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Hypervalent Iodine-Mediated Intramolecular *trans*-Aminocarboxylation and Oxoaminocarboxylation of Alkynes: Divergent Cascade Annulations of Isocoumarins under Metal-Free Conditions

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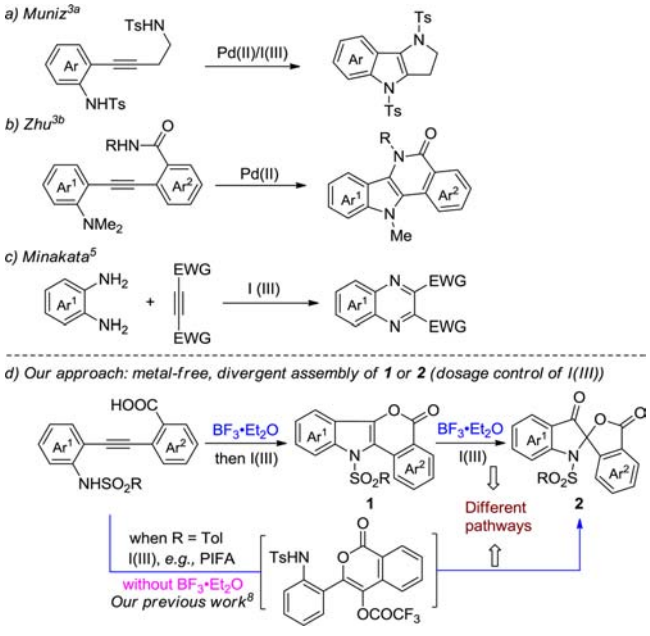
Supporting Information

ABSTRACT: An exclusive *trans*-aminocarboxylation and oxoaminocarboxylation of diarylalkynes were realized through hypervalent iodine-mediated cascade annulations under metal-free conditions, leading to divergent assembly of fused or spiro polycyclic heterocycles with a dosage of the hypervalent iodine oxidant. The mechanisms for the formation of both products are proposed.

Currently, cascade reactions (or one-pot transformations), during which multistep reactions proceed in a single manipulation without isolation or purification of any of the intermediates, have received much attention due to the obvious reason for their efficiency, especially for the assembly of complex molecular structures.[1,2] Such a strategy has been proven and adopted as a powerful synthetic means for the conversion of internal alkynes into biologically interesting polycyclic[3] or spiro[4] heterocycles. A literature survey on intramolecular *trans*-addition of nitrogen and/or oxygen across triple bonds presented only two examples: (1) Pd(II)/I(III)-based intramolecular annulation of internal alkyne through successive C−N bond formations[3a] (Scheme 1a); (2) Pd(II)-catalyzed intramolecular diamination of diarylacetylene accompanied by a C(sp^3)−N bond cleavage, affording the bioactive indoleisoquinolinones[3b] (Scheme 1b). Both of these methods evidently require the use of a transition-metal catalyst. It is worth noting that the first intermolecular, metal-free "syn"-addition across the triple bond of the two nitrogens in 1,2-phenylenediamines in an internal alkyne was realized by using hypervalent I(III) as the oxidant (Scheme 1c).[5] However, to the best of our knowledge, there is no report about the direct addition of nitrogen and oxygen across diarylalkyne into a fused polycyclic skeleton under metal-free conditions.

Hypervalent iodine reagents,[6] a class of readily available, "green" nonmetal oxidants, have been widely used in various bond-forming reactions.[7] However, reports on their applications in cascade or one-pot processes involving several bond-forming sequences in forming complex heterocycles are scarce.[8] Recently, we reported such an application in a cascade annulation reaction of internal alkynes which afforded spiro heterocycles with high efficiency and a wide scope.[9] As part of our ongoing research, we explored the possibility of extending the method to the synthesis of either fused or spiro polycyclic compounds such as **1** and **2**[10] (Scheme 1c), whose analogues have been shown to possess antifungal activity. In this letter, we report our discovery of an exclusive, one-pot heteroannulation process featuring BF_3·Et_2O-

Scheme 1. Cascade Annulations of Internal Alkynes



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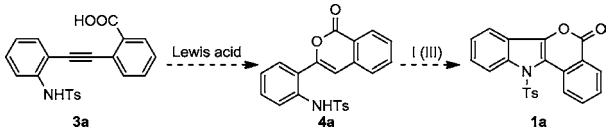
catalyzed *O*-addition of carboxylic acid to diarylalkyne and the subsequent PIDA-mediated dehydrogenative C−N bond formation or spirocyclization under metal-free conditions. To our knowledge, these fused and spiro heterocycles (Scheme 1c) are not readily accessible by any of the known methods.[11]

Initially, we envisaged that, in the presence of a Brønsted or Lewis acid, diarylacetylene **3a** would likely be converted into 6-*endo-dig* intermediate **4a** (Scheme 2), which might undergo

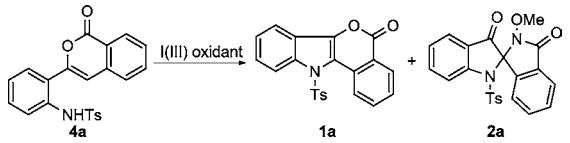
Scheme 2. Hypothezied Lactonization Followed by Dehydrogenative C−N Bond Formation for Intramolecular *trans*-Aminocarboxylation of Alkynes



oxidative cyclization to give polycyclic product **1a** through an I(III)-mediated dehydrogenative C−N bond formation.[12] To our delight, the introduction of $BF_3{\cdot}Et_2O$ selectively led to the formation of the 6-*endo-dig* intermediate **4a** in nearly quantitative yield (see the Supporting Information for details).[13]

Intermediate **4a** was then used as the model substrate to search for the optimal reaction conditions for the second dehydrogenative C−N bond formation step. Additive-screening studies including TFE, HFIP, TFA, TsOH, $BF_3{\cdot}Et_2O$, TMSOTf revealed that a Lewis acid catalyst ($BF_3{\cdot}Et_2O$ or TMSOTf) was indispensable for the conversion of **4a** into the desired product **1a**, with spiro compound **2a** formed as a byproduct (Table 1, entries 1−8). A reduced amount of $BF_3{\cdot}Et_2O$ led to a slight improvement in yield, furnishing **1a** as virtually the sole product

Table 1. Optimization of the I(III)-Mediated Dehydrogenative C−N Bond Formation[a]



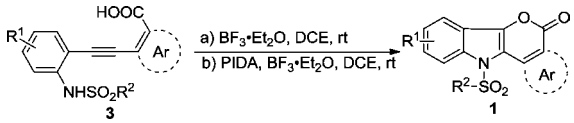
entry	[O]	additive	solvent	t (h)	yield (%)[b] (**1a**:**2a**)
1[c,d]	PIDA	–	DCE	24	NR
2[c,d]	PIFA	–	DCE	24	NR
3[e]	PIDA	TMSOTf	DCE	0.5	52:19
4[e]	PIDA	$BF_3{\cdot}Et_2O$	DCE	0.5	80:5
5[c,e]	PIDA	TFE	DCE	24	NR
6[c,e]	PIDA	HFIP	DCE	24	NR
7[c,e]	PIDA	TFA	DCE	24	NR
8[c,e]	PIDA	TsOH	DCE	24	NR
9	**PIDA**	**$BF_3{\cdot}Et_2O$**	**DCE**	**1**	**86:trace**
10[f]	PIDA	$BF_3{\cdot}Et_2O$	DCE	4	85:trace
11	PIDA	$BF_3{\cdot}Et_2O$	THF	1	78:trace
12	PIDA	$BF_3{\cdot}Et_2O$	DMF	1	74:trace
13	PIDA	$BF_3{\cdot}Et_2O$	MeCN	1	80:trace
14	PhIO	$BF_3{\cdot}Et_2O$	DCE	12	84:trace
15	PIFA	$BF_3{\cdot}Et_2O$	DCE	0.25	55:15

[a]Reaction conditions: **4a** (0.4 mmol), oxidant (0.44 mmol), additive (0.2 mmol) in solvent (4 mL) at rt unless otherwise stated. [b]Isolated yield. [c]The reaction was conducted at rt to 80 °C. [d]The reaction was conducted without additives. [e]The reaction was conducted using 0.4 mmol of additive. [f]The reaction was conducted using 0.08 mmol of additive.

in 86% yield (Table 1, entry 9). Further lowering of the amount of $BF_3{\cdot}Et_2O$ resulted in only a significantly prolonged reaction time without benefiting the yield (Table 1, entry 10). Several other common organic solvents, e.g., THF, DMF, and MeCN, also worked equally well (Table 1, entries 11−13). On the other hand, trials with other I(III)-reagents showed that while PhIO gave an equally satisfactory yield of 84%, PIFA led to a mixture of **1a** and **2a** with a much lower yield for **1a** (Table 1, entries 14−15).

Under optimized conditions, a series of diarylacetylenes **3** were prepared (see the Supporting Information for details) to investigate the scope of this newly established method (Table 2).

Table 2. Scope of the Intramolecular *trans*-Aminocarboxylation of Alkynes[a]



entry	R^1	Ar	R^2	**1**	yield (%)[b]
1	H	Ph	Tol	**1a**	86
2	4-Me	Ph	Tol	**1b**	90
3	4-F	Ph	Tol	**1c**	81
4	4-Cl	Ph	Tol	**1d**	84
5	4-Br	Ph	Tol	**1e**	80
6	4,6-diMe	Ph	Tol	**1f**	75
7	H	5-Me-Ph	Tol	**1g**	88
8	H	5-OMe-Ph	Tol	**1h**	85
9	H	5-F-Ph	Tol	**1i**	84
10	H	5-Br-Ph	Tol	**1j**	85
11	4-Me	5-Me-Ph	Tol	**1k**	87
12	4-Me	5-F-Ph	Tol	**1l**	84
13	4-Me	4-Cl-Ph	Tol	**1m**	88
14	H	Ph	Ph	**1n**	80
15	H	Ph	^{p}ClPh	**1o**	73
16	H	Ph	^{n}Bu	**1p**	82
17	4-Me	thiophene	Tol	**1q**	72

[a]Reaction conditions: substrates **3** (0.4 mmol) and $BF_3{\cdot}Et_2O$ (3 equiv) in DCE (4 mL) at rt for 10 h, filtrated by short pad of silica gel, and then reacted with PIDA (1.1 equiv) and $BF_3{\cdot}Et_2O$ (0.5 equiv) at rt for 1 h. [b]Isolated yield.

First, we evaluated the electronic effect of substituent R^1 (Table 2, entries 1−5). It was found that an electron-donating group (Me) was marginally more favored than electron-withdrawing groups (F, Cl, Br). The steric effect was apparent, as **1f** was obtained in a lower yield (Table 2, entry 6). The substituent effect at the phenyl ring containing the carboxyl moiety was found to be minimal (Table 2, entries 7−13). Other sulfonyl R^2 groups gave slightly lowered yields relative to the tosyl group (Table 2, entries 14−17). On the other hand, no desired product was obtained with R^2 being a benzyl or trifluoro methylsulfonyl group (not shown). Finally, the thiophene ring could be well tolerated under the optimized conditions, giving the preferred product **1q** in a moderate yield of 72% (Table 2, entry 17).

Encouraged by the above findings, we proceeded to realize the two-step reaction in a one-pot fashion. A series of experimental variables, including the amount of the catalyst, the solvent, the temperature, and the type of hypervalent iodine oxidant, were systematically examined (see the Supporting Information for details). After many trials, we determined the most ideal conditions to be 1.0 equiv of $BF_3{\cdot}Et_2O$ in DCE at 80 °C for 8

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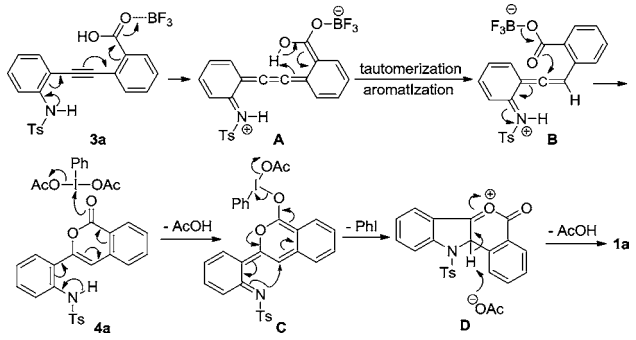
h followed by treatment with 1.1 equiv of PIDA at room temperature for another 0.5 h. The examples, bearing different substitutions on the two aromatic rings, were all achieved in moderate to good yields. (The results were summarized in pp S6−S7 of the Supporting Information.)

A plausible mechanism has been proposed and is depicted in Scheme 3. The acid moiety in **3a**, after being activated by the

Scheme 3. Proposed Mechanism for the Formation of 1a

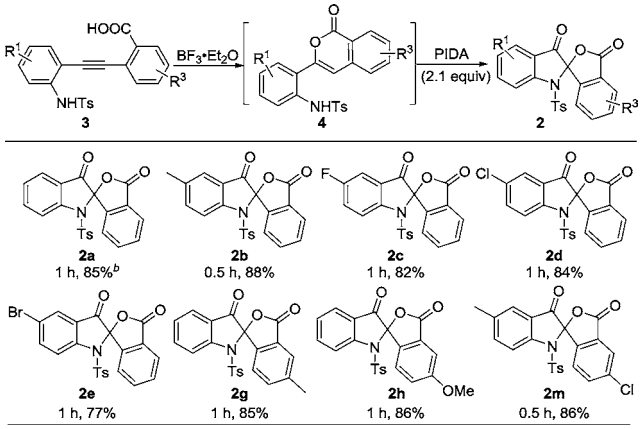


Lewis acid $BF_3{\cdot}Et_2O$, was converted to the ylide intermediate **A**. Tautomerization/aromatization of **A** furnished intermediate **B**, which underwent an intramolecular 1,4-addition reaction to afford the 6-*endo*-*dig* intermediate **4a**. Oxidation of **4a** by PIDA, accompanied by the loss of one acetic acid, gave rise to intermediate **C**. Then intermediate **C** went through intramolecular cyclization to generate precursor **D** after releasing one molecule of iodobenzene and acetate anion. The final product **1a** was generated from intermediate **D** via an acetate anion-promoted deprotonative rearomatization process, with two more additional rings being formed in this cascade reaction.

A completely different product was formed, in good yield, when **4** was treated with 2.1 equiv of PIDA (Scheme 4).

The additional equivalent of PIDA was probably used to convert **1** into **2**, and the higher yield values for **2** (Scheme 4) relative to those for **1** suggested this conversion to be close to completion, since the spiro compounds formed as a byproduct to **1** during the usage of the first equivalent of PIDA were very

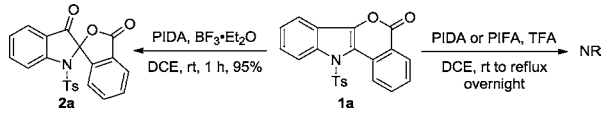
Scheme 4. Oxoaminocarboxylation of Alkynes for the Formation of Spirocycles[a]



[a]All the reactions were carried out with substrates **3** (0.4 mmol) and $BF_3{\cdot}Et_2O$ (1 equiv) in DCE (4 mL) at 80 °C overnight and then with PIDA (2.1 equiv) at rt for 0.5−1 h. All yield values refer to isolated yields.

minor (Table 1). As expected, after being treated with a combination of PIDA and $BF_3{\cdot}Et_2O$, **1a** was converted to the spiro product **2a** in excellent yield (Scheme 5).[14] Further

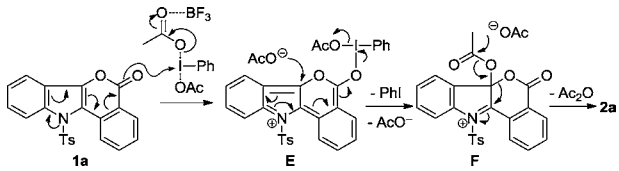
Scheme 5. Conversion of Fused Heterocycle 1a to Spirocycle 2a



investigation revealed that, in the absence of $BF_3{\cdot}Et_2O$, no reaction occurred under the oxidative conditions despite the addition of TFA and further heating. This result revealed that $BF_3{\cdot}Et_2O$-mediated formation of **2a** underwent a pathway different from the direct spirocyclization process as we had observed in our previous work.[9]

Here we put forward a possible mechanism for this novel $BF_3{\cdot}Et_2O$-catalized oxidative spirocyclization reaction, taking **1a** as an example (Scheme 6). First, oxidation of **1a** by $BF_3{\cdot}Et_2O$-activated

Scheme 6. Proposed Mechanistic Pathway for the Conversion of Fused Heterocycle 1a to Spirocycle 2a



PIDA, accompanied by the loss of one acetate anion, gave rise to intermediate **E**. Then, the nucleophilic attack of the acetate anion at the most electrophilic carbon in intermediate **E** afforded intermediate **F** after releasing one iodobenzene and one acetate anion. Promoted by the released acetate anion, ring opening of the lactone moiety occurred in intermediate **F**, followed by a subsequent 1,2-addition of the nucleophilic benzoate to the iminium moiety, providing the spirocyclic product **2a**.[15]

In conclusion, we have discovered new strategies for *trans*-aminocarboxylation and oxoaminocarboxylation of alkynes via an unusual reaction sequence involving $BF_3{\cdot}Et_2O$ catalyzed O-addition of carboxylic acid to an alkyne and subsequent PIDA-mediated oxidative indolization and spirocyclization. This methodology features three unusual events: (1) regioselective catalytic ring closure of internal alkynes to construct the 6-*endo*-*dig* intermediates without the need for a π-Lewis acid; (2) one-pot synthesis of polycyclic products from diarylacetylenes under metal-free conditions; (3) divergent assembly of polycyclic or spiro heterocyclic compounds with the dosage of the hypervalent iodine oxidant. Further studies on the application of the method are in progress 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.5b02611.

Experimental procedure, compound characterization data,and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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(13) The reaction of diarylacetylene **3a** by using 2.0 equiv of Cu(II) or Cu(I) as catalyst resulted in a 5-*exo-dig* compound **6a** which could not be converted to **1a** or **2a** under further oxidative conditions (see the Supporting Information for details).

(14) We also carried out the reaction under anhydrous and anoxybiotic conditions, by applying 4 Å molecular sieves and nitrogen protection. The result indicated that **2a** could be achieved in an excellent 93% yield, which suggested that the carbonyl oxygen was not from the water or the oxygen in air.

(15) A control experiment of the oxidative rearrangement reaction of **1a** in $CDCl_3$ was carried out to capture the acetic anhydride (Ac_2O). The NMR spectra showed that Ac_2O was indeed generated during the reaction. The result is in agreement with the reaction pathway depicted in Scheme 6 (see the Supporting Information for details).

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