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3-Component reactions for accessing heterocycle-rich topologies: trapping of pyrrole-stabilized carbenes *via* net bimolecular C–H or N–H insertion

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The intermolecular trapping of free carbenes derived from diazo precursors is well documented in the literature. We have recently reported the generation of free carbenes derived from 2-alkynyliminoheterocycles, a process that is both 100% atom economical and metal free. Here, we expand the synthetic utility of heteroaryl-stabilized, free carbenes by demonstrating a host of intermolecular third-component trapping reactions. Terminal alkynes, *N*-Boc carbamates, and NH-amides are shown to be suitable third-component traps. Strategic selection of the three reaction partners (*i.e.*, the 2-alkynyliminoheterocycle, the electron-deficient alkyne partner, and the trapping moiety) enables access to product diversity of variable topology and a high degree of heterocycle incorporation.

Introduction

Free carbenes and their metal-bound carbenoid counterparts have enabled synthetic methodology through a diverse display of reactivity, including: cyclopropanation, ylide generation, and X–H/C–H insertion.[1–6] Diazo compounds can produce free carbenes through ejection of molecular nitrogen under thermal[4,5] or photochemical[1–3] conditions (Fig. 1a). Davies and co-workers pioneered the broad application of intermolecular trapping of free carbenes to allow for rapid construction of highly functionalized and complex products.[7,8] However, the intermolecular trapping reactions of heteroaryl-substituted free carbenes are less explored and underutilized.[9]

We recently described the formal (3 + 2) cycloaddition between 2-alkynyliminoheterocycles and electron-deficient alkynes to afford heteroaryl free carbene intermediates (Fig. 1b).[10] In addition to the reactivity displayed by free carbenes **C** in the initial report (including, but not limited to, C–H insertion, (3,2)-sigmatropic rearrangement, 1,3-dipole formation, and carbene metathesis), we have demonstrated the ability to access complex polycyclic cyclopropanes *via* intramolecular capture of the carbene by tethered alkenes.[11] In exploring the reactivity of various electron-deficient alkynes, we observed an unexpected product **3** (34%) when reacting the allyl ether **1** with the terminal conjugated 1-yne-3-one derivative **2** (Fig. 1c).

This unexpected product had incorporated two equivalents of ynone **2**, one that produced the carbene intermediate **D** and a second that had become incorporated through a formal C–H insertion event of the carbenic carbon atom into the terminal

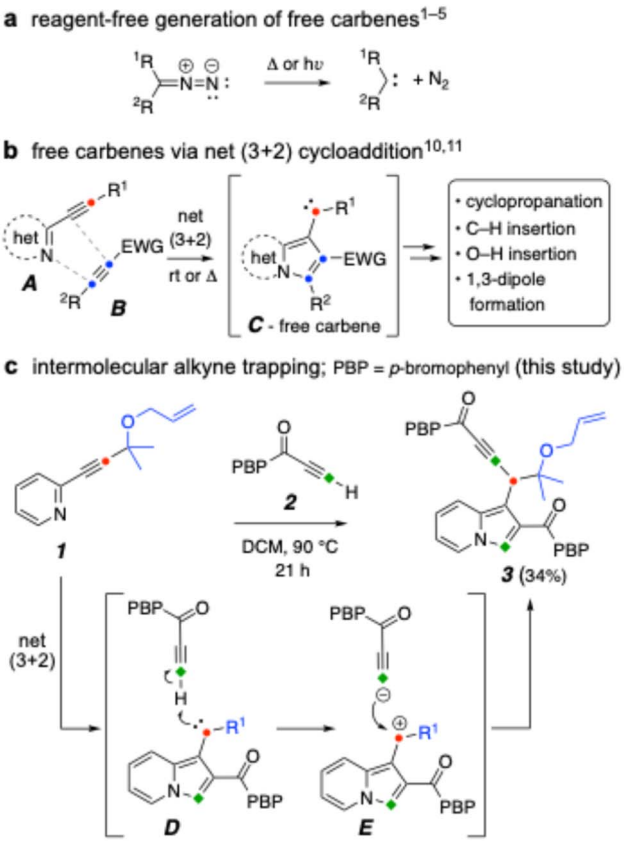

Fig. 1 (a) Diazo compounds as free carbene precursor, (b) (3 + 2) cycloaddition of 2-alkynyliminoheterocycles **A** with electron-deficient alkynes **B** to produce a free carbene **C**, and (c) unexpected intermolecular trapping of free carbene **D** with terminal alkyne **2**.

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alkyne C–H bond of **2**. This can be rationalized *via* a deprotonation–ion pair collapse (see intermediates **D** to **E**, Fig. 1c), a process precedented by work of Koenigs and coworkers for the capture of a different class of free carbene by a terminal alkyne.[12] The formation of **3** led us to initiate a study of additional examples in which various types of a third component might efficiently trap heteroaryl-substituted carbenes. We report here on the results of these investigations of three-component reactions, which provide structurally novel heterocyclic products in a single operation.

Results and discussion

Additional examples of these three-component reactions involving trapping by a terminal alkyne are shown in Fig. 2. Product **3** (*cf.* Fig. 1c) had incorporated two equivalents of the ynone **2**, one functioning as the electrophilic alkyne (*cf.* **B**) and the second to trap the carbene **D**. Another example of this is seen in products **7a**/**b** in which two copies of methyl propiolate (**5a**), another electrophilic terminal alkyne, have been engaged. We recognized that the versatility of this three-component process would be increased if three different molecules could be integrated into the products. We set out to achieve this outcome by using two different types of alkynes, one to function as the electrophilic moiety to drive carbene formation and the second, a terminal alkyne, to capture the carbene.

In the presence of dimethyl acetylenedicarboxylate (**5b**, DMAD), the alkynylpyridine **4a**, and 1-ethynyl-4-(trifluoromethyl)benzene (**6a**), could be transformed to the corresponding trapped product **7c** (43%). Many of the subsequent experiments utilized DMAD as the electron-deficient alkyne because DMAD, unlike electron-deficient terminal alkynes, is, of course, unable to participate in C–H insertion chemistry. Formation of the 1-methoxycyclohexane derivative **7d** (42%) shows that a bulky quaternized alkyl substituent on the terminus of the alkynylpyridine is tolerated. Phenylacetylene (**6b**) trapped the carbene to form **7e**. However, this required the use of a large excess of **6b** (1 : 1 cosolvent) to achieve the yield of 57%, implying that this least acidic of the terminal alkynes **6a–e** is relatively slow at engaging the electron-rich carbene. 3-Ethynylpyridine (**6c**) was sufficiently electron-poor to participate as the trapping component to generate **7f** (41%). The highest yielding alkyne trap was *N*-methyl-*N*-phenylpropiolamide (**6d**), leading to the amide derivative **7g** (84%). We varied the loading of **6d** from 1.2 to 5.0 equivalents and observed increased yields at higher loadings of the terminal alkyne (1.2 equiv.; 62%, 1.75 equiv.; 73%, and 5.0 equiv.; 84%).

We were also interested in whether a propiolate derivative trap would compete with the more electrophilic DMAD to produce the carbene. Using the indole-containing propiolate derivative **6e** (along with the azetidinylated alkyne **4d**), we observed the formation of **7h** in 61% yield. It is notable that the methine hydrogen atom at C3 of the azetidine (vicinal to the carbene) did not interfere by way of a 1,2-insertion event into the initially propargylic C–H bond, a process that earlier was shown to be efficient (*i.e.*, fast) for carbenes containing simple alkyl substituents.[10] The ring strain associated with the formation of an *exo*-alkylidene azetidine likely reduces the rate of this intramolecular process. Notice that a similar factor was relevant to the compatibility of the cyclopropane ring during the formation of **7b** described earlier.

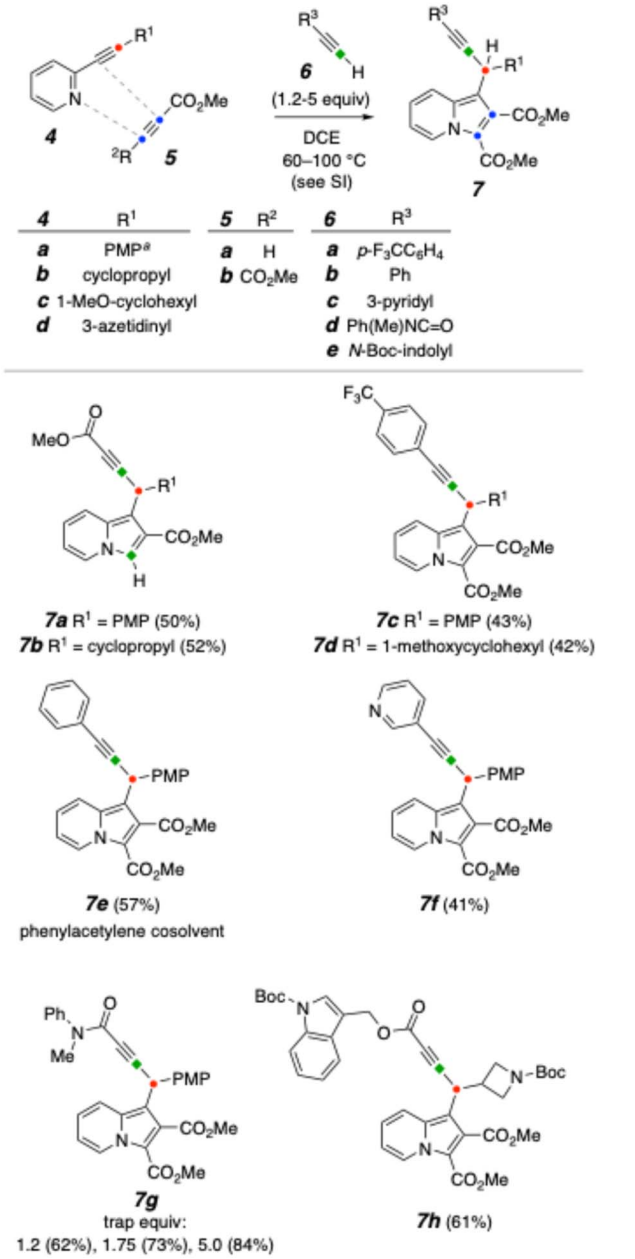

Fig. 2 Third-component trapping of free carbenes derived from alkynylpyridines **4a–d** with terminal alkynes **6a–e**. [a]*p*-Methoxyphenyl.

In exploring a broader scope of functional groups that would serve as the carbene trapping agent (*i.e.*, the third component), we found that *N*-Boc-carbamates were effective. This discovery greatly expanded the opportunities and utility of this methodology, given the large pool of valuable and commercially available amine-containing coupling partners. The results of carbamate trapping are shown in Fig. 3; DMAD was held

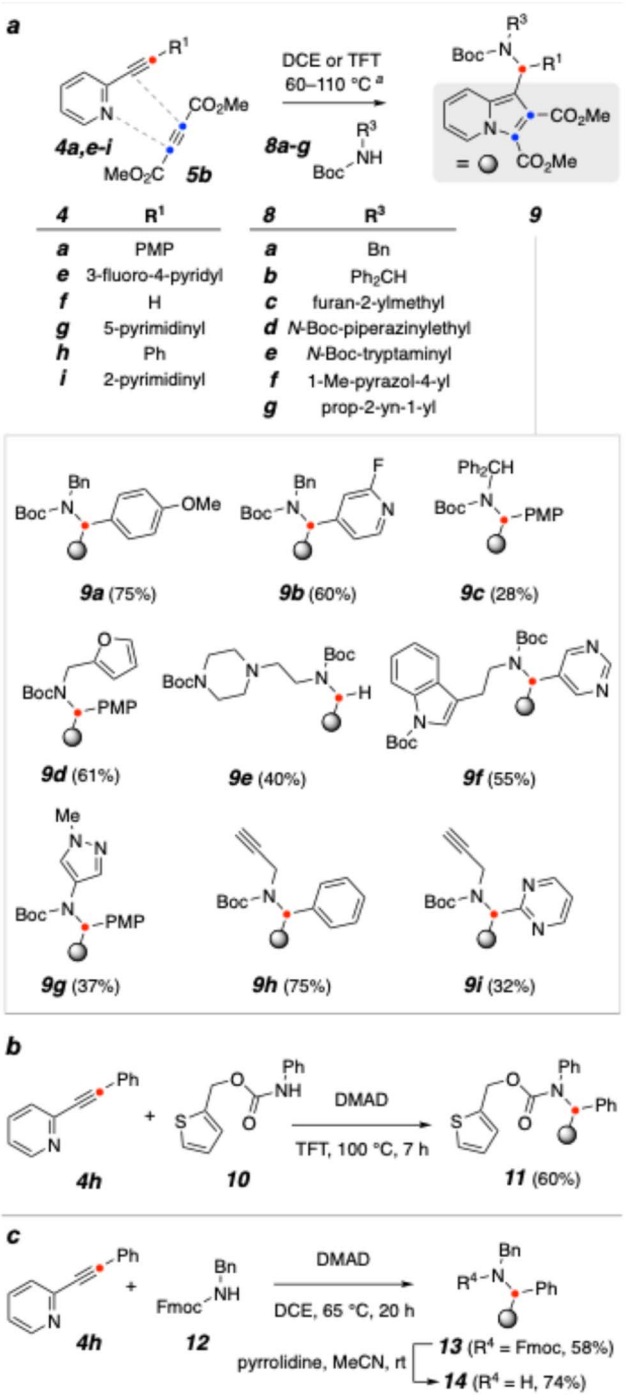

Fig. 3 Third-component trapping by (a) *N*-Boc-carbamates (**8a–g**), (b) thiophen-2-ylmethyl phenylcarbamate (**10**), and (c) *N*-Fmoc-benzylamine (**12**). [a]see SI for reaction temperatures.

constant as the electrophilic alkyne partner. *N*-Boc-benzylamine (**8a**) trapped the carbene to provide **9a** (75%). Use of a 3-fluoro-4-pyridyl substrate **4e** led to **9b** (60%). The trapping with *N*-Boc-diphenylmethanamine (**8b**) to give **9c** proceeded with lower efficiency (28%), showing that the steric bulk of the BocNH compound can be a limitation. An array of heterocycle-containing traps is tolerated: *N*-Boc-furfurylamine (**8c**) gave **9d** (61%); the piperazine derivative **8d** gave **9e** (40%); the indole derivative **8e** gave **9f** (55%); and the amino pyrazole derivative **8f** gave **9g** (37%). In principle, *N*-Boc-propargylamine (**8g**) could have inserted at either the N–H or terminal alkyne C–H bond. We only observed products of NH trapping: namely, **9h** (75%) and **9i** (32%), the formation of which is perhaps a function of the relative acidity of the two potential sites of reaction.

We sought to further capitalize on the carbamate substitution as a handle to append heterocycle functionality. Accordingly, the thiophen-2-ylmethyl carbamate **10** was found to trap efficiently, leading to adduct **11** (60%, Fig. 3b). Attempts to deprotect several of the *N*-Boc-carbamate products described in Fig. 3a under typical conditions (TFA/chloroform, rt) showed surprisingly complex behavior. This prompted us to examine the Fmoc-carbamate **12**, which gave **13** (58%, Fig. 3c). In contrast to Boc-removal attempts under acidic conditions, this product could be smoothly deprotected to the secondary amine **14** when exposed to pyrrolidine in acetonitrile.

We also found that amide and urea derivatives behaved well in the three-component reaction (Fig. 4). The secondary amide, *N*-methylbenzamide, was a particularly effective trap leading to the tertiary amide **15** (86%). The structure of **15** was validated by X-ray diffraction analysis (see p. S83, SI). The primary acetamide also participated to give **16** (54%). A dibenzoazepine-5-carboxamide derivative established that a urea would engage the carbene, here to produce **17** (62%).

Iminoheterocycles other than pyridine have been shown to be effective carbene precursors.[10] Here we used *N*-Boc-carbamates as the third component to establish the effectiveness of several different alkynyl-substituted heterocycles in this three-component approach (Fig. 5). The 2-alkynylthiazole **18** was trapped with *N*-Boc-benzylamine (**8a**), *N*-Boc-aniline (**8h**), and the *N*-Boc-valine derivative **8i** to give **19** (76%), **20** (70%), and **21** (55%), respectively. The valine adduct **21** was formed as a 1.1 : 1.0 mixture of coeluting diastereomers, suggesting that it is unlikely that a high degree of stereoselectivity could be found in these NH insertion reactions. In comparison to its pyridine analogue **4a**, the thiazole substrate **18** requires higher

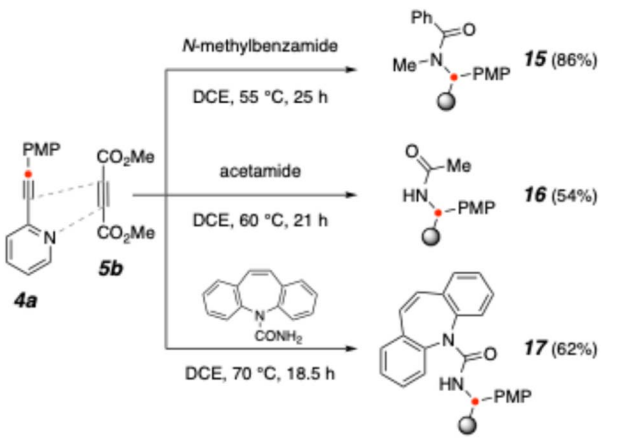

Fig. 4 Amides and a urea trapping of the carbene produced from the alkynylpyridine **4a** and DMAD (**5b**).

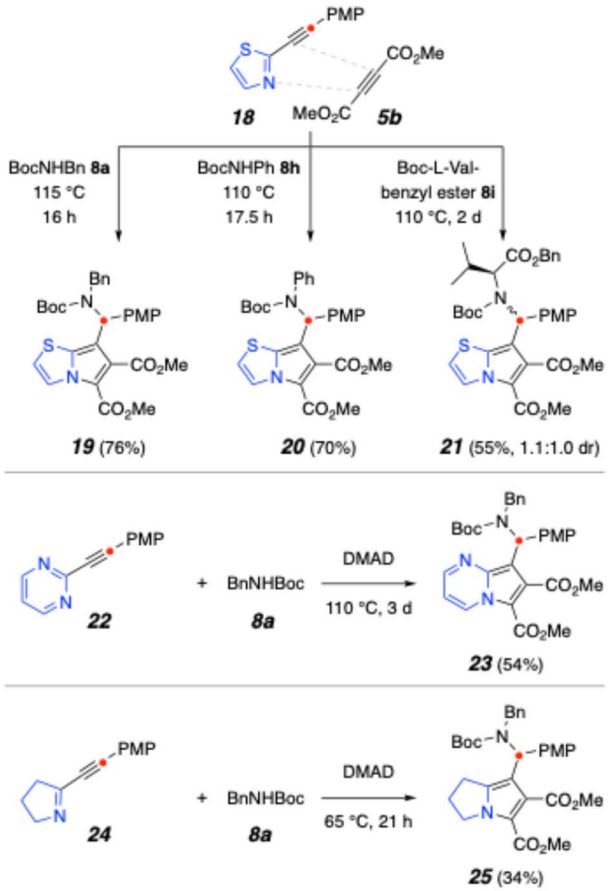

Fig. 5 Alkynyliminoheterocycles other than pyridine (thiazole **18**, pyrimidine **22**, and dihydropyrrole **24**) can also participate in the three-component coupling.

temperatures to achieve full conversion. The pyrimidine substrate **22** was even slower to react, although it still afforded the product **23** in respectable yield (54%). Lastly, we studied a non-aromatic iminoheterocycle, the dihydropyrrole derivative **24**. Although this substrate generated the carbene more quickly, it proved to be less efficient in producing the three-component trapped product **25** (34%).

We surveyed several other (modestly acidic) carbon species to explore whether we could identify any additional C–H insertion events analogous to the alkynylations described in Fig. 2. Somewhat surprisingly, we were unsuccessful in attempts to use any of cyclopentane-1,3-dione, dimethyl malonate, malononitrile, or HCN to achieve this outcome. An exception was the use of chloroform, a reactant that has been studied in some detail for its ability to engage N-heterocyclic carbenes (NHCs) through net C–H insertion.[13,14] Indeed the chloroform adduct **26** was isolated in 74% yield when **4a** and **5b** were heated in $CHCl_3$ at 100 °C (Fig. 6). The structure of **26** was validated by X-ray diffraction analysis (see p. S83, SI). When this reaction was performed in a 14 : 1 volume ratio of $CDCl_3$: $CHCl_3$, the isotopomers **26** and **27** were formed in a 54 : 46 ratio, indicative of a substantial isotope effect ($k_H/k_D \approx 16$) in cleavage of the C–H bond in the product-determining step. This, however, does not

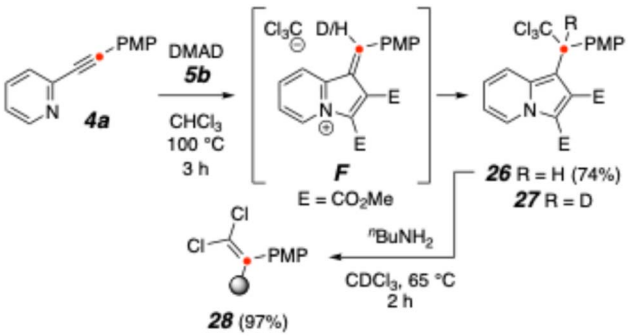

Fig. 6 Formal carbene insertion into the C–H bond of $CHCl_3$.

differentiate between a concerted or stepwise (*via* the ion pair **F**) process for interception of the free carbene. A reported DFT analysis[14] of this mechanistic dichotomy for the reaction of NHCs with chloroform[13] favored a stepwise, ion pair pathway. Interestingly, treatment of the chloroform adduct **26** with

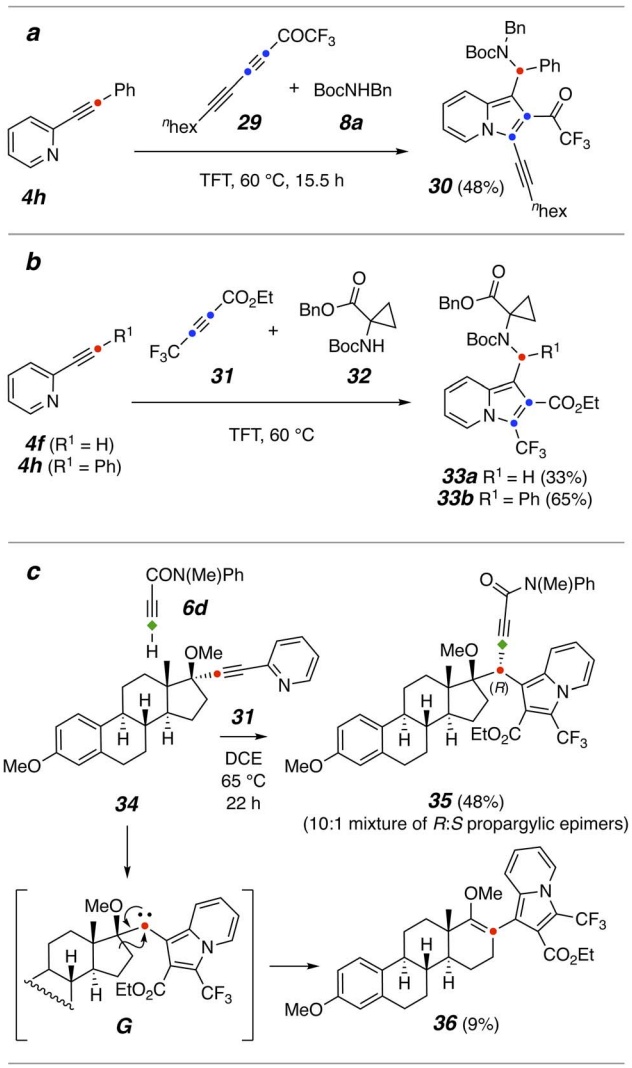

Fig. 7 Electron-deficient alkyne partners other than DMAD participate in three-component coupling reactions.

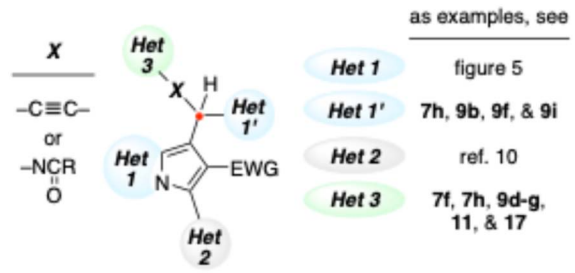

Fig. 8 Topologies of heterocycle-bearing, pyrrole derivatives accessible by reactions of pyrrole-stabilized free carbenes with third-component traps. Heterocycles can be integrated into the products at the positions designated as Het1/Het1′ (from the alkynyliminoheterocycle), Het2 (from the electron-deficient alkyne), and Het3 (from the carbene trapping agent).

^{n}BuNH$_2$ resulted in clean formation of the dichloroalkene **28** (97%) *via* E2-elimination.

Several additional examples that show further diversity in the types of products that can be accessed using this three-component assembly are presented in Fig. 7. Electron-deficient alkyne partners other than DMAD can be used. The trifluoromethyl diynyl ketone **29** reacted with the alkynylpyridine **4h** and *N*-Boc-benzylamine (**8a**) to afford the alkyne-substituted indolizine **30** (48%) as a single regioisomer (Fig. 7a). Each of the alkynylpyridine derivatives **4f** and **4h** engaged trifluorobutynoate **31** and the *N*-Boc-cyclopropylamine **32** as the second and third components to produce the trifluoromethyl substituted indolizine **33a** (33%) and **33b** (65%), respectively (Fig. 7b). Comparison of the outcome of 2-ethynylpyridine (**4f**) *vs.* that of its phenyl-substituted analogue **4h** reveals that the terminal alkyne substrate is, overall, a less efficient participant in the three-component reaction (*cf.* also the marginal yield of product **9e**, Fig. 3).

Finally, we probed whether the three-component reaction could be applied in the context of an even more complex molecular setting. We prepared the estradiol derivative **34**, to which a requisite alkynyliminoheterocycle functionality is appended (Fig. 7c). When heated in the presence of the trifluorobutynoate **31** and *N*-methyl-*N*-phenylpropiolamide (**6d**), the (steroidylalkynyl)pyridine **34** was converted into the indolizine derivative **35** (48%) as a 10 : 1 coeluting mixture of epimers at the newly created (propargylic) stereogenic center (a DP4+ NMR analysis[15] suggested that the major epimer has the *R* configuration; see SI, Section III). The level of diastereoselectivity (relative asymmetric induction) in this transformation is notable, as is the formation of a small amount of the cyclic enol ether **36** (9%), presumably arising from the ring-expansion/rearrangement indicated in species **G**.[16]

Conclusions

In conclusion, we have demonstrated that free carbenes generated by the formal (3 + 2) cycloaddition between 2-alkynyliminoheterocycles and electron-deficient alkynes can trap a variety of third components. Secondary *N*-Boc carbamates, amides, and ureas as well as acidic terminal alkynes are functionalities capable of efficiently participating in the third-component trapping event. Notably, the pK_a's of the CH or NH are similar across this series of effective third components, suggestive of a stepwise process to account for the net C–H/N–H insertion event.

Each of the three reaction partners – the alkynyliminoheterocycle, the electron-deficient alkyne, and the carbene trapping agent – can be varied, demonstrating the potential for formation of a diverse collection of poly-heteroaromatic products. The generic structure in Fig. 8 shows the topologies of pyrrole-templated compounds that can be accessed and summarizes the locations in the product at which heterocyclic moieties can be installed.

Author contributions

Conceptualization: ALG; methodology and data curation: ALG, KBT; data interpretation, writing – original draft of manuscript and reviewing/editing final version: all authors; funding acquisition: TRH.

Conflicts of interest

There are no conflicts to declare.

Data availability

The NMR raw data can be accessed at: **https://doi.org/10.6084/m9.figshare.29321516**.

CCDC 2492945 and 2492946 contain the supplementary crystallographic data for this paper.[17a,b]

Supplementary information: experimental procedures used to prepare each new chemical entity (NCE); line listings of spectroscopic characterization data for each NCE; copies of all ^{1}H and ^{13}C 1D NMR spectra and selected sets of 2D NMR data; .zip file of Gaussian .out files of the conformers used in the DP4+ analysis of **35**. See DOI: **https://doi.org/10.1039/d5sc05345e**.

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17 (*a*) CCDC 2492945: Experimental Crystal Structure Determination, 2025, DOI: **10.5517/ccdc.csd.cc2pp3l3**; (*b*) CCDC 2492946: Experimental Crystal Structure Determination, 2025, DOI: **10.5517/ccdc.csd.cc2pp3m4**.