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An Atom-Economic Synthesis of Nitrogen Heterocycles from Alkynes

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Supporting Information

ABSTRACT: A robust route to 2,4-disubstituted pyrrole heterocycles relying upon a cascade reaction is reported. The reaction benefits from operational simplicity: it is air and moisture tolerant and is performed at ambient temperature. Control over the reaction conditions provides ready access to isopyrroles, 2,3,4-trisubstituted pyrroles, and 3-substituted pyrollidin-2-ones.

The finite nature of chemical feedstocks coupled with the negative impacts of manufacturing waste streams necessitates the continued development of increasingly efficient processes for the preparation of valuable synthetic building blocks.[1] In this regard, our group has demonstrated that simple addition reactions between differentially substituted alkynes can be interfaced with subsequent isomerizations to generate functional molecules while upholding high levels of atom-economy.[2] These one-pot reactions benefit from the ability to conduct multiple chemical transformations in a single reaction vessel, providing their intended target while minimizing waste associated with traditional isolation and purification protocols.[3]

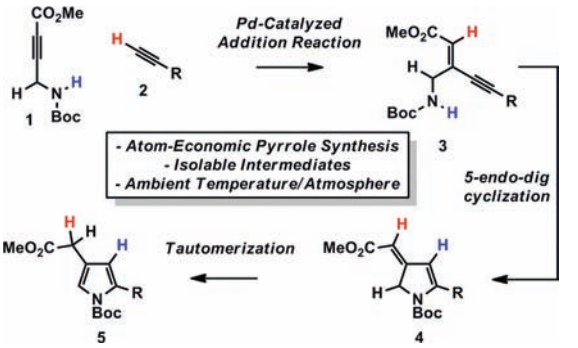
We envisioned that such a strategy could be applied to the efficient production of valuable pyrrole heterocycles from alkyne starting materials (Scheme 1).[4] The addition of terminal alkyne **2** to suitably activated propargyl amine **1** under alkyne cross-coupling conditions[5] would result in ynenoate **3**, whose isomerization via a 5-*endo-dig* cyclization and tautomerization would then provide pyrrole **5** (Scheme 1).[6]

While this sequence represents an efficient, isohypsic[7] entry into 2,4-disubstituted pyrroles,[8] we anticipated that intermediates **3** and **4** could serve as strategic points of product diversification if suitable conditions could be found for their selective preparation.[9] In this regard, we viewed the design of a flexible route to topologically varied five-membered nitrogen heterocycles as an intriguing challenge for atom-economic reaction design.[10]

We anticipated that electron-deficient propargyl amine **1**[11] would serve as a suitable acceptor in an alkyne cross-coupling reaction. It should be noted that propargyl amides similar to **1** are prone to 5-*endo-dig* cyclization, affording the corresponding oxazole heterocycle.[12] In this regard, the current method provides a novel avenue of reactivity for these versatile building blocks, while avoiding such an isomerization process.

Initial investigations employing phenyl acetylene (**2a**) as the donor alkyne with toluene as the solvent[13] revealed that product distributions depend on the ratio of $Pd(OAc)_2$ to the tris-(2,6-dimethoxyphenyl)phosphine (TDMPP) ligand (Table 1).[14] Accordingly, an equimolar amount of ligand and metal cleanly afforded ynenoate **3a** as a single geometrical isomer (entry 1),

Scheme 1. Pyrroles from Alkynes



whereas decreasing the amount of TDMPP resulted in competitive formation of isopyrrole **4a** (entries 2 and 3). Importantly, pyrrole formation was not observed under the reaction conditions, and increasing either the reaction time or temperature resulted in complex mixtures and poor mass recovery.

While both free and phosphine-ligated $Pd(OAc)_2$ were ineffective at promoting isomerization to the pyrrole product, we quickly found that $Pd(OTFA)_2$ resulted in clean formation of pyrrole **5k** from ynenoate **3k** (Table 2).[2b] In this case, both acetonitrile and benzonitrile complexes of $PdCl_2$ (entries 4 and 5) were not as effective as $Pd(OTFA)_2$, which promoted the desired cyclization and tautomerization in near quantitative yield. Once again, TDMPP was found to inhibit both of these transformations (compare entries 1 and 3), suggesting that a nonphosphine-ligated Pd species is responsible for catalysis.[15]

The results presented in Tables 1 and 2 led us to adopt a set of optimized conditions for the one-pot synthesis of either pyrrole or enyne products (Table 3). Thus, treatment of **1** with a variety of aromatic alkynes in the presence of $Pd(OAc)_2$ (0.75 mol %) and TDMPP (0.75 mol %) in PhMe at room temperature afforded the corresponding ynenoate **3** in 77−97% isolated yields after 6 h. Nonaromatic donor alkynes generally required slightly longer reaction times (12−24 h), and provided ynenoates **3** in 64−97% isolated yield.

Alternatively, pyrroles can be obtained in yields ranging from 60 to 99% in a two-stage, one-pot process. For aromatic donors, addition of $Pd(OTFA)_2$ (1.5 mol %) following complete conversion to the ynenoate resulted in the cyclized/isomerized product after only 6 h. Once again, nonaromatic donors require slightly longer reaction times and higher catalyst loadings (5.0 mol % $Pd(OTFA)_2$) but nevertheless returned good to excellent yields of the desired

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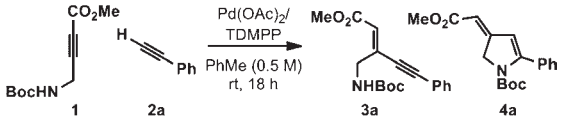
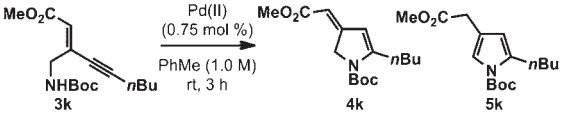
Table 1. Optimization of Selective Ynenoate Formation[a]



entry	$Pd(OAc)_2$ (mol %)	TDMPP (mol %)	ratio (**3a**/**4a**)[b]	conversion[b] (%)
1	3.0	3.0	20/1	100
2	3.0	1.5	3/2	100
3	3.0	0.8	1/5	100

[a] All reactions were performed using 0.1 mmol of **1** and **2a**. [b] Determined by ^{1}H NMR.

Table 2. Optimization of Pyrrole Formation[a]



entry	Pd(II)source	TDMPP (mol %)	ratio (**4k**/**5k**)[b]	conversion[b] (%)
1	$Pd(OTFA)_2$	–	1/20	100
2	$Pd(OTFA)_2$	0.4	1/20	95
3	$Pd(OTFA)_2$	0.8	1/2	72
4	$PdCl_2(CH_3CN)_2$	–	1/1	47
5	$PdCl_2(PhCN)_2$	–	1/20	52

[a] All reactions performed with 0.1 mmol of **3k**. [b] Determined by ^{1}H NMR.

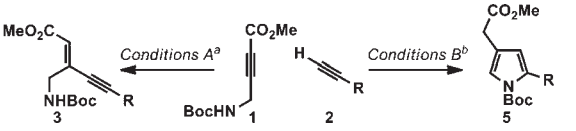
products after 24 h. Importantly, these reactions are performed in screw-cap vials under an ambient atmosphere, with commercial grade alkynes and benchtop solvents. Furthermore, yields remain consistent upon scale-up, as both entries 1 and 11 have been performed on half-gram and gram scales, respectively.

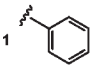
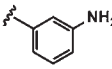
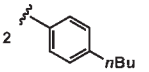
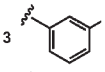
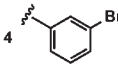
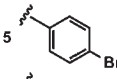
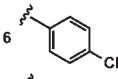
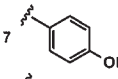
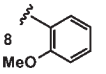
As evidenced by the breadth of substrates in Table 3, this method tolerates a wide range of substituted donor alkynes. Ortho-, meta-, and para-substituted aromatic alkynes with both electron-donating and -withdrawing groups participate effectively (entries 7−9 and entries 3 and 6, respectively). Given the involvement of Pd(II) species throughout both the coupling and the isomerization steps, aryl bromides do not interfere with the reaction (entries 4 and 5). The basic nitrogen of an unprotected aniline is also tolerated in the coupling portion of the cascade (entry 9); however, cyclization to the pyrrole requires more rigorous conditions, starting from ynenoate **3i**.

In addition to aromatic donors, aliphatic alkynes undergo efficient coupling and isomerization. Importantly, both free and acetylated propargyl alcohols react smoothly under the standard conditions (entries 13−15). We note the use of a 1,3-enyne as a donor (entry 10) which provides an efficient synthesis of desirable C-vinyl pyrroles.[16]

Having established a robust set of conditions for the formation of 2,4-disubstituted pyrroles, we turned our attention to the synthesis of additional derivatives by exploiting the reactivity of intermediates **3** and **4**. We were particularly intrigued by the utility of isopyrroles, which we identified as suitable donors for ene-type addition reactions (Scheme 2).[17] To this end,

Table 3. One-Pot Synthesis of Ynenoates or Pyrroles



Entry	R =	Ynene (Yield)[c] Pyrrole (Yield)[c]	Entry	R =	Ynene (Yield)[c] Pyrrole (Yield)[c]
1		**3a** (90%) **5a** (80%)	9		**3i** (77%) (12 h) **5i** (82%)[d]
2		**3b** (83%) **5b** (97%)	10		**3j** (97%) **5j** (96%)
3		**3c** (86%) **5c** (89%)	11		**3k** (83%) (18 h) **5k** (97%)
4		**3d** (95%) **5d** (75%)	12		**3l** (74%) (24 h) **5l** (60%)
5		**3e** (74%) **5e** (86%)	13		**3m** (95%) (24 h) **5m** (70%)
6		**3f** (78%) **5f** (90%)	14		**3n** (74%) **5n** (74%)
7		**3g** (84%) **5g** (81%)	15		**3o** (64%) **5o** (70%)
8		**3h** (78%) (12 h) **5h** (99%)	16		**3p** (86%) (24 h) **5p** (68%)

[a] Conditions A: **1** (0.1 mmol, 1 equiv), Donor Alkyne **2** (0.1 mmol, 1 equiv), PhMe (1.0 M), $Pd(OAc)_2$ (0.75 mol %), TDMPP (0.75 mol %), 6 h, rt. Reaction times other than 6 h are included in parentheses. [b] Conditions B: **1** (0.23 mmol, 1 equiv), Donor Alkyne **2** (0.23 mmol, 1 equiv), PhMe (1.0 M), (Entries 1−8, 10): $Pd(OAc)_2$ (0.75 mol %), TDMPP (0.75 mol %), 6 h, rt; then $Pd(OTFA)_2$ (2.0 mol %), 6 h, rt. (Entries 11−16): $Pd(OAc)_2$ (1.5 mol %), TDMPP (1.5 mol %), 24 h, rt; then $Pd(OTFA)_2$ (5.0 mol %), 24 h, rt. [c] Isolated yields. [d] From **3i** (0.1 mmol, 1 equiv), $Pd(OAc)_2$ (5.0 mol %), THF (0.25 M), 60 °C, 14 h. [e] BDMS = Benzyldimethylsilane.

ynenoate **3k** was cyclized to isopyrrole **4k** in the presence of $Pd(OAc)_2$ (3 mol %) in THF in quantitative yield.[18] Gratifyingly, **4k** underwent addition to both Echenmoser's salt (**7**) and diazene **8**, affording products of C−C and C−N bond formation respectively. In addition, oxygenation adjacent to the methyl ester could be effected by simply stirring **4k** overnight open to the atmosphere in the presence of SiO_2.[19] The ability to intercept isopyrrole **4k** provides an attractive, atom-economical avenue for direct derivatization of the pyrrole side chain.[20]

The use of Pd catalysis to effect the cyclization of **3k** offers additional avenues for substitution of the pyrrole nucleus. For example, we reasoned that 2,3,4-trisubstituted heterocycles **9** could be accessed by trapping vinyl-palladium intermediate **4′**, which is generated during the *5-endo-dig* cyclization (Scheme 3).[21] Thus, exposure of ynenoate **3k** to $Pd(OAc)_2$ in the presence of acrolein and LiBr afforded **9a** via a reductive Heck-type addition reaction.[22] Alternatively, allylation in the 3-position could be effected with allyl chloride in the presence of $PdCl_2(CH_3CN)_2$ and propylene oxide as a suitable acid scavenger.[23] This method complements current strategies for the functionalization of 2,4-disubstitued pyrroles, which remains a challenging transformation.[24]

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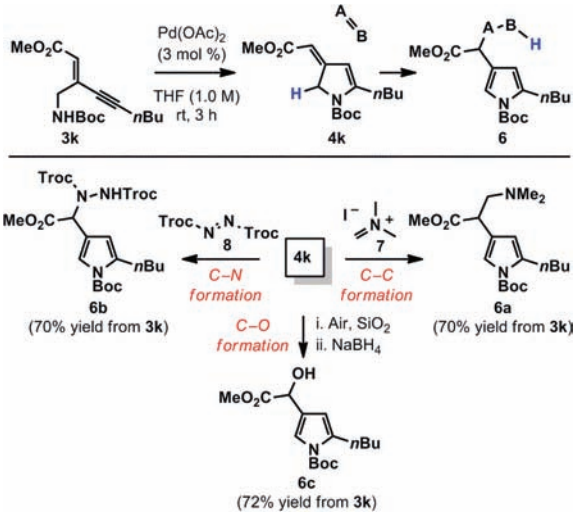
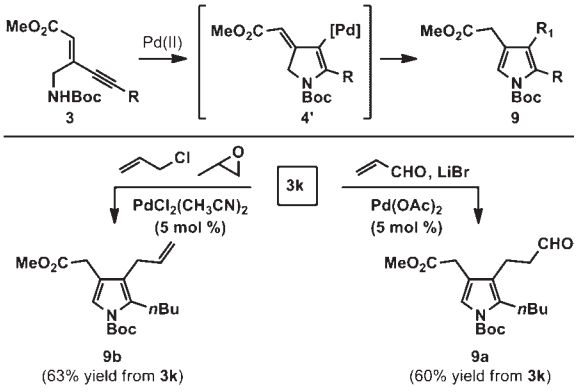
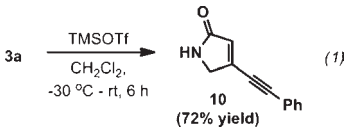
Scheme 2. Reactivity of Isopyrrole Intermediates



Scheme 3. Synthesis of 2,3,4-Trisubstituted Pyrroles



In addition to pyrrole heterocycles, 3-substituted pyrollidin-2-ones are available via a one-pot deprotection, cyclization sequence (eq 1). Thus, exposure of ynenoate **3a** to TMS-OTf in CH_2Cl_2 afforded **10** in 72% isolated yield, demonstrating an alternative, chemoselective cyclization that highlights the versatility of our overall strategy in accessing structurally distinct five-membered nitrogen heterocycles.



(1)

In summary, we have developed an atom-economic synthesis of 2,4-disubstituted pyrroles. The method utilizes readily available alkynes and employs a Pd(II)-mediated cascade reaction. By exerting control over the conditions, we have also shown that several intermediates along the pathway can be intercepted for further functionalization. These include an ene addition reaction with an isopyrrole, as well as access to 2,3,4-trisubstituted pyrroles and 3-substituted pyrollidin-2-ones. This method benefits from operational simplicity as all reactions were performed using benchtop solvents under an ambient atmosphere at room temperature. Current efforts are directed toward the further functionalization of these intermediates, and results will be presented in due course.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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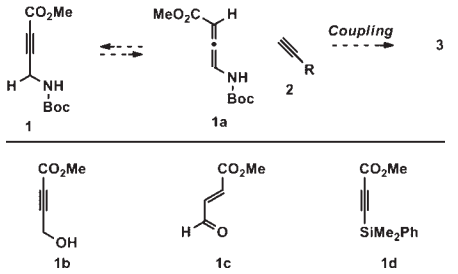
see: Kwong, C. K.-W.; Fu, M. Y.; Lam, C. S.-L.; Toy, P. H. *Synthesis* **2008,** 2307.



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(10) Recent efforts in drug discovery have underscored the importance of accessing distinct molecular architectures from a single reaction sequence: Gray, B. L.; Schreiber, S. L. *J. Comb. Chem.* **2007**, *9*, 1028.

(11) Acceptor **1** is prepared in two steps from commercially available Boc-propargyl amine. See Supporting Information for details.

(12) Wipf, P.; Aoyama, Y.; Benedum, T. E. *Org. Lett.* **2004,** *6,* 3593.

(13) The reaction is tolerant of a variety of solvents. In this study PhMe displayed the best compromise between reaction time and yield.

(14) The coordination of TDMPP to Pd has been discussed: Ma, J.-F.; Kojima, Y.; Yamamoto, Y. *J. Organomet. Chem.* **2000,** *616,* 149.

(15) Attempts to isomerize **3k** or **4k** to **5k** under basic and acidic conditions returned low isolated yields of the desired product. **3k** could be cyclized to **5k** under thermal conditions but required unacceptably high temperatures (>100 °C) and reaction times (>48 h).

(16) Trofimov, B. A.; Sobenina, L. N.; Demenev, A. P.; Mikhaleva, A. I. *Chem. Rev.* **2004,** *104,* 2481.

(17) For a related ene reaction using 3-methyleneindolines see: Tidwell, J. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994,** *116,* 11797.

(18) Following complete conversion, the reaction mixture is filtered through a short column of fluorosil to provide analytically pure samples of the isopyrrole. See Supporting Information for details.

(19) Reduction of crude reaction mixtures with $NaBH_4$ simplified product mixtures which were typically composed of alcohol **6c** and the corresponding ketone.

(20) Functionalization of **5k** would require stoichiometric amounts of activating agents and would reduce the overall atom economy of this process.

(21) We note that $Pd(OAc)_2$ and $PdCl_2$ alone are not as effective as $Pd(OTFA)_2$ in the conversion of **3k** to **5k** (Table 2). Nevertheless, under the conditions described in Scheme 3, substituted isopyrrole products were not detected. We speculate that the additional additives present under these conditions promote the isomerization of ispoyrrole intermediates into the corresponding pyrrole products.

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