


 Cite this: *Chem. Commun.*, 2024, 60, 428

 Received 12th October 2023,  
 Accepted 5th December 2023

DOI: 10.1039/d3cc05023h

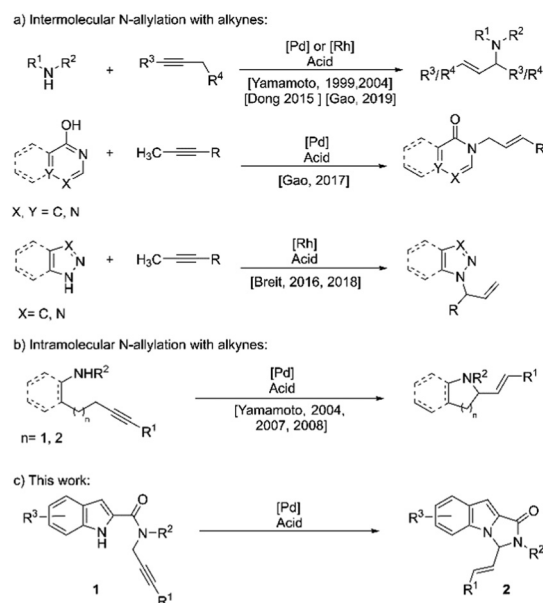
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# Pd/Brønsted acid catalysed intramolecular N-allylation of indoles and pyrroles with alkynes for the synthesis of N-fused heterocycles†

 Saswat Ranjan Bhoi,‡ Chhanda Debnath‡ and Shikha Gandhi \*

We, herein, report a Pd(0) and Brønsted acid-catalyzed redox-neutral intramolecular N-allylation of indoles and pyrroles with alkynes for the synthesis of biologically important imidazolidinone-fused N-heterocycles. The allylation is completely atom-economical and is applicable to a wide range of substrates. The methodology eliminates the use of a leaving group or an oxidizing agent, often employed for the allylation of nucleophiles. To the best of our knowledge, N-allylation of indoles and pyrroles with alkynes has not been reported to date.

Allylation of nucleophiles is one of the most widely employed reactions in organic synthesis. The installation of an allyl group is generally accomplished *via* the allyl-metal intermediate, often generated by the use of a leaving group on an allyl moiety, commonly known as the Tsuji–Trost reaction.<sup>1</sup> However, the approach is not atom-economical and often requires an additional step for installing the leaving group. An alternative approach proceeds *via* allylic C–H oxidation, thus requiring a stoichiometric amount of oxidant.<sup>2</sup> Nucleophilic addition to the allyl-metal complex generated from allenes is another alternative, which, however, requires preformed allenes.<sup>3</sup> Undoubtedly, one of the best approaches available for these allylations is the atom-economical, redox-neutral addition of nucleophiles to alkynes, with the allyl-metal intermediate being generated *via* propargylic C–H activation and an *in situ* generation of allenes.<sup>4</sup> This reaction has, since its discovery, been applied to the allylation of several carbon<sup>5</sup> and hetero-nucleophiles,<sup>6–8</sup> employing either Pd or Rh complexes. The allylation of amines with alkynes has also been explored, mostly focused around intermolecular versions (Scheme 1a).<sup>8a–f</sup> The intramolecular versions, in comparison, have hardly gained any attention (Scheme 1b).<sup>8g–i</sup> Despite some progress in the area, the N-allylation of indoles and pyrroles using alkynes as allyl-metal precursors has not found any



Scheme 1 Transition metal catalysed N-allylation with alkynes.

entries in the literature. The wide prevalence of N-heterocycles and their derivatives in biologically active compounds<sup>9</sup> intrigued us to explore the above-mentioned allylation of indoles and pyrroles with alkynes.

Fused polycyclic N-heterocycles form the structural core of a large number of pharmaceutically relevant compounds.<sup>10</sup> N-fused indoles and pyrroles, particularly imidazo[1,5-a]indoles and pyrrolo[1,2-c]imidazoles, and their derivatives have been found to exhibit a range of biological activities such as CNS depressants,<sup>11</sup> light-dependent TNF- $\alpha$  antagonists,<sup>12</sup> NPS antagonists,<sup>13</sup> and aldose reductase inhibitors,<sup>14</sup> among others. These motifs have also found applications in optoelectronics.<sup>15</sup>

We envisioned that substrates of the type **1** (Scheme 1c), with suitably N-tethered alkyne, would provide direct access to imidazo[1,5-a]indole and pyrrolo[1,2-c]imidazole skeletons *via* an intramolecular allylation with the allyl metal complex

Department of Chemical Sciences, Indian Institute of Science Education and Research, Berhampur 760010, India. E-mail: sgandhi@iiserbpr.ac.in

 † Electronic supplementary information (ESI) available: Experimental details, 1 mmol synthesis, NMR data. CCDC 2259848. For ESI and crystallographic data in CIF or other electronic format see DOI: <https://doi.org/10.1039/d3cc05023h>

‡ These authors contributed equally to this work.



generated from the alkyne. Considering the regioselectivity desired, a combination of Pd(0) and a Brønsted acid was anticipated to be a suitable catalyst system for the reaction.<sup>5–8</sup> We herein report the results of our studies on Pd and acid-catalyzed synthesis of fused N-heterocycles *via* a direct intramolecular *N*-allylation with alkynes (Scheme 1c). To the best of our knowledge, this constitutes the first example of an *N*-allylation of indoles with alkynes.

At the outset, our model substrate **1a** was heated at 110 °C with 5 mol% of Pd(PPh<sub>3</sub>)<sub>4</sub> and 10 mol% of benzoic acid in toluene under an Argon atmosphere. Gratifyingly, after 12 h, the intended product **2a** was isolated as a single *E*-isomer in 45% yield (Table 1, entry 1). The structure and stereochemistry of **2a** were confirmed by NMR and X-ray diffraction analysis. An increase in yield was observed by increasing the amount of acid catalyst to 30 mol% (Table 1, entry 2). Adding 10 mol% of triphenylphosphine additionally to the reaction did not lead to much improvement in the yield (Table 1, entry 3). Test reactions showed that both Pd complex and acid were crucial for the reaction to proceed (Table 1, entries 4 and 5). The use of Pd<sub>2</sub>(dba)<sub>3</sub> as the Pd source led to a slight decrease in the yield (Table 1, entry 6). No reaction was observed when Pd(OAc)<sub>2</sub> was used as the catalyst (Table 1, entry 7). We then screened the effect of different phosphine ligands on the reaction using 5 mol% of Pd(PPh<sub>3</sub>)<sub>4</sub> and 30 mol% benzoic acid as the catalysts. The use of 10 mol% of tri(*o*-tolylphosphine) improved the yield to 70% (Table 1, entry 8). Other phosphines with electron-rich phenyl substituents were found to be inferior ligands than tri(*o*-tolylphosphine) (Table 1, entries 9–11). To our delight, tris(2-

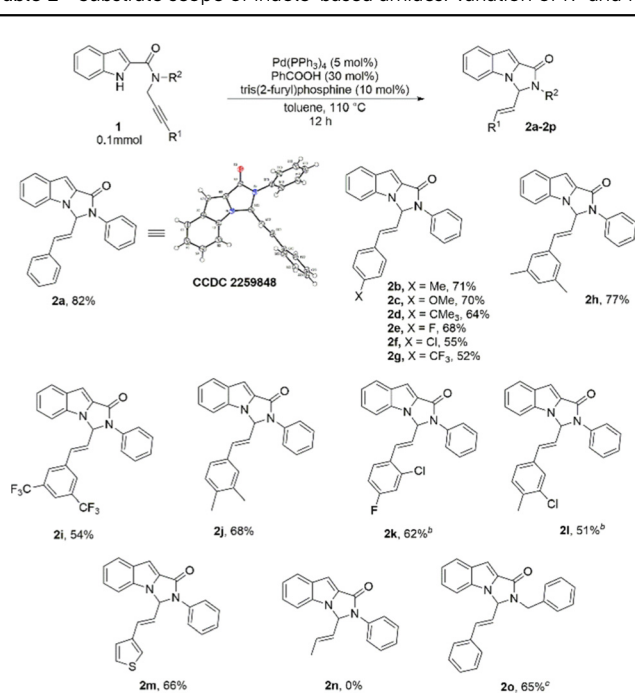
furyl)phosphine was found to be a better ligand and improved the yield to 82% (Table 1, entry 12). The use of dioxane as a solvent with same reaction led to a major drop in the yield (Table 1, entry 13). Tri(*p*-fluorophenyl)phosphine as ligand with electron-deficient phenyl substituents led to a substantial decrease in yield (Table 1, entry 14). We also tested an aliphatic phosphine, which, however, was found to be an inferior ligand to aromatic phosphines (Table 1, entry 15). A bidentate phosphine was also tested, but the desired product was isolated in only 18% yield after 12 h (Table 1, entry 16).

With the optimized reaction conditions, we then set out to explore the substrate scope of the reaction (Table 2). The scope with respect to changing R<sup>1</sup> on the alkyne part was first studied. Phenyl rings with electron-donating as well as electron-withdrawing substituents at the 4-position were well tolerated, and the corresponding substrates formed the cyclized products in good yields (Table 2, **2b–2g**). 3,5-disubstituted phenyl rings were also tested, and the substrates **1h** and **1i** reacted well under the standard reaction conditions (Table 2, **2h**, **2i**). In most cases, phenyl rings with electron-donating groups proved to be slightly better substituents than phenyl rings with electron withdrawing groups. Several other disubstituted phenyl rings, with substituents at different positions of the ring were screened and in all the cases, the products could be isolated in reasonably good yields (Table 2, **2j–2l**). A heterocyclic substituent, 3-thienyl, was also explored, and gratifyingly, the product **2m** was formed in 66% yield (Table 2, **2m**). The aliphatic substituent, methyl, however, was not found to be suitable and the desired product was not formed under the standard reaction conditions when **1n** was used as the substrate

Table 1 Optimization of reaction conditions<sup>a</sup>

| Entry           | [Pd]                               | Ligand                                   | Yield <sup>b</sup> (%) |
|-----------------|------------------------------------|--|------------------------|
| 1 <sup>c</sup>  | Pd(PPh <sub>3</sub> ) <sub>4</sub> | —  | 45                     |
| 2               | Pd(PPh <sub>3</sub> ) <sub>4</sub> | —  | 56                     |
| 3               | Pd(PPh <sub>3</sub> ) <sub>4</sub> | PPh <sub>3</sub>                         | 58                     |
| 4 <sup>d</sup>  | —                                  | —  | —                      |
| 5 <sup>e</sup>  | Pd(PPh <sub>3</sub> ) <sub>4</sub> | —  | —                      |
| 6               | Pd <sub>2</sub> (dba) <sub>3</sub> | PPh <sub>3</sub>                         | 52                     |
| 7               | Pd(OAc) <sub>2</sub>               | —  | —                      |
| 8               | Pd(PPh <sub>3</sub> ) <sub>4</sub> | P( <i>o</i> -tolyl) <sub>3</sub>         | 70                     |
| 9               | Pd(PPh <sub>3</sub> ) <sub>4</sub> | P( <i>p</i> -tolyl) <sub>3</sub>         | 53                     |
| 10              | Pd(PPh <sub>3</sub> ) <sub>4</sub> | P(2,4,6-trimethylphenyl) <sub>3</sub>    | 57                     |
| 11              | Pd(PPh <sub>3</sub> ) <sub>4</sub> | P( <i>o</i> -methoxyphenyl) <sub>3</sub> | 62                     |
| 12              | Pd(PPh <sub>3</sub> ) <sub>4</sub> | P(2-furyl) <sub>3</sub>                  | 82                     |
| 13 <sup>f</sup> | Pd(PPh <sub>3</sub> ) <sub>4</sub> | P(2-furyl) <sub>3</sub>                  | 46                     |
| 14              | Pd(PPh <sub>3</sub> ) <sub>4</sub> | P( <i>p</i> -fluorophenyl) <sub>3</sub>  | 24                     |
| 15              | Pd(PPh <sub>3</sub> ) <sub>4</sub> | PCy <sub>3</sub>                         | 34                     |
| 16              | Pd(PPh <sub>3</sub> ) <sub>4</sub> | DPEPhos                                  | 18                     |

<sup>a</sup> Unless noted otherwise, reaction conditions: **1a** (0.1 mmol), Pd catalyst (5 mol%), ligand (10 mol%), benzoic acid (30 mol%) in dry toluene (0.7 mL) were heated at 110 °C under argon in a Schlenk tube for 12 h. <sup>b</sup> Isolated yields. <sup>c</sup> Benzoic acid (0.01 mmol, 10 mol%). <sup>d</sup> In absence of Pd catalyst. <sup>e</sup> In absence of benzoic acid. <sup>f</sup> Dry dioxane as solvent (0.7 mL).

Table 2 Substrate scope of indole-based amides: variation of R<sup>1</sup> and R<sup>2a</sup>

<sup>a</sup> Isolated yields. <sup>b</sup> Reaction was run for 24 h. <sup>c</sup> Pd catalyst (10 mol%), no ligand.



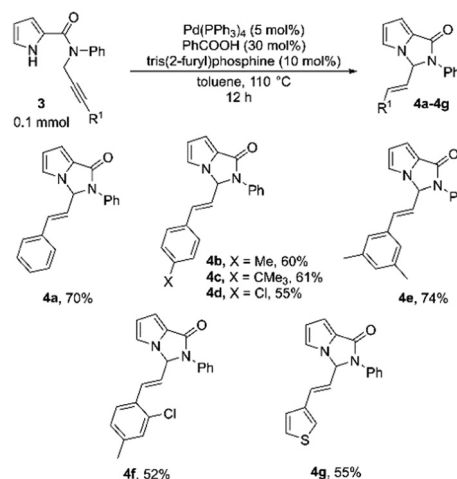
(Table 2, **2n**).<sup>4c,8f,16</sup> We also attempted changing R<sup>2</sup> substituent on the amide Nitrogen from phenyl to benzyl and the corresponding product was obtained in 65% yield (Table 2, **2o**).

The reaction showed versatility with respect to changing substituents on the indole ring (Table 3). Introduction of electron-withdrawing groups at position 5 of the indole afforded the products in high yields (Table 3, **2p–2t**). Notably, a combination of these substituents with different R<sup>1</sup> groups was also found to be suitable, and the corresponding substrates formed the products in consistently good yields (64–86%; Table 3, **2q, 2r, 2t**). The substrates with electron-releasing substituents at position 5 were also tested and these too reacted remarkably under the standard reaction conditions, even with several different R<sup>1</sup> substituents (Table 3, **2u–2x**). We also explored the effect of substitutions at positions 6 and 7 of the indole ring, and to our delight, the reaction was well tolerant of these substitutions (Table 3, **2y, 2z**).

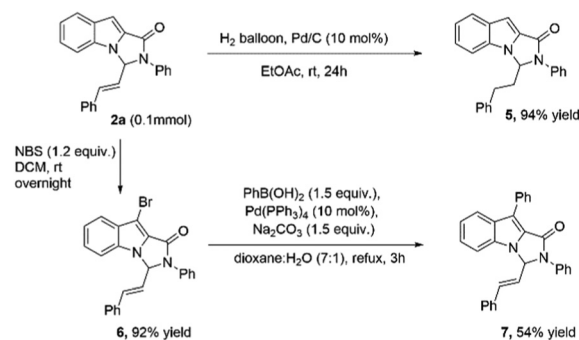
Encouraged by the results on the indole-based *N*-substituted propargyl amides, we then proceeded to explore the cyclization of pyrrole-based amides **3a–3g** (Table 4). The scope of this system with respect to different substituents on the alkyne was screened. The substrate **3a** with R<sup>1</sup> as phenyl, under the optimized reaction conditions, reacted smoothly, and the product was formed in 70% yield (Table 4, **4a**). Satisfyingly, substituted phenyl rings with both electron-releasing as well as electron-withdrawing substituents at different positions could be employed, and the corresponding products were isolated in moderate to good yields (52–74%; Table 4, **4b–4f**). The 3-thienyl substituent was also tolerated, and the substrate **3g** formed the cyclized product in 55% yield (Tables 4, **4g**).

To illustrate the synthetic utility of the product, **2a** was first subjected to hydrogenation using 10% Pd/C. The reduction of

Table 4 Substrate scope of pyrrole-based amides: variation of R<sup>1a</sup>

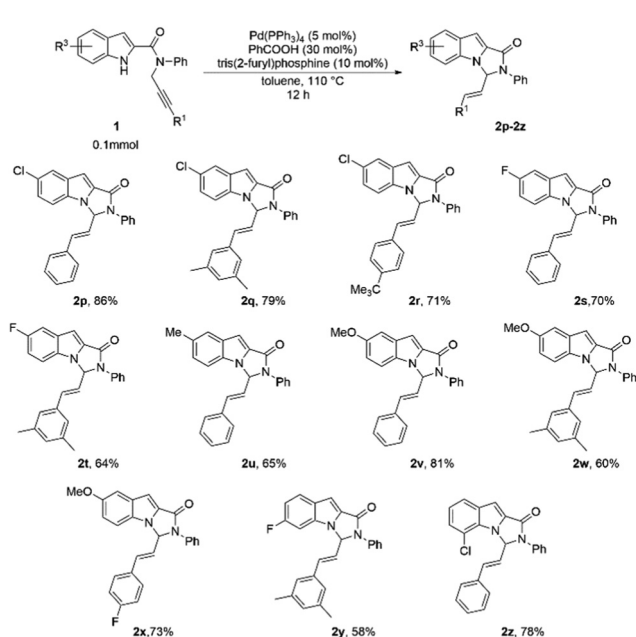


<sup>a</sup> Isolated yields.



Scheme 2 Synthetic transformations of product **2a**.

Table 3 Substrate scope of indole-based amides: Variation of R<sup>3a</sup>



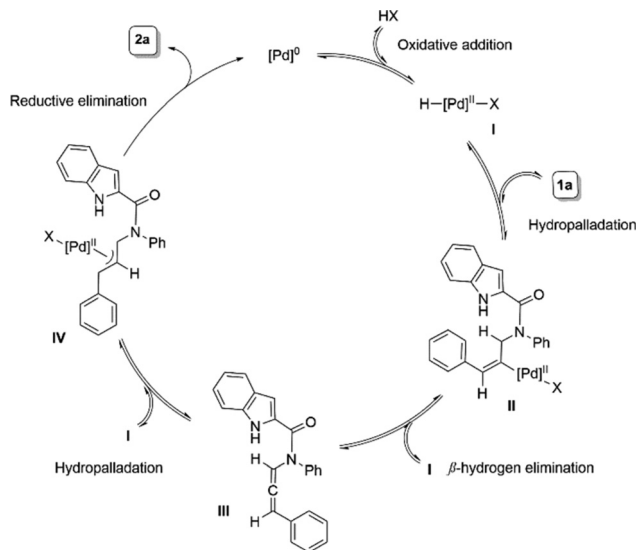
<sup>a</sup> Isolated yields.

allylic double bond proceeded satisfactorily, and the product **5** was formed in 94% yield (Scheme 2). The indole moiety could also be derivatized further using NBS leading to the product **6**, which upon Suzuki coupling with phenylboronic acid led to the product **7** (Scheme 2).

Based on the literature reports<sup>4,5d,8f</sup> and our mechanistic studies,<sup>17</sup> we hypothesize that Pd(0) forms a Pd-carboxylate species **I** upon oxidative addition with the carboxylic acid. An insertion of **I** into the alkyne of substrate **1a** generates species **II**. A subsequent  $\beta$ -hydrogen elimination releases the allene intermediate **III**, which, upon hydropalladation with **I**, forms the active  $\pi$ -allyl species **IV**. The selective nucleophilic insertion of N–H of indole then releases product **2a** and regenerates Pd(0) (Scheme 3).

We have developed the first catalytic intramolecular *N*-allylation of indoles and pyrroles with alkynes. The reaction employs a Pd(0) and Brønsted acid combined catalytic system. The use of alkynes as allene surrogates enables a direct, completely atom-economic allylation without employing a leaving group, oxidizing agent, or an additional step for the formation of allenes. Biologically important N-fused heterocycles, imidazo[1,5a]indoles, and pyrrolo-[1,2c]imidazoles could be accessed in





Scheme 3 Most probable mechanism.

high yields under the reaction conditions. The system demonstrates a broad substrate scope and installs a synthetically relevant allyl substituent with the concomitant generation of a stereogenic center. The development of an asymmetric version of the reaction is currently ongoing.

Financial supports by IISER Berhampur and the Science and Engineering Research Board (SERB), Government of India (CRG/2018/000130) are gratefully acknowledged by the authors. C. D. thanks the Ministry of Education for PMRF. The authors are thankful to Dr C. S. Purohit, School of Chemical Sciences, NISER Bhubaneswar for his help in recording the X-ray data.

## Conflicts of interest

There are no conflicts to declare.

## Notes and references

- (a) G. Wu, J.-R. Wu, Y. Huang and Y.-W. Yang, *Chem. – Asian J.*, 2021, **16**, 1864–1877; (b) B. M. Trost, *Tetrahedron*, 2015, **71**, 5708–5733; (c) J. F. Hartwig and L. M. Stanley, *Acc. Chem. Res.*, 2010, **43**, 1461; (d) J. Tsuji, *Palladium Reagents and Catalysts: New Perspectives for the 21st Century*, John Wiley & Sons, Chichester, 2004, pp. 431–517.
- (a) P. S. Wang and L. Z. Gong, *Acc. Chem. Res.*, 2020, **53**, 2841–2854; (b) A. M. Kazerouni, Q. A. McKoy and S. B. Blakey, *Chem. Commun.*, 2020, **56**, 13287–13300; (c) F. Liron, J. Obler, M. M. Lorion and G. Poli, *Eur. J. Org. Chem.*, 2014, 5863–5883.
- (a) J. Liu, Q. Zhou, Y. Lin, Z.-L. Wu, T. Cai, W. Wen, Y. Huang and Q. Guo, *ACS Catal.*, 2023, **13**, 6013–6022; (b) H. Xu, M. Wang, Y. Liang, Y. Zhao and Z. Shi, *Nat. Synth.*, 2022, **1**, 227–234; (c) R. Blicek, M. Taillefer and F. Monnier, *Chem. Rev.*, 2020, **120**, 13545–13598; (d) P. Koschker and B. Breit, *Acc. Chem. Res.*, 2016, **49**, 1524–1536; (e) T. Lu, Z. Lu, Z.-X. Ma, Y. Zhang and R. P. Hsung, *Chem. Rev.*, 2013, **113**, 4862–4904; (f) E. Beccalli, A. Bernasconi, E. Borsini, G. Brogini, M. Rigamonti and G. Zecchi, *J. Org. Chem.*, 2010, **75**, 6923–6932; (g) Y. Yamamoto, M. Al-Masum and N. Asao, *J. Am. Chem. Soc.*, 1994, **116**, 6019–6020.
- (a) G. Cera and G. Maestri, *Chemcatchem*, 2022, **14**, e202200295; (b) A. M. Haydl, B. Breit, T. Liang and M. J. Krische, *Angew. Chem., Int. Ed.*, 2017, **56**, 11312–11325; (c) B. M. Trost, *Chem. – Eur. J.*, 1998, **4**, 2405–2412.

- For selected examples of allylation of carbon nucleophile with alkynes, see: (a) W. Ren, Q.-M. Zuo, Y. Niu and S. Yang, *Org. Lett.*, 2019, **21**, 7956–7960; (b) G. Cera, M. Lanzi, D. Balestri, N. D. Ca', R. Maggi, F. Bigi, M. Malacria and G. Maestri, *Org. Lett.*, 2018, **20**, 3220–3224; (c) F. A. Cruz and V. M. Dong, *J. Am. Chem. Soc.*, 2017, **139**, 1029–1032; (d) S. Gao, Z. Wu, X. Fang, A. Lin and H. Yao, *Org. Lett.*, 2016, **18**, 3906–3909; (e) N. T. Patil, D. Song and Y. Yamamoto, *Eur. J. Org. Chem.*, 2006, 4211–4213; (f) N. T. Patil, I. Kadota, A. Shibuya, Y. S. Gyoung and Y. Yamamoto, *Adv. Synth. Catal.*, 2004, **346**, 800–804.
- For selected examples of allylation of oxygen nucleophile with alkynes, see: (a) Y. Ogiwara, K. Sato and N. Sakai, *Org. Lett.*, 2017, **19**, 5296–5299; (b) Z. Li and B. Breit, *Angew. Chem., Int. Ed.*, 2016, **128**, 8580–8583; (c) W. Zhang, A. R. Haight and M. C. Hsu, *Tetrahedron Lett.*, 2002, **43**, 6575–6578; (d) B. M. Trost, W. Brieden and K. H. Baringhaus, *Angew. Chem., Int. Ed. Engl.*, 1992, **31**, 1335–1336.
- For selected examples of allylation of sulphur nucleophile with alkynes, see: (a) C. Lu, H. Chen, D. Chen, H. Wang, Z. Yang, J. Gao and H. Jin, *Org. Biomol. Chem.*, 2016, **14**, 10833–10839; (b) K. Xu, V. Khakyzadeh, T. Bury and B. Breit, *J. Am. Chem. Soc.*, 2014, **136**, 16124–16127.
- For selected examples of intermolecular allylation of nitrogen nucleophile with alkynes, see: (a) C.-J. Lu, X. Yu, D. Chen, H. Wang, Q. Song and J. Gao, *Org. Biomol. Chem.*, 2019, **17**, 3545–3551; (b) D. Berthold and B. Breit, *Org. Lett.*, 2018, **20**, 598–601; (c) C.-J. Lu, D. Chen, H. Chen, H. Wang, H. Jin, X. Huang and J. Gao, *Org. Biomol. Chem.*, 2017, **15**, 5756–5763; (d) A. M. Haydl, L. J. Hilpert and B. Breit, *Chem. – Eur. J.*, 2016, **22**, 6547–6551; (e) Q.-A. Chen, Z. Chen and V. M. Dong, *J. Am. Chem. Soc.*, 2015, **137**, 8392–8395; (f) I. Kadota, A. Shibuya, L. M. Lutete and Y. Yamamoto, *J. Org. Chem.*, 1999, **64**, 4570–4571. For selected examples of intramolecular allylation of nitrogen nucleophile with alkynes, see: (g) M. Narsireddy and Y. Yamamoto, *J. Org. Chem.*, 2008, **73**, 9698–9709; (h) N. T. Patil, H. Wu and Y. Yamamoto, *J. Org. Chem.*, 2007, **72**, 6577–6579; (i) Y. Yamamoto, *et al.*, *Tetrahedron Lett.*, 2005, **46**, 2101–2103; (j) L. M. Lutete, I. Kadota and Y. Yamamoto, *J. Am. Chem. Soc.*, 2004, **126**, 1622–1623.
- D. J. Faulkner, *Nat. Prod. Rep.*, 2001, 1–49.
- (a) I. Ngantchou, B. Nyasse, C. Denier, C. Blonski, V. Hannaert and B. Schneider, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 3495; (b) V. Sharma, P. Kumar and D. Pathak, *J. Heterocycl. Chem.*, 2010, **47**, 491–502; (c) L. S. Fernandez, M. S. Buchanan, A. R. Carroll, Y. J. Feng, R. J. Quinn and V. M. Avery, *Org. Lett.*, 2009, **11**, 329; (d) M. Nettekoven, J.-M. Plancher, H. Richter, O. Roche and S. Taylor, WO US 2007/0135416 A1, 2007; (e) J.-F. Liu, Z.-Y. Jiang, R.-R. Wang, Y.-T. Zheng, J.-J. Chen, X.-M. Zhang and Y.-B. Ma, *Org. Lett.*, 2007, **9**, 4127.
- (a) W. B. Wright, *US Pat.*, 3565902, 1971; *Chem. Abstr.*, 1971, **75**, 36033; (b) M. Varasi, F. Heidemperger, C. Caccia and P. Salvati, *PCT Int., Appl.*, WO 9532209, 1995; *Chem. Abstr.*, 1995, **124**, 232456.
- M. E. Voss, P. H. Carter, A. J. Tebben, P. A. Scherle, G. D. Brown, L. A. Thompson, M. Xu, Y. C. Lo, G. Yang, R.-Q. Liu, P. Strzemiński, J. G. Everlof, J. M. Trzaskos and C. P. Decicco, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 533–538.
- F. Micheli, R. Di Fabio, A. Giacometti, A. Roth, E. Moro, G. Merlo, A. Paio, E. Merlo-Pich, S. Tomelleri, F. Tonelli, P. Zarantonello, L. Zonzini and A. M. Capelli, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 7308–7311.
- (a) W. Kong, X. Chen, M. Wang, H. Dai and J. Yu, *Org. Lett.*, 2017, **20**, 284–287; (b) I. Yamawaki, Y. Matsushita, N. Asaka, K. Ohmori, N. Nomura and K. Ogawa, *Eur. J. Med. Chem.*, 1993, **28**, 481–498.
- (a) L. A. Oparina, N. A. Kolyvanov, I. A. Ushakov, L. P. Nikitina, O. V. Petrova, L. N. Sobenina, K. B. Petruschenko and B. A. Trofimov, *Int. J. Mol. Sci.*, 2023, **24**, 3404; (b) B. Banerji, S. Chatterjee, K. Chandrasekhar, S. Ghosh, K. Mukherjee and C. Mandal, *J. Org. Chem.*, 2018, **83**, 13011–13018.
- A diene was isolated under standard reaction conditions. Please see ESI† for more details. For example of Pd catalyzed 1,3-diene formation from propargylic alkynes, see: N. T. Patil, Z. Huo, G. B. Bajracharya and Y. Yamamoto, *J. Org. Chem.*, 2006, **71**, 3612–3614.
- For mechanistic studies, please see ESI†.

