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Pd-Catalyzed Branching Cyclizations of Enediyne-Imides toward Furo[2,3-*b*]pyridines

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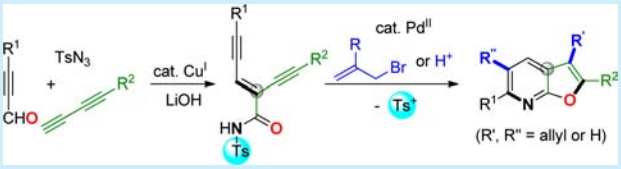
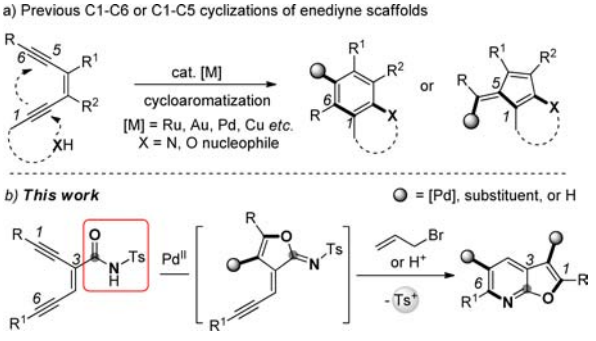
Supporting Information

ABSTRACT: The convergent synthesis of a class of enediyne-imides as well as their palladium-catalyzed branching cyclizations, which can be accomplished in two ways leading to a set of polysubstituted furo[2,3-*b*]pyridines upon using the *N*-tosyl carboxamide moiety as an *N*,*O*-bisnucleophile, are presented.



Since the discovery of natural enediyne antibiotics, the cycloaromatization of (*Z*)-hexa-1,5-diyn-3-enes has attracted tremendous attention and has emerged as a reliable method for the generation of aromatic compounds.[1] In this regard, the thermal and photoinduced benzannulation of enediynes has been studied extensively over the past decades.[2] Remarkably, there have recently been some fascinating examples of transition-metal-catalyzed cascade reactions,[3] which have also been developed for the construction of benzene- and fulvene-fused heterocyclic frameworks from readily available enediyne substrates bearing heteroatom nucleophiles in a substituent attached to the triple bonds via C^1-C^6 or C^1-C^5 ring-closure routes, respectively (Scheme 1a).[4] Inspired by this progress, we speculated that embedding a

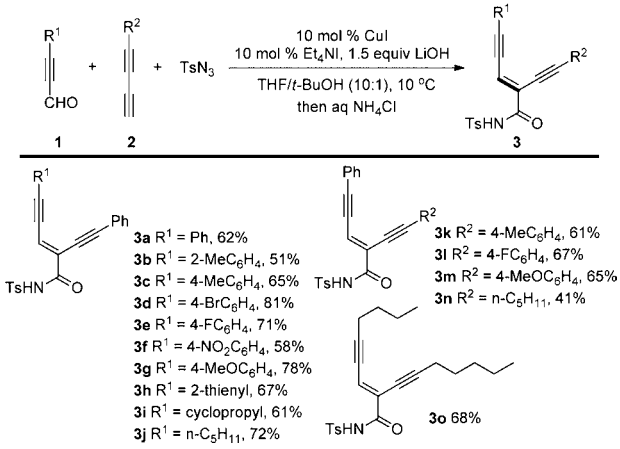
Scheme 1. Annulations of Eneynes Tethered to Heteroatom Nucleophiles



nucleophilic functional group at the double bond of enediynes might result in other cyclization modes of enediyne motifs treated by transition-metal catalysts.[5] Herein we present a convergent synthesis of cross-conjugated[6] enediyne-imides and a study of their sequential palladium-catalyzed cyclization through in situ generated imidate intermediates,[7] which gives rise to a class of polysubstituted furanopyridine with high chemo- and regioselectivity (Scheme 1 b).[8]

We recently developed an approach to conjugated enynes that involved the CuI-catalyzed formal (*E*)-selective olefination of ynals **1** with monoalkynes and sulfonyl azides via *in situ* generated metallo-ynamides.[9] Subsequent studies disclosed that this protocol could afford *N*-tosyl enediyne-carboxamides **3**, which are difficult to synthesize according to known methods,[10] by using diynes **2** as the substrate instead of monoalkynes (Scheme 2). Specifically, exposure of substituted ynals **1** to aryl-

Scheme 2. Convergent Synthesis of Enediynes 3[a]



[a]Yields shown are of isolated products.

or alkyl-substituted diynes **2** and tosyl azide in the presence of CuI (10 mol %) and LiOH (1.5 equiv) in a mixture of THF/*t*BuOH (10:1) at 10 °C provided enediyne-imides **3a**–**o** in 41–81% isolated yields with excellent geometric selectivity at the newly formed double bond (E/Z > 95:5) according to the ^{1}H NMR spectra of the crude reaction products.[11]

The cyclization of **3a** was initially explored in the presence of 3-bromoprop-1-ene (**4a**) and palladium catalysts in air at 60 °C (Table 1). Whereas almost no conversion of **3a** was observed without any catalysts, $Pd(OAc)_2$ (3 mol %) yielded a mixture of

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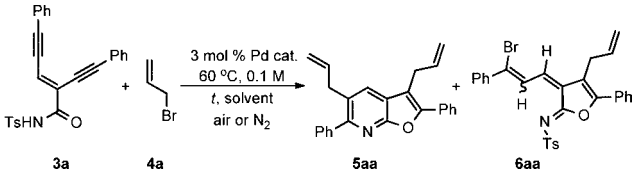
Table 1. Optimization of Reaction Conditions[a]



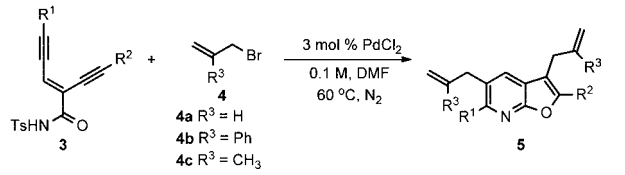
entry	Pd cat.	condition	t (h)	**5aa** (%)[b]	**6aa** (%)[b]
1	none	DMF, air	12	–	–
2	$Pd(OAc)_2$	DMF, air	24	41	8
3	$Pd(acac)_2$	DMF, air	8	71	trace
4	$PdCl_2$	DMF, air	4	76	trace
5	$PdCl_2$	DMA, air	3	73	trace
6	$PdCl_2$	MeCN, air	10	42	28
7	$PdCl_2$	THF, air	21	18	45
8	$PdCl_2$	toluene, air	20	trace	73
9	$Pd(OAc)_2$	toluene, air	21	trace	76
10	$PdCl_2$	DMF, N_2	4	81	trace
11	$Pd(PPh_3)_4$	DMF, N_2	12	–	–

[a]Imide **3a** (0.2 mmol), and Pd catalyst (3 mol %) in solvent (2 mL), then **4a** (2.0 mmol) at 60 °C. [b]Yields of isolated products.

3,5-diallyl-furo[2,3-*b*]pyridine **5aa** (41%) and bromide **6aa** (8%) in DMF after 24 h (entries 1 and 2). After exploring a set of palladium(II) salts, $PdCl_2$ was identified as the optimal catalyst for the synthesis of **5aa** (entries 2−4). In the presence of $PdCl_2$, it was found that solvents significantly influenced the reaction outcomes (entries 4−8). While the tandem reaction proceeded quickly in DMF or DMA to form **5aa** as the predominating product, the conversion of **3a** occurred sluggishly in either MeCN or THF, affording mixtures of **5aa** and **6aa** in varying ratios, respectively (entries 6 and 7). In contrast, switching the solvent to toluene almost only gave the regioselective HBr adduct **6aa** as a mixture of geometric isomers relating to the newly formed bromo-alkene unit (Z/E = 3:1) in 73% combined yield (entry 8).[12] These results indicated that the current reaction initially proceeds via a 5-*endo-dig* oxypalladation/carbodepalladation process to provide an *oxy*-cyclization intermediate, which then undergoes competitive *N*-nucleophilic palladation and HBr addition reactions to furnish furopyridine **5aa** or bromide **6aa**, respectively. The distinct ability of DMF and DMA to accelerate the conversion of **3a** could be partially explained by their Brønsted basicity to trap the eliminated HBr.[13] Dipolar solvents with strong Lewis basicity should facilitate the *N*-nucleophilic palladation of alkyne by prompting the cleavage of the N−S bond between the imidate nitrogen atom and tosyl group to form a nitrogen nucleophilic partner,[14d] although these solvents might simultaneously coordinate with the Pd(II) species and thereby weaken the Lewis acidity of palladium catalysts.[14,15] On the other hand, for the reaction in nonpolar solvents such as toluene, the cleavage of the N−S bond was inhibited, resulting in HBr adduct **6aa** as the major product (entries 8 and 9).[16] Under a nitrogen atmosphere, a cleaner conversion of **3a** was achieved with $PdCl_2$ as the catalyst, whereas $Pd(PPh_3)_4$ was totally ineffective (entries 10 and 11).

Under the optimal conditions (Table 1, entry 10), a set of enediyne-imides **3** participated in the reaction with **4a** smoothly, giving the desired products **5** in good yields (Table 2, entries 1−14). Both alkyl and aryl substituents on the termini of enediyne units were well tolerated. The substitution patterns of aryl moieties had little effect on this reaction, forming **5ba** or

Table 2. Synthesis of 3,5-Diallylfuro[2,3-*b*]pyridine 5[a]



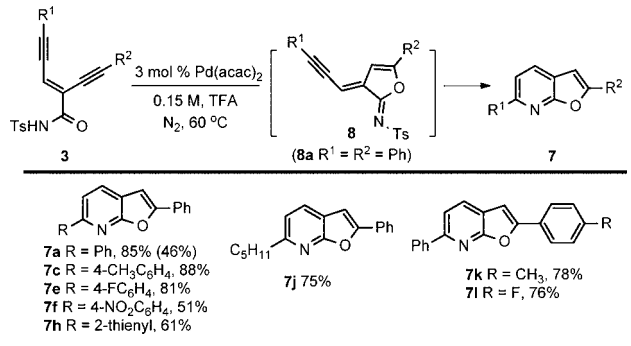
entry	**3**	R^1	R^2	R^3	**5**	(%)[b]
1	**3a**	Ph	Ph	H	**5aa**	81
2	**3b**	2-$CH_3C_6H_4$	Ph	H	**5ba**	81
3	**3c**	4-$CH_3C_6H_4$	Ph	H	**5ca**	76
4	**3d**	4-BrC_6H_4	Ph	H	**5da**	73
5	**3e**	4-FC_6H_4	Ph	H	**5ea**	61
6	**3f**	4-$NO_2C_6H_4$	Ph	H	**5fa**	58
7	**3g**	4-$MeOC_6H_4$	Ph	H	**5ga**	75
8	**3h**	2-thienyl	Ph	H	**5ha**	77
9	**3i**	cyclopropyl	Ph	H	**5ia**	75
10	**3j**	*n*-C_5H_{11}	Ph	H	**5ja**	71
11	**3l**	Ph	4-FC_6H_4	H	**5la**	67
12	**3m**	Ph	4-$MeOC_6H_4$	H	**5ma**	87
13	**3n**	Ph	*n*-C_5H_{11}	H	**5na**	72
14	**3o**	*n*-C_4H_9	*n*-C_5H_{11}	H	**5oa**	83
15	**3a**	Ph	Ph	Ph	**5ab**	61
16	**3a**	Ph	Ph	CH_3	**5ac**	67

[a]Imides **3** (0.2 mmol), $PdCl_2$ (3 mol %), **4** (2.0 mmol), DMF (2 mL), 60 °C, N_2. [b]Yields of isolated products.

5ca from *ortho*- and *para*-substituted arenes in similar yields, respectively (entries 2 and 3). An aryl bromide substrate also produced the targeted **5da** in 73% yield (entry 4), providing the possibility of further manipulation. Nevertheless, the reaction of substrates with an electron-donating substituent on the aromatic ring (entries 7 and 12) proceeded in better yield than those of the electron-withdrawing counterparts (entries 5, 6, and 11). In addition, a thienyl group was tolerated in this reaction (entry 8). On the other hand, 2-substituted propenes **4b** and **4c**, no matter whether they contained aryl or alkyl substituents, underwent the reaction with **3a** smoothly to yield the targeted **5ab** and **5ac** (entries 15 and 16). Unfortunately, cinnamyl bromide could not afford the desired product presumably due to the steric issue encountered in the coupling step.

The palladium-catalyzed branching annulation protocol was further exploited in the absence of allylic bromide **4** for the synthesis of furopyridines **7** (Scheme 3).[17] Under the optimal

Scheme 3. Synthesis of 2,6-Disubstituted Furopyridines 7[a]



[a]Yields shown are of isolated products. Yield in parentheses is obtained in AcOH.

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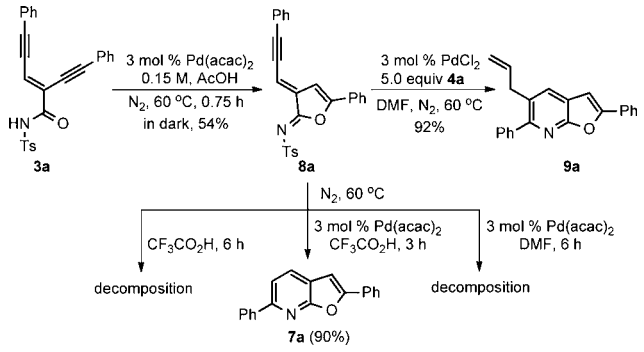
conditions for obtention of **5aa**, only a traceless cyclization product was formed from imide **3a**. Gratifyingly, this reaction proceeded smoothly in acetic acid under N_2 at 60 °C, giving the desired product **7a** in 39% yield after 12 h. When using $Pd(acac)_2$ as the catalyst, it was observed that substrate **3a** quickly converted into furan **8a**, which slowly gave **7a** in 46% yield along with some decomposition compounds. A stronger acid such as TFA instead of AcOH enabled a cleaner conversion of **3a** to **7a** (85%) in the presence of $Pd(acac)_2$ within 3 h. A blank experiment in the absence of palladium catalysts in TFA afforded no products except the recovered **3a** (91%), revealing that the palladium catalyst was necessary for this cascade sequence. Illustrative examples of the reaction scope were also shown in Scheme 3. Accordingly, both aryl- and heteroaryl-substituted substrates as well as alkyl-substituted compounds readily participated in this transformation, forming the corresponding products **7** in 41−88% yield, respectively.

To gain deeper insight into the reaction mechanism, the light-labile (*E*)-alkenyl furan **8a** was successfully isolated in 54% yield by terminating the reaction of **3a** in acetic acid after 0.75 h for subsequent studies (Scheme 4). While the treatment of **8a**

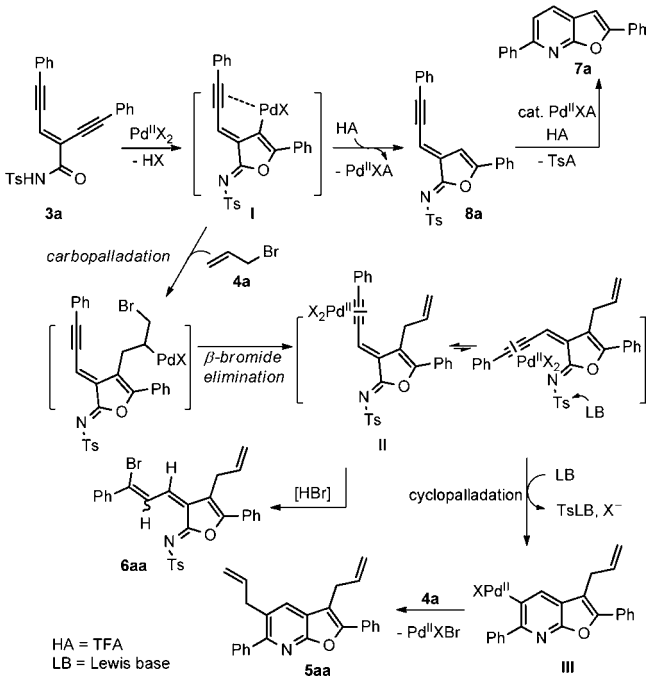
Scheme 4. Two-Step Synthesis of Furo[2,3-*b*]pyridines



with $Pd(acac)_2$ in TFA gave **7a** in 90% yield, **8a** could not convert into **7a** and decomposed completely in the absence of Pd(II) catalysts or an external acid at 60 °C after 6 h. These results suggested that both palladium catalysts and external acids are critical for this annulation reaction, although the mechanism details were not very clear.[18] Moreover, exposure of **8a** to **4a** and $PdCl_2$ in DMF should furnish 2,5,6-substituted furopyridine **9a** in 92% yield, offering a flexible method for the synthesis of a class of substituted furanopyridines.

A possible mechanism for the Pd-catalyzed branching cyclizations of enediyne-imides **3** toward furopyridines is depicted in Scheme 5. Initial coordination of alkyne units of **3a** to the Pd(II) catalyst would induce a *trans*-oxypalladation[19b] *via* a 5-*endo*-dig pathway to generate the vinyl-palladium species **I**, which would be partially stabilized by coordination with the tethered alkyne moiety. In acidic media, protonolysis of **I** furnishes imidate **8a**, which then undergoes cycloisomerization to yield the product **7a** with the elimination of the tosyl groups. On the other hand, the species **I** undergoes a coupling reaction with the allylic bromide **4a** leading to intermediate **II** *via* olefin insertion and *β*-bromide elimination.[19] Subsequent olefin *E*/*Z* isomerization[20] and *N*-nucleophilc cyclopalladation of the intermediate **II**, with the assistance of dipolar Lewis basic solvents to break the N−S bond, gives access to another palladium species **III**. The latter intermediate couples with **4a** to form **5aa**, while releasing the Pd(II) catalyst.

Scheme 5. Proposed Mechanism



In summary, we have presented the single-step construction of cross-conjugated enediyne-imides as well as their palladium-catalyzed branching cyclizations through imidate intermediates. It was found that, upon using the *N*-tosyl carboxamide moiety as an *N*,*O*-bisnucleophile, the cyclization of this type of enediynes could be accomplished in two ways leading to a set of polysubstituted furo[2,3-*b*]pyridines. Additional studies on reaction mechanism details and the synthetic potential of 3-substituted enediyne scaffolds for the creation of facile strategies toward valuable fused ring systems are now in progress.

■ ASSOCIATED CONTENT

Supporting Information

X-ray crystallographic data of **3e**, **5ab**, and (*Z*,*Z*)-**6aa**; experimental procedures and characterization data of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

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Notes

The authors declare no competing financial interest.

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(11) Crystallographic data of **3e** (CCDC 965933), **5ab** (CCDC 965934), and (*Z*,*Z*)-**6aa** (CCDC 973098) are deposited in the Cambridge Crystallographic Data Center and also available in the Supporting Information.

(12) Isolated (*Z*,*Z*)-**6a** can convert to a mixture of (*Z*,*Z*)-**6a** and (*E*,*Z*)-**6a** at 25 °C.

(13) Addition of either an external base or oxiranes results in the *N*-allylation of **3a**.

(14) The *N*-cyclization was proposed to occur upon Pd(II)/Lewis base cocatalysis. For reviews of synergistic catalysis, see: (a) Shao, Z.; Zhang, H. *Chem. Soc. Rev.* **2009**, *38*, 2745. (b) Allen, A. E.; MacMillan, D. W. C. *Chem. Sci.* **2012**, *3*, 633. For a palladium/amine cocatalyzed α-allylic alkylation of aldehydes, see: (c) Ibrahem, I.; Córdova, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 1952. For a supposed procedure of DBU-prompted sulfonyl dissociation, see: (d) Yu, X.; Xin, X.; Wan, B.; Li, X. *J. Org. Chem.* **2013**, *78*, 4895.

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