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Ag(I)-Catalyzed Indolization/C3-Functionalization Cascade of 2-Ethynylanilines via Ring Opening of Donor−Acceptor Cyclopropanes

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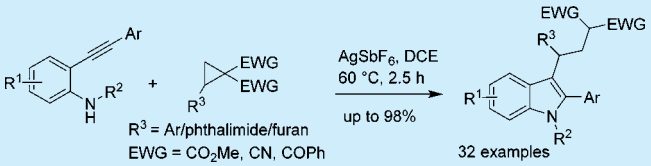
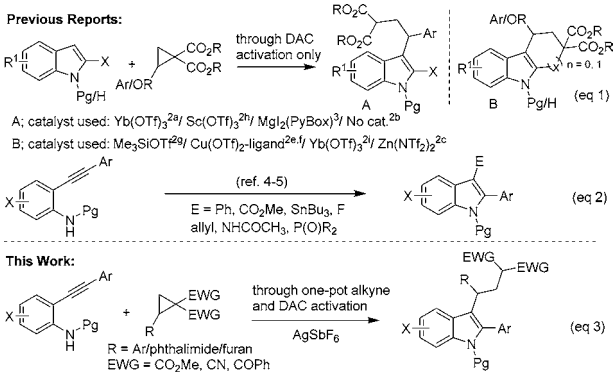
Supporting Information

ABSTRACT: A $AgSbF_6$-catalyzed cascade involving the ring opening of donor−acceptor cyclopropanes (DACs) preceded by the cyclization of *N*-protected 2-ethynylaniline is described. The method discloses a step-economy route to 2,3-disubstituted indole, where a Ag catalyst is found to trigger the cascade by activating both alkyne and DACs. Various functionalities at different ends of both substrates offer rapid access to 2,3-disubstituted indole derivatives in one pot in good to excellent yields. Elaboration of the cascade product to useful intermediates is also depicted.



Donor−acceptor cyclopropanes (DACs) are acknowledged as functional in organic synthesis because of their unique reactivity and versatile reagent nature, which allows a multitude of chemical transformations.[1] In particular, ring-opening reactions of DACs with a variety of nucleophiles[1] offer easy access to various functionalized molecules. In recent years, indoles have been frequently used as nucleophiles against DACs. Intermolecular Friedel−Crafts reactions[2] between DACs and indoles have been exemplified especially by the groups of Tang,[2b,d] Ivanova,[2h] Kerr,[2f,g,j,k] and Pagenkopf[2i] using different Lewis acid catalysts (Scheme 1, eq 1). Johnson et al. reported an enantioconvergent Friedel−Crafts alkylation at the C3 position of indoles with DACs[3a] (eq 1), whereas Fu et al. used alkylidenemalonates instead of DAC.[3b] All the aforementioned transformations commenced with indoles, taking advantage of its nucleophilicity and cyclopropane bond activation that are reported to be achieved by the use of conventional Lewis acid catalysts of Cu, Zn, Sc, In, Yb, and Mg.

Scheme 1. Literature Reports and Present Work



On the other hand, cyclization of 2-ethynylaniline derivatives and subsequent functionalization at the C3 position by trapping with suitable electrophiles has proven to be an efficient means for the construction of substituted indoles via transition metal catalysis (Scheme 1, eq 2).[4] This gives access to 2,3-disubstituted indoles. In 2016, isocyanates and phosphine oxides were reported to be used as electrophiles in combination with 2-ethynylanilines to access 3-carboxamides and phosphinoylindoles, respectively.[5] The differential reactivity of 2-ethynylaniline toward various electrophiles prompted us to explore alternative efficient routes for the synthesis of C3-functionalized indoles. To the best of our knowledge, an approach to 2,3-disubstituted indoles combining 2-ethynylanilines, a precursor of indole, and DACs as an electrophile has not yet been exploited. Anticipating that 2-ethynylanilines could be an ideal substitute of indoles toward DAC chemistry and their reaction would serve as a powerful tool for the addition of carbon nucleophiles to DACs, offering an expedient short-path strategy to 2,3-disubstituted indoles, we projected eq 3 (Scheme 1).

In addition, such indoles (Scheme 1, eq 3) are found to be important due to their synthetic utility[6] as building blocks for spirocyclic architectures and pharmaceuticals.[7] For example, bioisosteres of indoloylbuteric acid, containing a C3 chain of carboxylic acid derivatives (e.g., acylsulfonamide, acylsulfamide), are identified as CXCR2 antagonists.[7]

Herein, we describe a novel catalytic indolization of 2-ethynylanilines followed by ring opening of DACs in a cascade

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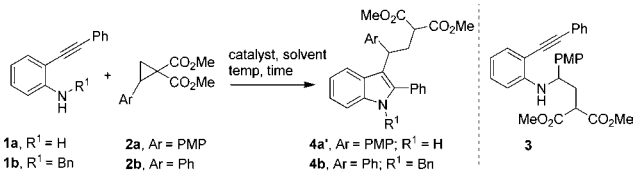
fashion, leading to the one-pot formation of 2,3-disubstituted indole derivatives. This method features the use of a $AgSbF_6$ catalyst, which successfully affects the tandem-type process by typical alkyne activation/cyclization followed by a coupling reaction with DACs via an unprecedented Ag(I)-mediated ring opening. This obviates the need for frequently used conventional Lewis acid catalyst (Cu, Zn, Sc, In, Yb, Mg) for such DAC chemistry.

Following the metal-catalyzed cyclization of 2-ethynylanilines,[4,5] we set forth to investigate the possibility of using 2-(phenylethynyl)aniline (**1a**) in Ag-catalyzed cyclization and subsequent functionalization at the C3 position by trapping with DACs. Unfortunately, DAC **2a** predominantly underwent a typical ring opening with the free NH_2 group of **1a** without prior cyclization, yielding **3** as the major product (55%) and the desired 2,3-disubstituted indole **4a′** in poor yield (30%). On the other hand, compounds **1a** and **2b** failed to react under similar reaction condition (see Supporting Information for details).

We surmised that this problem could be eliminated by protection of the free NH_2 group of **1a**. We started optimization studies using *N*-benzyl 2-ethynylaniline (**1b**) and DAC **2b** (Table 1) in the presence of a variety of metal catalysts. Because

Table 1. Optimization Studies of the Cascade Process[a]



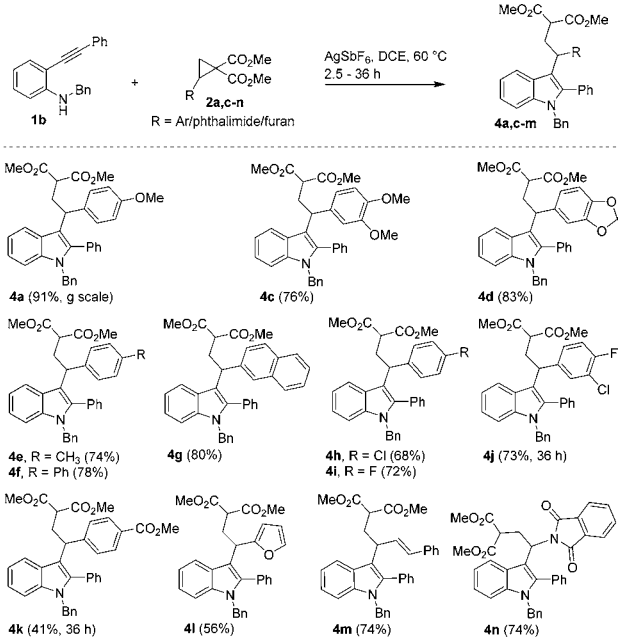
entry	cat. (mol %)	solvent	temp (°C)	time (h)	4b[b]
1	$Cu(OTf)_2$ (10)	DCE	rt	2	20%
2	$Zn(OTf)_2$ (10)	DCE	rt	24	NR[c]
3	AgOAc (10)	DCE	60	12	NR[c]
4	AgOTf (10)	DCE	60	5	60%
5	$AgBF_4$ (10)	DCE	60	5	58%
6	$AgClO_4$ (10)	DCE	60	5	42%[d]
7	$AgSbF_6$ (10)	DCE	60	5	83%
8	$AgSbF_6$ (10)	DCE	rt	30	ND[e]
9	$AgSbF_6$ (10)	THF	60	12	NR[f]
10	$AgSbF_6$ (10)	PhMe	60	12	NR[f]
11	$AgSbF_6$ (10)	CH_3CN	60	12	NR[c]
12	$AgSbF_6$ (10)	CCl_4	60	12	NR[c]
13	$AgSbF_6$ (5)	DCE	60	5	22%[g]

[a]Standard conditions: 0.4 mmol of each **1b** and DAC **2b**, 10 mol % of $AgSbF_6$, 3 mL of DCE at 60 °C. [b]Isolated yields after column purification. [c]No reaction. Both **1b** and **2b** were recovered. [d]Unreacted **2b** recovered. [e]Not determined. [f]No reaction. [g]Unreacted **2b** and indole of **1b**. PMP = *p*-methoxyphenyl. DCE = 1,2-dichloroethane.

$Cu(OTf)_2$ is known to activate both alkyne[8] and DACs, both **1b** and **2b** were subjected to the reaction in the presence of 10 mol % of $Cu(OTf)_2$ in $(CH_2Cl)_2$ at rt (Table 1, entry 1). Unfortunately, desired product **4b** was isolated in 20% yield from a complex mixture. However, screening with various Ag catalysts (Table 1, entries 3−7) showed improved yields of **4b**, with $AgSbF_6$ being the best, resulting in 83% yield. Investigation of the reaction in solvents other than $(CH_2Cl)_2$ (Table 1, entries 9−12) and lower catalyst ($AgSbF_6$) loading (Table 1, entry 13) gave reduced yields of the desired products. Following exhaustive optimization, it was found that the cascade cyclization/ring-opening process can be realized in the presence of 10 mol % of $AgSbF_6$ in $(CH_2Cl)_2$ at 60 °C to afford **4b** in 83% yield within 5 h (Table 1, entry 7). The reaction was found to be sluggish at rt, showing only 40% conversion after 30 h (entry 8).

With optimized reaction conditions in hand, we first explored the synthetic scope of the cascade cyclization/ring-opening process using **1b** with a variety of DACs. It is evident from Table 2 that the methodology worked well, revealing broad scope of the

Table 2. Effect of DACs on the Cascade Process[a]



[a]Conditions: 0.4 mmol of each **1b** and DAC **2**, 10 mol % of $AgSbF_6$, 3 mL of DCE at 60 °C. Isolated yields after column purification.

reaction encompassing different kinds of DACs to provide 2,3-disubstituted indole **4a,c−n** with 41−91% yields. During the course of examination of this substrate scope, we noticed that, in most cases, the cascade reaction was completed within 2.5 h, showing wide tolerance of substitution on DACs. DACs having electron-rich and electron-deficient groups afforded products **4a,c−n** in good yields within 2.5 h at 60 °C. It is noteworthy that the reaction of oxygen-substituted DACs **2a,c,d** and **1b** is accomplished at rt in 12 h, yielding up to 91% of the desired products. Cyclopropanes containing poor donor groups, such as aryl halide and aryl ester viz. **2j** and **2k**, also underwent desired cascade reaction under prolonged heating (36 h, 60 °C), giving 73 and 41% yields, respectively. A heterocycle bearing DAC **2l** was also found to be a suitable substrate under the reaction conditions, furnishing a moderate yield of **4l**. Styrenyl cyclopropanediester **2m** gave good yield of the desired product. The reaction of **1b** and *N*-phthalimide-DAC **2n** allowed access to GABA analogue **4n** in 74% yield, which has been reported to be obtained from indole and DAC **2n**.[2b]

As expected, DAC (R = H, Table 2) failed to undergo the cascade reaction, probably because the positive charge in the putative transition state could not be stabilized.

DACs **5a,b** consisting of cyano and keto groups were also found to be efficient toward $AgSbF_6$-catalyzed activation and, hence, the cascade process (Scheme 2), but these reactions require extended heating to furnish **6a,b** from **5a,b**. Monoester, aldehyde, and nitro-containing DACs were not competent reaction partners under the reaction conditions.

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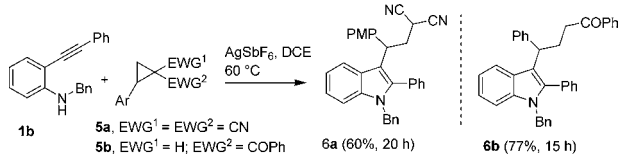
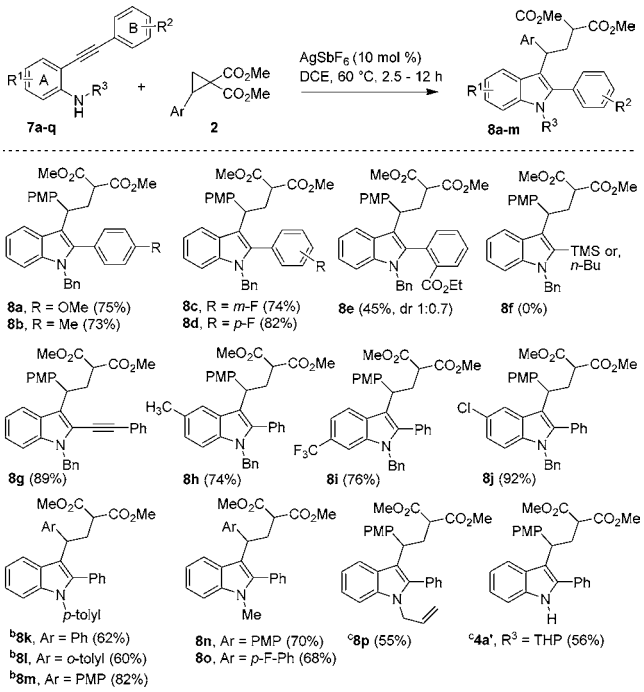
Scheme 2. Effect of Electron-Withdrawing Groups on the Cascade Process



Using the optimized reaction conditions, we further examined the generality of the method on variously substituted 2-ethynylanilines **7a−m** having different electronic properties (Table 3). 2-Ethynylanilines **7a−d** having electron-rich and

Table 3. Effect of Different 2-Ethynylanilines on the Ag-Catalyzed Cascade Process[a]

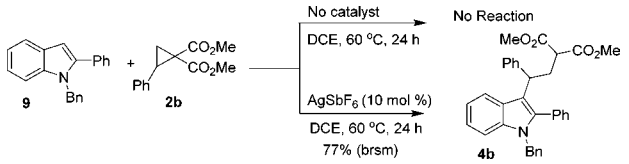


[a]Conditions: 0.4 mmol of each **7** and DAC **2**, 10 mol % of $AgSbF_6$, 3 mL of DCE at 60 °C. Isolated yields after column purification. [b]With AgOTf: 59% (**8k**, 12 h); 59% (**8l**, 12 h); 96% (**8m**, 2 h, rt). [c]1.5 h.

-deficient functionalities on ring B afforded products **8a−d** in synthetically viable yields. However, compound **7e** consisting of an *o*-ester group at ring B yielded **8e** in 45% yield with 1:0.7 dr. The possible reason for diastereomer formation is the axial chirality of ring B. Substrates bearing aliphatic groups (e.g., **8f**) at the alkyne end failed to undergo the cascade sequence, giving starting materials back. Interestingly, 2-ethynylaniline, containing a phenylacetylene moiety (**7g**) instead of the aryl ring, led to the completion of the reaction at rt within 2.5 h, yielding **8g** (89%). Our hypothesis behind using **7g** was to construct a tetrahydrocarbazole moiety in one pot. It was also observed that substrate **7** sharing a CH_3, CF_3, or Cl functionality on ring A served as good substrates, which afforded products **8h−j** in up to 92% yield. Indoles with *N*-aryl rings have also been documented and are found to be present in pharmaceutically active compounds.[9] Hence, *N*-*p*-tolyl-2-ethynylanilines **7k−m** were also employed under standard conditions and furnished indoles **8k−m** (Table 3) in good yields. AgOTf was also found to be a suitable catalyst for this transformation. Reaction of *N*-Me/allyl-substituted 2-ethynylanilines **7n−p** with **2** produced indoles **8n−p** in good yields, whereas THP-protected compound **7q** furnished **4a′** via in situ deprotection in the reaction medium. Under the reaction conditions, *N*-tosyl 2-ethynylaniline failed to react with **2a**.

Monitoring the reaction between **1b** and **2b**, we observed that the reaction proceeds via 2-substituted indole **9**, which was isolated in a considerable amount by aborting the reaction to elucidate the role of the Ag catalyst. A control experiment was performed in which 2-phenylindole **9** (1 equiv) was treated with DAC **2b** (1.2 equiv) in the presence and absence of Ag catalyst at 60 °C in DCE (Scheme 3). As a result, no addition product **4b**

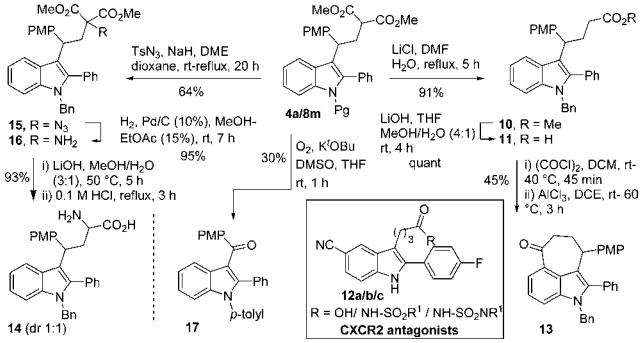
Scheme 3. Role of Ag(I) Catalyst in Activating DAC



was obtained in absence of the catalyst, keeping both of the starting materials intact. Use of the catalyst, although sluggishly (70% conversion after 24 h at 60 °C), led to the formation of the desired product. This indicates that $AgSbF_6$ may have a dual activation property, and compared to indole **9**, its precursor is more reactive toward DACs under the reaction conditions.

With a synthetically viable method in hand, we were inclined to elaborate these compounds to various synthetic intermediates (Scheme 4). Toward this end, we performed Krapcho deal-

Scheme 4. Synthetic Elaboration of the Cascade Product



koxycarboxylation of compound **4a** to afford **10** in 91% yield. Compound **10** was converted to corresponding acid **11** (an analogue of indolylbuteric acid **12a**) in quantitative yield. Acid **11** was then transformed to tricyclic indole **13** via Friedel−Crafts acylation. In another series, **4a** was transformed to homotryptophan analogue **14** with 56% overall yield. This included a three-step sequence: formation of azide **15**,[10] its reduction to amine **16**, and ester hydrolysis followed by decarboxylation.[11] Treatment of **8m** with O_2/K^{t}OBu in DMSO revealed a new pathway to 3-acylindole **17**, by selective oxidation of the side chain at C3 of indole.

In conclusion, we have developed the first example of Ag-catalyzed cyclization−C3-functionalization cascade of 2-alkynylaniline derivatives in the presence of various DACs. Unlike most of the reported methods for the ring opening of DACs, this protocol does not involve the use of typical transition metal catalysts. Electronically diverse substrates gave satisfactory

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results, showing good functional group tolerance for this simple step-economy process. Furthermore, we successfully employed the C3 side chain bearing indole for the construction of other useful compounds. We deem that an enantioselective version of this strategy would provide a potential route to access 2,3-disubstituted indoles in an enantioenriched form, which is under active investigation in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01057.

Experimental procedures and analytical data (^{1}H, ^{13}C NMR spectra and HRMS) for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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