H	Ph	4-FC$_6$H$_4$ (**2d**)	Me (**3a**)	**4d**	70
5	H	Ph	4-CF$_3$C$_6$H$_4$ (**2e**)	Me (**3a**)	**4e**	65
6	H	Ph	C$_6$H$_5$ (**2f**)	Me (**3a**)	**4f**	70
7	H	*n*-Bu	4-MeOC$_6$H$_4$ (**2a**)	Me (**3a**)	**4g**	Trace
8	H	Cyclopropyl	4-MeOC$_6$H$_4$ (**2a**)	Me (**3a**)	**4h**	40
9	5-F	Ph	4-MeOC$_6$H$_4$ (**2a**)	Me (**3a**)	**4i**	60
10	4-F	Ph	4-MeOC$_6$H$_4$ (**2a**)	Me (**3a**)	**4j**	40
11	4,5-(OMe)$_2$	Ph	4-MeOC$_6$H$_4$ (**2a**)	Me (**3a**)	**4k**	Trace
12	H	Ph	4-MeOC$_6$H$_4$ (**2a**)	Et (**3b**)	**4l**	56
13	H	Ph	4-MeC$_6$H$_4$ (**2b**)	Et (**3b**)	**4m**	60
14	H	Ph	4-FC$_6$H$_4$ (**2d**)	Et (**3b**)	**4n**	63
15	H	Ph	4-CF$_3$C$_6$H$_4$ (**2e**)	Et (**3b**)	**4o**	67
16	H	Ph	C$_6$H$_5$ (**2f**)	Et (**3b**)	**4p**	54
17	H	Cyclopropyl	4-MeOC$_6$H$_4$ (**2a**)	Et (**3b**)	**4q**	45
18	4-F	Ph	4-MeOC$_6$H$_4$ (**2a**)	Et (**3b**)	**4r**	48
19	H	Ph	4-MeOC$_6$H$_4$ (**2a**)	OMe (**3c**)	**4s**	NR

[a] Isolated yield based on 2-alkynylbenzaldehyde **1**.



Scheme 1. Possible mechanism for the silver triflate and triphenylphosphine co-catalyzed three-component reaction.

dehyde **1** with electron-rich group attached on the aromatic ring was employed (Table 2, entry 11). It might be due to the lower electrophilicity of the in situ-generated iminium. Pent-1-en-3-one **2b** was also a suitable partner in this reaction (Table 2, entries 12–18). However, no product was detected when methyl acrylate **2c** was employed as a substrate in the reaction (Table 2, entry 19). The possible mechanism was proposed as well (Scheme 1). We reasoned that in the presence of AgOTf, the triple bond might coordinate to the silver salt, and subsequently, the nitrogen atom of imine **A** could attack the triple bond via 6-*endo*-cyclization to afford an isoquinolinium intermediate **B**. Meanwhile, triphenylphosphine as a nucleophilic catalyst attacked the α,β-unsaturated ketone **3** leading to the enolate **C**, which then underwent intermolecular attack of the isoquinolinium intermediate **B** to generate phosphinium **D**. Finally, elimination of phosphine gave rise to the desired product **4**.

In summary, we have described a three-component reaction of 2-alkynylbenzaldehyde, amine, and α,β-unsaturated ketone catalyzed by the combination of AgOTf and PPh_3 as an activation system. This reaction proceeds smoothly under mild conditions, giving rise to the functionalized 1,2-dihydroisoquinolines in moderate to good yields. Further transformation combining metal catalysis and organocatalysis is under investigation in our laboratory, and the results will be reported in due course.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.09.005.

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10. *General procedure for the silver triflate and triphenylphosphine co-catalyzed reactions of 2-alkynylbenzaldehyde* **1**, *amine* **2**, *and α,β-unsaturated ketone* **3**: α,β-unsaturated ketone **3** (0.4 mmol 2.0 equiv) was added to a solution of 2-alkynylbenzaldehyde **1** (0.20 mmol), amine **2** (0.22 mmol, 1.1 equiv), AgOTf (0.02 mmol, 10 mol %), and PPh_3 (0.04 mmol 20 mol %) in THF (2.0 mL). The solution was then stirred at 70 °C. After completion of reaction as indicated by TLC, the solvent was evaporated. The residue was purified by flash chromatography on silica gel to provide the desired product **4**. Data of selected example: 3-(2-(4-Methoxyphenyl)-3-phenyl-1,2-dihydroisoquinolin-1-yl)but-3-en-2-one **4a**. ^1H NMR (400 MHz, $CDCl_3$) δ 2.37 (s, 3H), 3.64 (s, 3H), 5.41 (s, 1H), 5.98 (s, 1H), 6.08 (s, 1H), 6.62 (d, J = 9.2 Hz, 2H), 6.64 (s, 1H), 7.03–7.06 (m, 3H), 7.11–7.26 (m, 6H), 7.48 (d, J = 6.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 49.4, 77.4, 84.8, 133.7, 135.9, 146.1, 146.4, 147.9, 148.8, 148.9, 149.2, 149.7, 150.1, 150.5, 151.5, 154.7, 159.5, 163.0, 163.3, 170.0, 177.2, 222.6; HRMS calcd for $C_{26}H_{24}NO_2$ (M^++H): 382.1807, found: 382.1824. (For details, please see Supplementary data).