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Metal-Free Iodine(III)-Promoted Direct Intermolecular C−H Amination Reactions of Acetylenes

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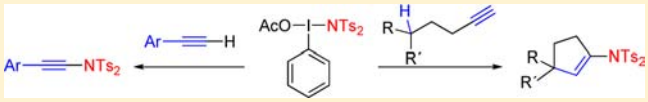
Supporting Information

ABSTRACT: A direct metal-free amination of arylalkynes has been developed, which proceeds by reaction of the terminal alkyne with the hypervalent iodine reagent PhI(OAc)NTs_2 within a single-step operation. This unprecedented intermolecular C−H to C−N bond conversion provides rapid access to the important class of ynamides. In addition to the title reaction, the related transformation between alkylated alkynes and the iodine(III) reagent is also discussed.

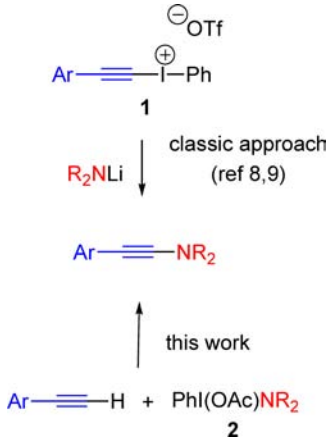


INTRODUCTION

Ynamides represent a unique building block for organic synthesis, and they have recently been referred to as a *modern functional group for the new millennium*.[1,2] Obviously, their synthesis from amides and acetylenes through a direct C−N bond formation is the most appreciable way of preparation. Despite certain efforts, such an approach remains largely unrealized. As to a noteworthy exception, Stahl,[3] Evano,[4] and Jiao[5] reported elegant copper-catalyzed aerobic coupling reactions, and useful protocols using stoichiometric amounts of copper were also reported.[6,7]

A particularly interesting entry to ynamides consists of an approach originally described by Stang,[8] who introduced acetylene−nitrogen bond-forming reactions using preformed acetylenyl iodonium(III) salts **1** (Scheme 1, top).[9,10] The reaction requires addition of a nitrogen nucleophile, usually in its metalated form, which reacts with the triple bond in **1** in a Michael-type addition followed by aryl migration to give the corresponding ynamide product.[9] Although this reaction has received extensive application,[11] it requires the individual preformation of both the metalated amides and the required reagent **1** incorporating the acetylene for posterior amination. As a consequence, construction of the corresponding reagent **1** is required for each acetylene, which may be less convenient, particularly in the cases of accessing a larger series of ynamides.

Scheme 1. Formation of Ynamides: Classic Multistep Approach Involving Preformed Acetylenyliodonium Salts (Top) and New Single Sequence Using Preformed 2 and Free Acetylene (Bottom)



We considered the development of an alternative direct metal-free oxidative Csp−N bond formation using free acetylenes as an economically interesting addition to the above-mentioned protocols. This idea originates from our recent interest in the use of hypervalent iodine(III) reagents[12] for metal-free amination reactions including diamination of alkenes[13] and 1,3-dienes,[14] and allylic amination reactions,[15] respectively. Isolation of a new class of hypervalent iodine(III) reagents[13a] ArI(OAc)$N(SO_2R)_2$, **2**, with a defined iodine−nitrogen bond has set the basis for development of new metal-free amination.[16−19] In an ongoing effort to explore the chemistry of **2**, its direct reaction with terminal alkynes was investigated with the aim to develop a direct metal-free Csp amination.

We here report a simple, rapid, and robust protocol for such a metal-free synthesis of ynamides from acetylenes involving an unprecedented C−H to C−N bond conversion (Scheme 1, bottom).

RESULTS AND DISCUSSION

Our efforts to accomplish such a transformation are summarized in Table 1. An initial approach followed earlier work[13,14] and employed a reagent combination of iodosobenzene diacetate and 2 equiv of bistosylimide for the amination of phenylacetylene **3a** as standard substrate. The desired ynamide **4a** formed but was isolated only in a low yield of 10% (Table 1, entry 1). An excess of an equimolar mixture[15] of the preformed

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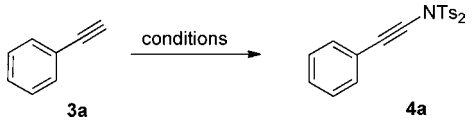
Table 1. Discovery and Optimization of Metal-Free Amination of Phenylacetylene (0.2 mmol scale)



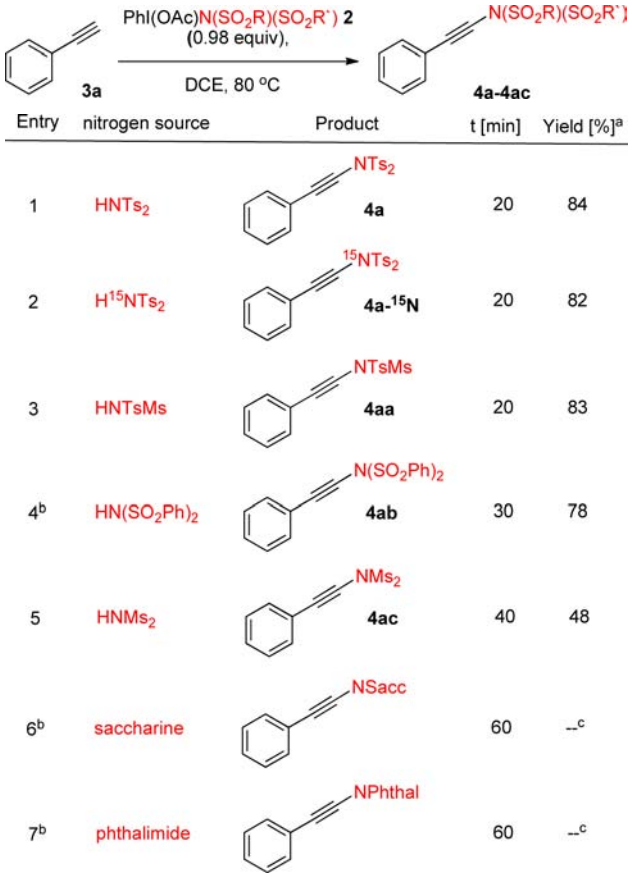
entry	conditions	yield (%)[a]
1	PhI(OAc)$_2$ (1.2 equiv), HNTs$_2$ (2.4 equiv), DCM, 50 °C, 15 h	10
2	PhI(OAc)(NTs$_2$), **2a** (1.4 equiv), HNTs$_2$ (1.5 equiv), DCM, 50 °C, 15 h	16
3	PhI(OAc)(NTs$_2$), **2a** (1.4 equiv), HNTs$_2$, (1.5 equiv), I$_2$ (0.1 equiv), DCM, 50 °C, 15 h	10
4	PhI(OAc)(NTs$_2$), **2a** (1.4 equiv), HNTs$_2$ (1.5 equiv), Bu$_4$NI (0.2 equiv), DCM, 50 °C, 15 h	12
5	PhI(OAc)(NTs$_2$), **2a** (1.4 equiv), HNTs$_2$ (1.5 equiv), Bu$_4$NI (1 equiv), DCM, 50 °C, 15 h	0
6	PhI(OAc)(NTs$_2$), **2a** (1.4 equiv), HNTs$_2$ (1.5 equiv), DCE, 70 °C, 15 h	31
7	PhI(OAc)(NTs$_2$), **2a** (1.4 equiv), HNTs$_2$ (0.1 equiv), DCM, 50 °C, 15 h	32
8	PhI(OAc)(NTs$_2$), **2a** (1.4 equiv), DCE, 80 °C, 15 h	56
9	PhI(OAc)(NTs$_2$), **2a** (0.9 equiv), DCE, 80 °C, 15 h	68
10	PhI(OAc)(NTs$_2$), **2a** (0.8 equiv), DCE, 80 °C, 15 h	61
11	PhI(OAc)(NTs$_2$), **2a** (1.0 equiv), PhCl, 80 °C, 15 h	59
12	PhI(OAc)(NTs$_2$), **2a** (1.0 equiv), DCE, 80 °C, 30 min	61
13	PhI(OAc)(NTs$_2$), **2a** (0.98 equiv), DCE, 80 °C, 20 min	84[b]

[a]Isolated yield after purification. [b]Aqueous workup.

reagent PhI(OAc)NTs$_2$, **2a**, and free bistosylimide led to only a minor increase in yield (entry 2). Addition of iodine or iodide had been successful in recent metal-free alkene diamination reactions;[20] however, it was entirely unsuccessful for the present case (entries 3–5). Changing the solvent from dichloromethane to dichloroethane allowed for working at higher temperature, which increased the yield to 31% (entry 6). A similar result was obtained in the presence of a catalytic amount of free imide (entry 7), while reagent **2a** alone increased the yield to 56% (entry 8). Using reagent **2a** as limiting component further increased the yield (entries 9 and 10). Experiments with other chlorinated solvents such as chlorobenzene had no beneficial consequences (entry 11). The observations from entries 1–10 suggested that an excess of **2a** and/or presence of acids or additives affect the yield of **4a**. Indeed, employing a shorter reaction time of 30 min resulted in an isolated yield of 61% (entry 12). Optimum conditions were obtained for a reaction with 0.98 equiv of **2a** and a short reaction time of 20 min. Upon rapid aqueous quench, the desired product **4a** was obtained analytically pure in 84% yield (entry 13).

The advantage of the present one-step methodology is further demonstrated by its ease of application in the synthesis of labeled products. To this end, reagent **2a** bearing a ^{15}N-labeled bistosylimido group was prepared and upon reaction with **3a** gave the ynamide **4a-^{15}N** in a comparable yield (Table 2, entry 2). This new reaction of ynamide formation is not limited to bistosylimide but proceeds with related nitrogen sources as well. Using alternative bissulfonimides bis-(phenylsulfoyl)imide, mesyltosylimide, and bismesylimide, the corresponding products PhCCN(SO$_2$Ph)$_2$ **4aa**, PhCCNMsTs **4ab**, and PhCCNMs$_2$ **4ac** were obtained in 48–83% yield, respectively (entries 3–5). In contrast, other nitrogen sources such as saccharine and phthalimide did not engage in carbon–

Table 2. Variation of Nitrogen Source in Metal-Free Amination of Phenylacetylene (0.2 mmol scale)



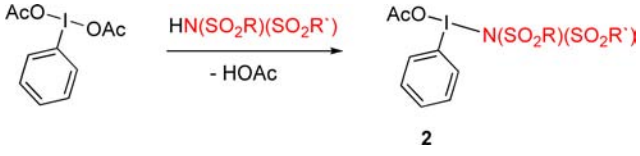
Entry	nitrogen source	Product	t [min]	Yield [%][a]
1	HNTs$_2$	**4a**	20	84
2	H^{15}NTs$_2$	**4a-^{15}N**	20	82
3	HNTsMs	**4aa**	20	83
4[b]	HN(SO$_2$Ph)$_2$	**4ab**	30	78
5	HNMs$_2$	**4ac**	40	48
6[b]	saccharine		60	--[c]
7[b]	phthalimide		60	--[c]

[a]Isolated yield after purification. [b]Without isolation of preformed **2**. [c]No reaction.

nitrogen bond formation under these conditions (entries 6 and 7).

This outcome is readily explained by our earlier observation that formation of reagents **2** is a pK_a-driven process, based on the high acidity of the bissulfonimides (Scheme 2).[13a] It

Scheme 2. Formation of Mixed Iodine(III) Reagents 2



proceeds through irreversible displacement of acetic acid and leads to a compound with an activated I–N bond. In contrast, the combination of iodosobenzene diacetate and saccharine or phthalimide[16] is entirely inefficient for the present transformation. Such a reagent combination would not provide a suitably electrophilic iodine(III) reagent as these two nitrogen sources do not display sufficient acidity.

Under the optimized conditions from Table 1, entry 10, a series of different acetylenes **3** was submitted to provide the corresponding ynamide products **4** in good to excellent yields (Table 3).

All reactions proceed readily within minutes by warming a mixture of **3** and the preformed reagent **2a**. To exemplify the ease of performance, reaction of **3a** was successfully conducted

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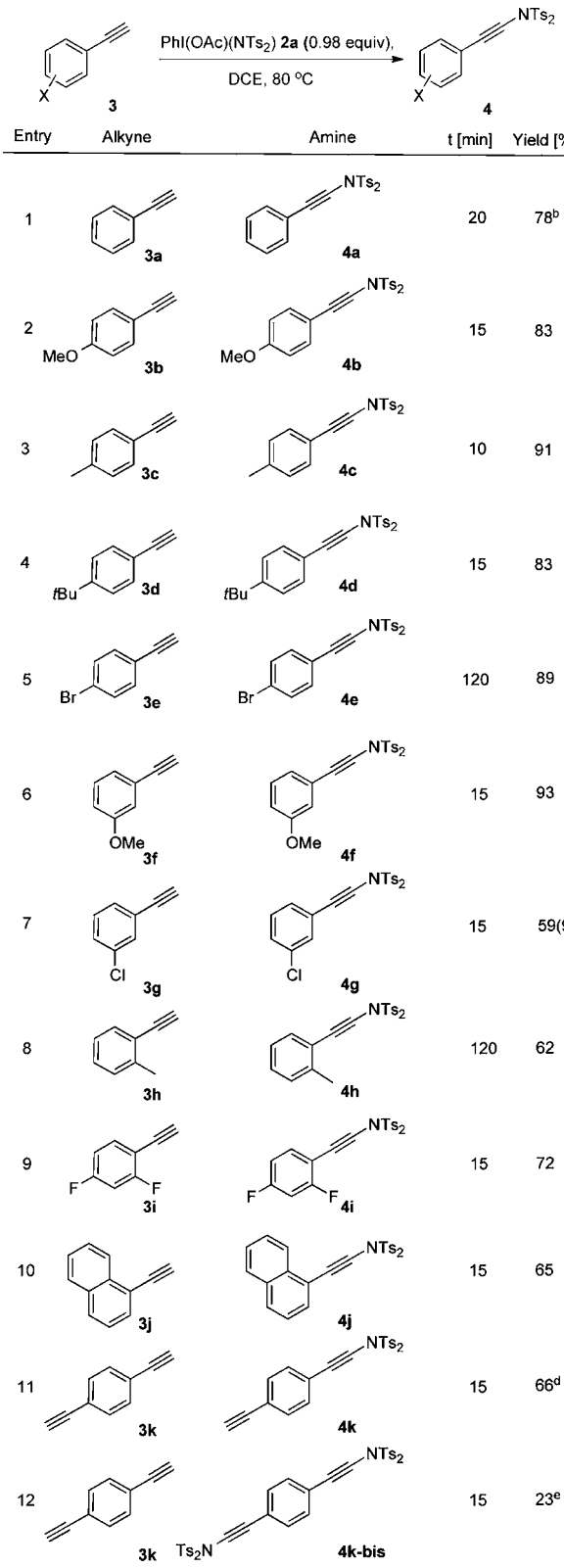
Table 3. Metal-Free Amination of 1-Aryl Acetylenes: Substrate Scope (0.2 mmol scale)



[a]Isolated yield after purification. [b]A 10 mmol reaction. [c]Yield in brackets is based on recovered starting material. [d]Two equivalents of alkyne. [e]Two equivalents of $PhI(OAc)NTs_2$.

on a 10 mmol scale, where the product was obtained from a single crystallization in 78% yield (entry 1). Regarding variation of the arene group, common functional groups and substituents are all tolerated and include para substitution (entries 2–5), meta substitution (entries 6 and 7), and ortho substitution (entry 8). The latter required a longer reaction time, probably due to steric hindrance in the initial step of acetylene functionalization. A 2,4-disubstitution and naphthyl derivative were equally reactive (entries 9 and 10). Finally, the bisacetylene **3k** underwent selective mono- and bisamination, depending on the relative ratio **3k**:**2a** (entries 11 and 12). In all cases, the obtained products **4** are stable compounds, which display high crystallinity due to the bissulfonimide group. Their structures are in agreement with spectroscopic data and for the two products **4a** and **4d** were unambiguously assured from X-ray analysis.[21]

With the development of this new direct Csp–N bond formation, interesting new ynamides are now accessible from reaction between a stable iodine(III) reagent **2a** and standard 1-aryl acetylenes **3**, which represent common bulk materials.[22] It is also the first amination process with reagents **2a** that proceeds readily without additional activation through a second bissulfonylimide.

For the present transformation, we propose a mechanism based on literature precedence that starts from dissociation of reagent **2a** followed by reversible coordination of the electrophilic iodine(III) to the aryl acetylene. The resulting complex **A** further acidifies the alkyne C–H bond, leading to internal deprotonation[23] and loss of acetic acid to form a σ-alkynyl iodine(III) **B** (Figure 1).

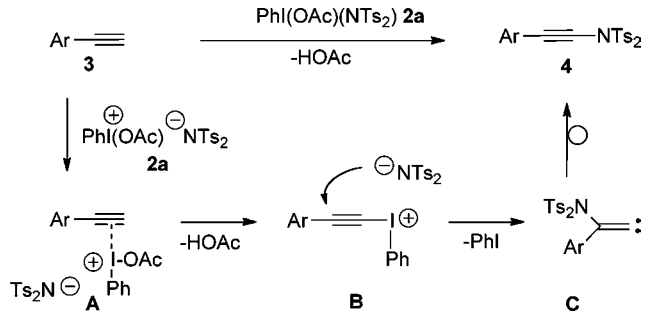
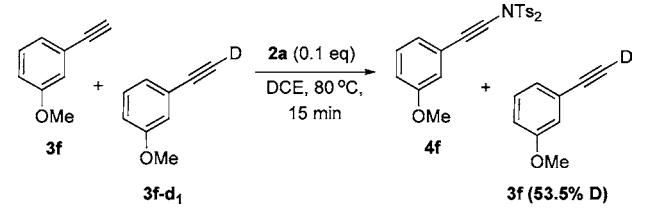


Figure 1. Mechanistic proposal.

A competition experiment for **3f** and its terminally deuterated derivative **3f**-d_1 resulted in an isotope effect k_H/k_D of 4.4, suggesting a rate-limiting carbon–iodine bond formation step (Scheme 3).[21] Interestingly, terminally silylated acetylenes such as $PhCCSiMe_3$ did not undergo the amination reaction. While this is in contrast to their successful role in stoichiometric formation of acetylenyl iodonium(III) salts,[24] direct applicability of terminal acetylenes under our conditions must be considered superior from a synthetic standpoint. Subsequent to formation of **B**, Michael addition[8,9,11] of the free

Scheme 3. Kinetic Isotope Effect in the Amination of 3f



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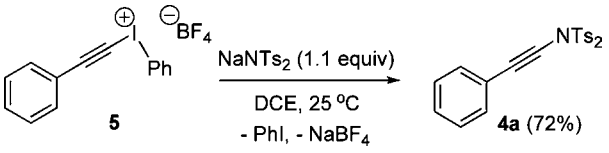
bistosylimide nucleophile forms an alkylidenecarbene **C** upon loss of iodobenzene.[25] Subsequent rearrangement provides the ynamide product **4**. A stoichiometric control experiment between the preformed known σ-alkynyl iodine(III) **5**[26] and bistosylimide gave **4a** in 76% isolated yield (Scheme 4),

Scheme 4. Stoichiometric Control Experiment



indicating the intermediacy of **B**. Interestingly, this reaction could be carried out at room temperature, suggesting that all steps from **B** to **4a** do not require high temperature and thereby verify that C−H cleavage is rate determining.

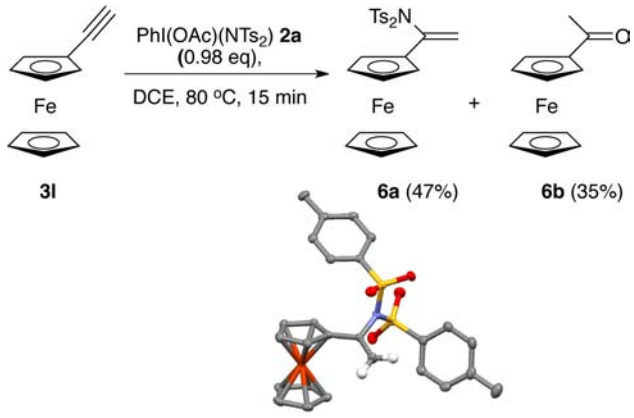
A reaction profile for amination of **3g** to **4g** is in agreement with the described results.[21] Only the terminal acetylene **3g** and ynamide **4g** were detected throughout the reaction, which suggests that states **B** and **C** are rather short-living intermediates.

Electronic influences are negligible in the amination reactions of acetylenes **3a**−**d**. The corresponding competition experiments all show closely related reaction rates resulting in values between 0.95 and 1.05 for k_H/k_X for these arenes with $\sigma_{p\text{-Hammett}}$ values in the range from −0.27 to −0.17. This is different for 4-bromophenyl acetylene **3e** ($\sigma_{p\text{-Hammett}}$ = 0.39), which in competition with **3a** gives a 1:3.8 ratio of **4e**:**4a**. In a more pronounced manner, 4-nitrophenyl acetylene does not engage in ynamide formation at all and is reisolated unchanged after 4 h in the presence of **2a**. These observations suggest the individual reactivity pattern change for electron-withdrawing substituents and that in these cases the importance of an initial interaction between the acetylene in **3** and the reagent **2a** is dominating. This step also underlines the superiority of reagents **2** with a labile iodine−nitrogen bond (Scheme 2), enabling rapid dissociation and alkyne coordination. Release of acetic acid throughout the reaction requires timely workup as products **4** were found unstable in the presence of acid.

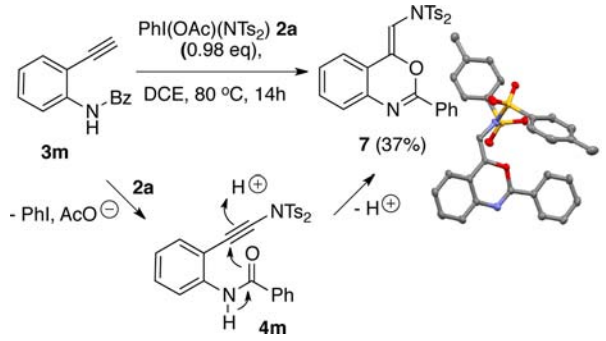
Alkylidene carbene intermediates of type **C** in reactions of alkynyl iodine(III) compounds have also remained elusive due to their high reactivity, but their involvement has been corroborated by analysis of the respective reaction products.[9] In the reaction of ferrocenyl acetylene **3l**, the expected ynamide did not form. Instead, the enimide **6a** could be isolated together with acetylferrocene **6b** (35%), its hydrolysis product. Formation of **6a** should proceed from the corresponding alkylidenecarbene intermediate upon aqueous workup (Scheme 5).

An investigation on *N*-benzoyl 2-acetylenyl aniline **3m** showed low conversion within the initial hour of reaction. This is in accord with the observed reduced reactivity of 2-methyl derivative **3h** from Table 2. Still, upon prolonged reaction time between **3m** and **2a**, formation of a single compound was observed. This was not the expected ynamide but its bicyclic derivative **7** (Scheme 6). We suggest formation of this product to occur through the expected ynamide product **4m**, which in the presence of acetic acid undergoes a subsequent proton-catalyzed 6-exo-dig cyclization to form **7** as a single alkene regioisomer. However, we cannot exclude an alternative pathway, which would proceed through intra-

Scheme 5. Isolation of Ferrocenyl Enimide 6a



Scheme 6. Domino Ynamide Formation/Condensation Reaction



molecular Michael addition by the amide resonance followed by addition of bistosylimide to the resulting vinyl iodonium intermediate. In any case, this example suggests that interesting additional product diversification is possible under the chosen reaction conditions.

Finally, we engaged in a brief evaluation of the amination of aliphatic alkynes. In this series, the corresponding alkylidene carbene intermediate should promote a C−H insertion reaction.[11o−q,27] As expected, treatment of 1-octyne **8a** with **2a** resulted in clean formation of the expected enimide **9a** (Table 4, entry 1), the structure of which was unambiguously confirmed by X-ray analysis.[21] Due to the acid lability of the product, short reaction times are required. However, the high volatility of the starting material resulted in low conversion, which was overcome by an excess of acetylene (entry 2). Substrates **8b**,**c** demonstrated that the carbene insertion reactions proceed equally well for primary and tertiary carbon centers (entries 3 and 4). The bisacetylene **8d** provides mono- or bisamination depending on the amount of iodine(III) reagent (entries 5 and 7), while only monoamination was observed for the longer homologue **8e** (entry 6). These new intermolecular amination/cyclization reactions underline the impressively broad synthetic possibilities in acetylene oxidation with **2a**.

Figure 2 shows the relevant mechanistic context of this cyclopentannelation. The reaction again starts from coordination of the electrophilic iodine(III) to the terminal acetylene (**D**) followed by formation of an acetylenyl iodine complex **E**, which undergoes a Michael addition with bistosylimide. Loss of iodobenzene leads to the alkylidene carbene intermediate **F**, which undergoes position-selective C−H insertion to arrive at

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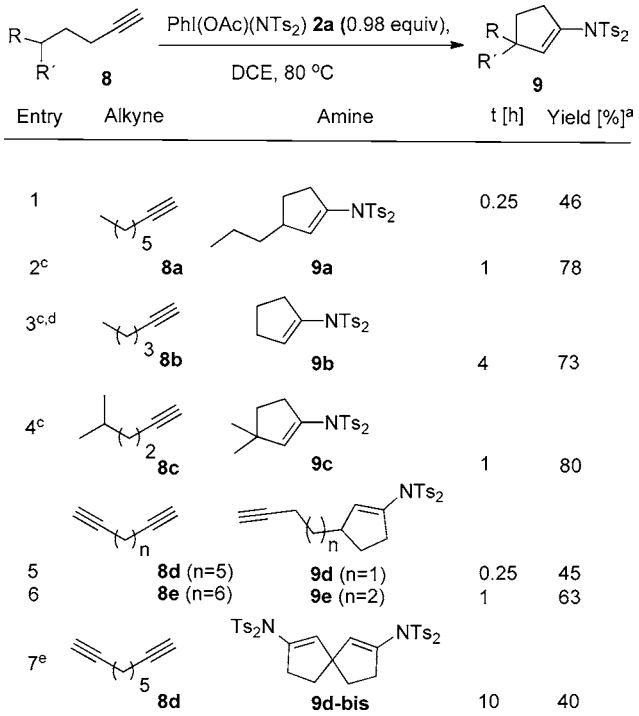
Table 4. Metal-Free Amination of 1-Alkynes: Cyclopentene Formation (0.2 mmol scale)



[a]Isolated yield after purification. [b]At 25 °C. [c]Five equivalents of alkyne. [d]At 50 °C. [e]Two equivalents of PhI(OAc)NTs$_2$ **2a**.

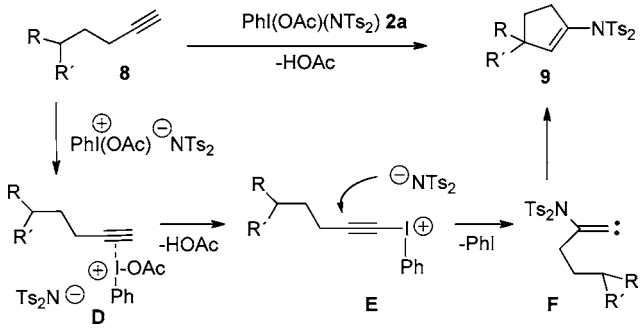


Figure 2. Mechanistic proposal.

product **9**. This mechanistic proposal is in full agreement with an earlier investigation on nucleophilic addition to alkynyl iodinonium reagents followed by intramolecular C−H insertion of an alkylidene carbene intermediate.[9]

Several reactions for nitrogen-based heterocycle formation have been reported in this context.[9] These reactions all require preformation of the acetylenyl iodonium group and proceed through the corresponding intramolecular Michael addition. Although known for carbon- and oxygen-based nucleophiles,[27,28] the present examples of an intermolecular amination/carbene insertion sequence are rare. As to an exception, Stang reported addition of sodium azide to a preformed octynyliodonium reagent to generate the azido derivative of **9a**.[29] Our examples from Table 4 now demonstrate that such reactions can be carried out readily through the use of preformed iodine(III) reagents such as **2a**.

In summary, we described conditions for new metal-free direct amination reactions of acetylenes. These reactions are operationally simple and require defined hypervalent iodine(III) **2a** as the only reagent. They proceed at a high rate, and a range of substituents and functional groups are tolerated. The presented examples demonstrate the broad reaction potential of PhI(OAc)NTs$_2$ with terminal acetylenes, which add to related metal-free reactions of diamination of alkenes[13,14] and benzylic[16b] and allylic[15] amination.

EXPERIMENTAL SECTION

Representative Synthesis of Ynamides: Compound 4a. Phenylacetylene, **3a** (22 μL, 0.204 mmol), was added to a solution of PhI(OAc)(NTs$_2$), **2a** (0.12 g, 0.200 mmol), in DCE (2.0 mL), and the reaction mixture was stirred at 80 °C. After 20 min the solution was quenched by addition of a 10% aqueous solution of sodium thiosulfate. Aqueous phase was extracted with DCM (3×). The combined organic layers were washed with brine (2×) and dried, and solvents were removed under reduced pressure. The title compound was obtained as a white solid.

Mp = 127−129 °C. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 2.50 (s, 6H), 7.3−7.4 (m, 3H), 7.39 (d, J = 7.8 Hz, 4H), 7.4−7.5 (m, 2H), 7.96 (d, J = 8.4 Hz, 4H). ^{13}C NMR (100 MHz, CDCl$_3$): δ = 21.8, 75.6, 77.8, 121.9, 128.3, 128.7, 128.8, 129.8, 132.0, 135.1, 146.0. IR ν(cm^{-1}): 3065, 2923, 1595, 1382, 1365, 1169, 1082, 848, 808, 765, 656, 530. HRMS (ESI-MS): calcd for $C_{22}H_{19}NO_4NaS_2$, 448.0653; found, 448.0654.

Representative Cyclopentene Annulation: Compound 9a. 1-Octyne **8a** (30 μL, 0.204 mmol) was added to a solution of PhI(OAc)(NTs$_2$), **2a** (0.12 g, 0.200 mmol), in DCE (2.0 mL), and the reaction mixture was stirred at 80 °C. After 20 min the solution was quenched by addition of a 10% aqueous solution of sodium thiosulfate. Aqueous phase was extracted with DCM (3×). The combined organic layers were washed with brine (2×) and dried, and solvents were removed under reduced pressure. The crude reaction mixture was purified by column chromatography (silica gel, hexanes/EtOAc, 9:1, v/v), and the title compound was obtained as a white solid.

Mp = 92−94 °C. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 0.88 (t, J = 6.9 Hz, 3H), 1.2−1.4 (m, 4H), 1.5−1.6 (m, 1H), 2.1−2.2 (m, 1H), 2.3−2.4 (m, 2H), 2.44 (s, 6H), 2.6−2.7 (m, 1H), 5.50 (q, J = 1.9 Hz, 1H), 7.32 (d, J = 8.3 Hz, 4H), 7.86 (d, J = 8.3 Hz, 4H). ^{13}C NMR (100 MHz, CDCl$_3$): δ = 14.0, 20.5, 21.6, 28.9, 33.1, 37.3, 43.1, 128.4, 129.4, 135.2, 136.6, 140.8, 144.8. IR ν(cm^{-1}): 3060, 2927, 1596, 1510, 1365, 1340, 1161, 1111, 856, 669, 546. HRMS (ESI-MS): calcd for $C_{22}H_{27}N_2O_6NaS_2$, 456.1279; found, 456.1274.

ASSOCIATED CONTENT

Supporting Information

Complete experimental details and characterization data for new compounds, including CIF files on the X-ray crystallographic analyses of compounds **4a**, **4d**, **6a**, **7**, and **9a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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