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Metal-Free Synthesis

Tandem Aryne-Capture/Sigmatropic Rearrangement as a Metal-Free Entry to Functionalized *N*-Aryl Pyrrolidines

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Dedicated to Sarah Hicks, a young chemist who died at Hillsborough

Abstract: We report a new method for the synthesis of novel *N*-aryl proline analogues. By reacting an aryne precursor with *N*-(2-malonyl) tetrahydropyridines in the presence of tetrabutylammonium fluoride (TBAF), a tandem aryne-capture/anion isomerisation/[2,3]-sigmatropic rearrangement is induced, leading to good yields of 3-substituted *N*-aryl-2-acylpyrrolidines. These products are known subunits of biological probes, sensors and drug-like fragments, and are not easily accessed directly by other methods. The reaction is also notable as the first [2,3]-rearrangement of cyclic ammonium ylides at room temperature.

Pyrrolidines are key structural features of many biologically active natural products and synthetic substances, and there has been a concomitant interest in methods for the synthesis of these rings.[1,2] Within this diverse class of molecules, the 2-acylpyrrolidine motif is well-known as a component of proteins (in the amino acid proline) and proline analogues occur as subunits of many biologically active synthetic substances, including pharmacologically relevant molecules and functional probes such as ion sensors (Figure 1).[3] Though the *N*-aryl and *N*-naphthyl proline is present in many such drug-like substances,[4] methods to access these structures are limited, with the Ullmann–Goldberg reaction[5] being most often used to prepare the molecules (Scheme 1 a), a process which usually necessitates elevated temperatures and high catalyst loading.[6] Due to this scarcity of synthetic methods, there has been recent interest in the development of novel methods to deliver *N*-aryl pyrrolidines.[7]

We hypothesized that [2,3]-sigmatropic rearrangements of *N*-aryl tetrahydropyridines could potentially offer an efficient entry to *N*-aryl pyrrolidines analogues, but access to the necessary *N*-aryl ammonium ylides needed for the reaction is non-trivial: because of the ambident reactivity of *N*-arylamines, metal-catalysed carbene capture by nitrogen is impractical for anilines,[8] and access to *N*-aryl ammonium salt ylide precursors by means of alkylation of anilines[9] is also challenging.

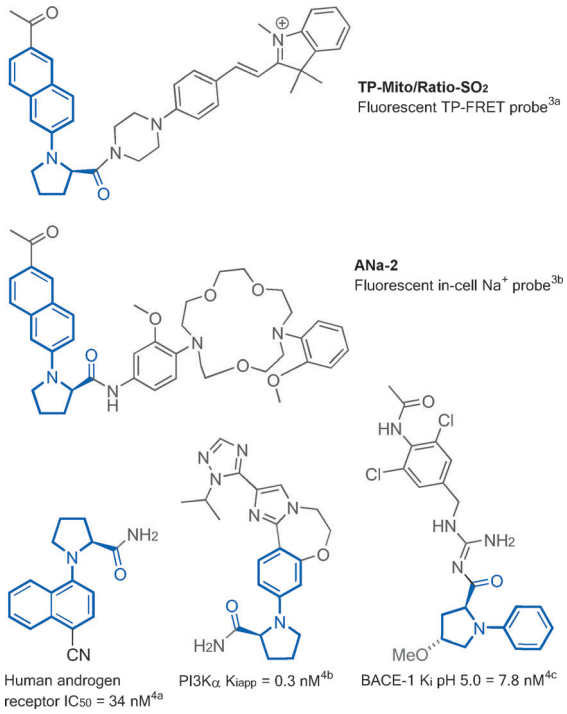

Figure 1. Bioactive synthetic *N*-aryl prolines.

To circumvent these obstacles, we were attracted by the concept of a metal-free tandem aryne-capture/[2,3]-rearrangement, which would circumvent the need for salt formation, and would avoid issues with carbenoid capture. Though tandem aryne capture/aza-Claisen rearrangements involving allyl amines are known[10] (Scheme 1 b), when we commenced this study this proposal was conceptually unique. Thus, as shown in Scheme 1 c, we postulated that reaction of *N*-alkyl tetrahydropyridines **1** (readily available from the corresponding *N*-alkyl pyridinium salts[11]) with an aryne[12,13] **2**, would be followed by isomerization of the first-formed sp^2-anion **3** to the more stable ylide **4**, which would undergo sigmatropic rearrangement to give *N*-arylated pyrrolidine **5**; however, since rearrangements of analogous *N*-alkyl-tetrahydropyridinium ylides typically require elevated temperature,[14,15] (unlike acyclic ammonium ylides, which rearrange rapidly at ambient or low temperatures[16]) it was envisaged that heating might be required to execute the final step of the cascade. As well as theoretically

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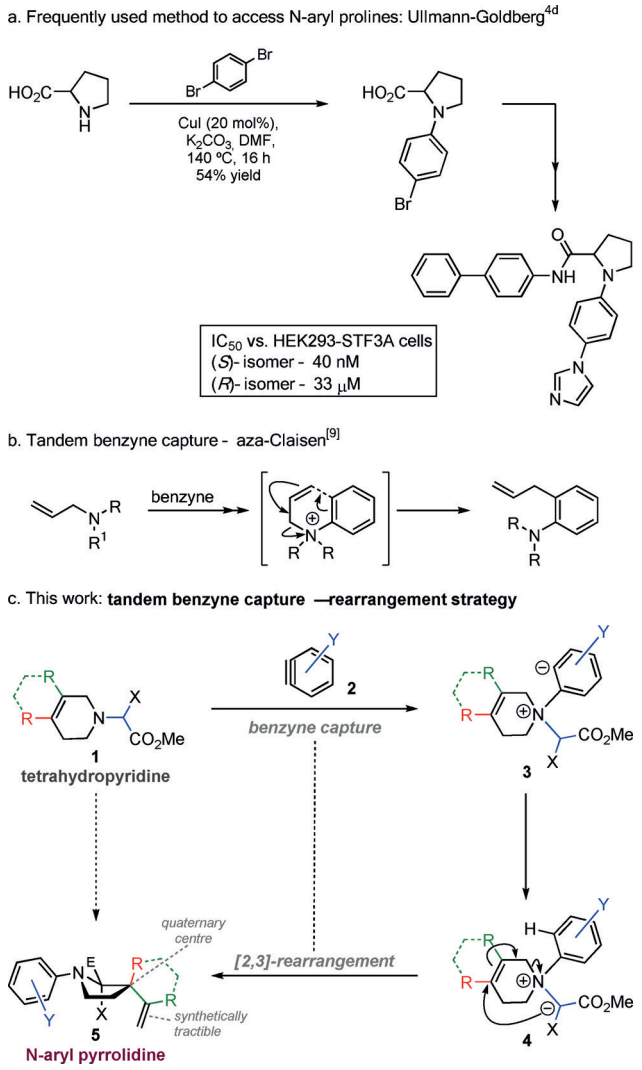
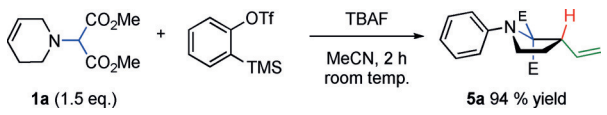
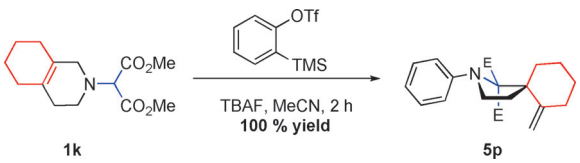


Scheme 1. Context and strategy for metal-free *N*-aryl pyrrolidine synthesis.



Scheme 2. Tandem benzyne-capture/[2,3]-rearrangement reaction: efficient access to *N*-phenyl proline derivatives.

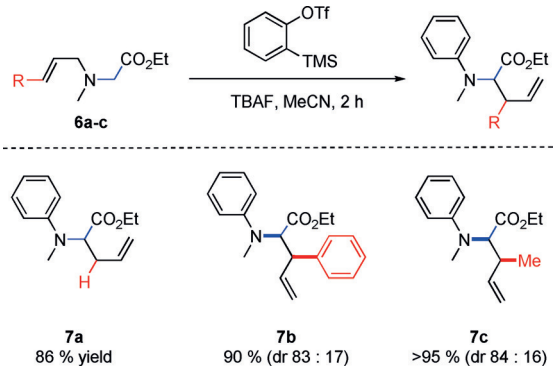


Scheme 3. Facile preparation of spiro-pyrrolidines by tandem benzyne-capture/[2,3]-rearrangement of octahydroisoquinolines.

allowing metal-free access to *N*-aryl pyrrolidine analogues bearing dense contiguous substitution (including adjacent quaternary centres, a demanding structural motif difficult to access by other means[17]), the method would also allow further synthetic modification and diversification by manipulation of the pendant 3-alkenyl substituent. We report herein the realization of this strategy and its application to the efficient preparation of a range of *N*-aryl proline analogues (Scheme 2).

Our studies commenced with the reaction of tetrahydropyridine **1a**; a mixture of this heterocycle and (2-triflyloxy-1-trimethylsilyl)benzene in dry acetonitrile was reacted with TBAF over a two-hour period at room temperature (Scheme 3). We were delighted to witness the validation of our hypothesis, with the hoped-for novel *N*-aryl pyrrolidine derivative **5a** being formed directly, at room temperature, and isolated in 94% yield after chromatography. This confirmed that the reaction was capable of delivering highly functionalized pyrrolidines in a one-pot process. Based on the prior art referred to above, it is noteworthy that the rearrangement component of the tandem proceeds at room temperature. The reasons for this enhanced reactivity compared to reactions of salt-derived ylides are not immediately apparent at present, but the observed room temperature rearrangement of an ammonium ylide bearing a monocyclic alkene is unprecedented and likely offers a comment on the mechanistic nuances of such processes. The existing rationale for the requirement for elevated temperature is the additional activation energy required to bring to juxtaposition the reactive termini of an ylide containing a cyclic alkene,[12] but this is clearly not the case for the reaction under examination here. This point is currently under investigation in our laboratories.

Armed with this remarkable result we turned our attention to examining the scope of the process, firstly probing the effect of substitution in the tetrahydropyridines component. Thus, a range of readily-accessible tetrahydropyridines reacted smoothly under the conditions shown above, yielding aryl proline derivatives **5b**–**5j**, in generally good yields (Scheme 4).

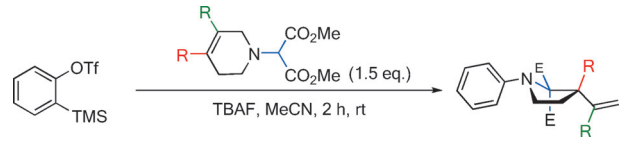


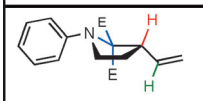
Scheme 4. Tandem benzyne-capture/[2,3]-rearrangement of *N*-allylsarcosines.

The process generates contiguous quaternary centres with ease (Table 1, **5a**–**d**, **5j**).

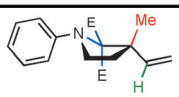
The next phase of our investigation examined the scope in the benzyne component (Table 2): once again we were pleased to observe generally efficient reaction of arynes **2b**–**2g** with amine **1a**, leading to aryl-substituted proline analogues **5k**–**5n**. As expected based on predictive models,[18] good regio-

Table 1. Substrate scope in tetrahydropyridines component for the tandem benzyne-capture/[2,3]-rearrangement reaction. a) Isolated yields.

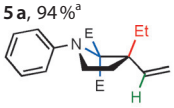




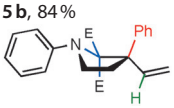
5a, 94%[a]



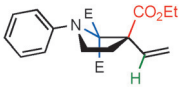
5b, 84%



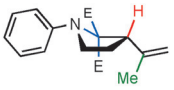
5c, 97%



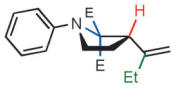
5d, 83%



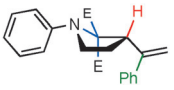
5e, 57%



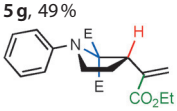
5f, 67%



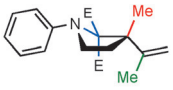
5g, 49%



5h, 93%

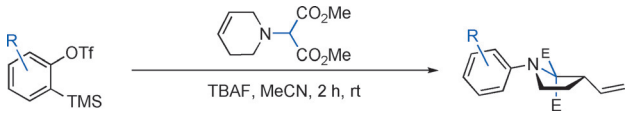


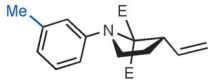
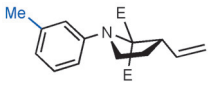
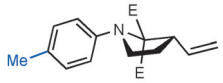
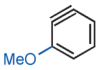
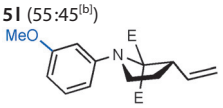
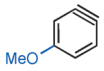
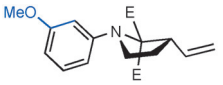
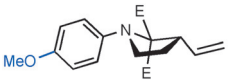
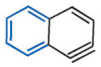
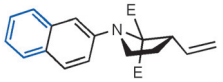
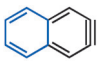
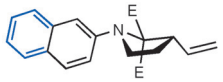
5i, 37%



5j, 95%

Table 2. Scope in benzyne component for the tandem capture/[2,3]-rearrangement reaction.



Entry	Aryne	Yield[a]	Product
1	 **2b**	75%	 **5k**
2	 **2c**	81%	 **5k**  **5l** (55:45[b])
3	 **2d**	77%	 **5m**
4	 **2e**	66%	 **5m**  **5n** (55:45[b])
5	 **2f**	52%	 **5o**
6	 **2g**	45%	 **5o**

a) Isolated yield after chromatography. b) Ratio estimated from ^{1}H NMR spectra.

control was observed in reactions of 3-substituted benzynes bearing either electron-withdrawing (entry 1) and electron-donating groups (entry 3), whereas 4-substituted benzynes reacted to give mixtures of regioisomeric products (entries 2 and 4); 1- and 2-naphthynes gave only 2-naphthyl products (entries 5 and 6).

As mentioned, a significant benefit of this reaction is the facile ability to directly access pyrrolidines with dense ring-substitution. The power of this feature of the transformation is particularly well-demonstrated in the reaction of tetrahydroisoquinoline-derived amine **1k** (prepared in two steps from commercially available 5,6,7,8-tetrahydroisoquinoline): under standard reaction conditions: spirocyclic proline derivative **5p** again containing two contiguous quaternary centres (and a spiro linkage structurally related to motifs seen in nanomolar beta-secretase 1 (BACE) inhibitors[19]) was isolated in quantitative yield (Scheme 3). It is difficult to imagine how such a densely functionalised cyclic amine could otherwise be accessed in one step from readily available chemical start-points.

We have also briefly examined the use of the conditions in the reaction of *N*-allyl sarcosines **6a–c** (Scheme 6).[20] The reactions examined proceed in excellent yield, to give aminoesters **7a–c** with good stereoselectivity (in which terminal allyl substitution is present).[21]

In summary, we have developed a new metal-free tandem reaction process for the synthesis of *N*-aryl proline derivatives. The transformation is tolerant to a range of functional groups and provides ready access to the compounds in generally good yields. We believe that this method will be of some utility to the chemical community.

Acknowledgements

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Keywords: metal-free · N-aryl pyrrolidine · sigmatropic rearrangement · tandem · ylides

[1] For reviews, see: a) A. C. B. Burtoloso, R. M. P. Dias, B. Bernardim, *Acc. Chem. Res.* **2015**, *48*, 921–934; b) C. Bhat, S. G. Tilve, *RSC Adv.* **2014**, *4*, 5405–5452; c) M.-Y. Han, J.-Y. Jia, W. Wang, *Tetrahedron Lett.* **2014**, *55*, 784–794; d) G. Pandey, P. Banerjee, S. R. Gadre, *Chem. Rev.* **2006**, *106*, 4484–4517; e) J. P. Michael, *Nat. Prod. Rep.* **1999**, *16*, 675–696.

[2] For recent examples, see: a) Z. Yuan, W. Wei, A. Lin, H. Yao, *Org. Lett.* **2016**, *18*, 3370 – 3373; b) K. Liu, C. Zhu, J. Min, S. Peng, G. Xu, J. Sun, *Angew. Chem. Int. Ed.* **2015**, *54*, 12962 – 12967; *Angew. Chem.* **2015**, *127*, 13154 – 13159; c) A. R. Reddy, C.-Y. Zhou, Z. Guo, J. Wei, C.-M. Che, *Angew. Chem. Int. Ed.* **2014**, *53*, 14175 – 14180; *Angew. Chem.* **2014**, *126*, 14399 – 14404; d) A. Feula, S. S. Dhillon, R. Byravan, M. Sangha, R. Ebanks, M. A. Hama Salih, N. Spencer, L. Male, I. Magyary, W.-P. Deng, F. Muller, J. S. Fossey, *Org. Biomol. Chem.* **2013**, *11*, 5083 – 5093; e) K. D. Hesp, M. Stradiotto, *Org. Lett.* **2009**, *11*, 1449 – 1452; f) Q.-H. Deng, H.-W. Xu, A. W.-H. Yuen, Z.-J. Xu, C.-M. Che, *Org. Lett.* **2008**, *10*, 1529 – 1532; g) Z. Liu, J. F. Hartwig, *J. Am. Chem. Soc.* **2008**, *130*, 1570 – 1571; h) C. J. Hayes, A. E. Sherlock, M. P. Green, C. Wilson, A. J. Blake, M. D. Selby, J. C. Prodger, *J. Org. Chem.* **2008**, *73*, 2041 – 2051; i) M. C. Marcotullio, V. Campagna, S. Sternativo, F. Costantino, M. Curini, *Synthesis* **2006**, 2760 – 2766; j) X. Han, R. A. Widenhoefer, *Angew. Chem. Int. Ed.* **2006**, *45*, 1747 – 1749; *Angew. Chem.* **2006**, *118*, 1779 – 1781; k) Y. Terada, M. Arisawa, A. Nishida, *Angew. Chem. Int. Ed.* **2004**, *43*, 4063 – 4067; *Angew. Chem.* **2004**, *116*, 4155 – 4159; l) F. A. Davis, B. Yang, J. Deng, *J. Org. Chem.* **2003**, *68*, 5147 – 5152; m) F. A. Davis, T. Fang, R. Goswami, *Org. Lett.* **2002**, *4*, 1599 – 1602.

[3] a) X. Yang, Y. Zhou, X. Zhang, S. Yang, Y. Chen, J. Guo, X. Li, Z. Qinga, R. Yang, *Chem. Commun.* **2016**, *52*, 10289 – 10292; b) A. R. Sarkar, C. H. Heo, M. Y. Park, H. W. Lee, H. M. Kim, *Chem. Commun.* **2014**, *50*, 1309.

[4] See, for instance: a) K. Aikawa, T. Miyawaki, T. Hitaka, Y. N. Imai, T. Hara, J. Miyazaki, M. Yamaoka, M. Kusaka, N. Kanzaki, A. Tasaka, M. Shiraishi, S. Yamamoto, *Bioorg. Med. Chem.* **2015**, *23*, 2568 – 2578; b) T. P. Heffron, R. A. Heald, C. Ndubaku, B. Wei, M. Augistin, S. Do, K. Edgar, C. Eigenbrot, L. Friedman, E. Gancia, P. S. Jackson, G. Jones, A. Kolesnikov, L. B. B. Lee, J. D. D. Lesnick, C. Lewis, N. McLean, M. Mörtl, J. Nonomiya, J. Pang, S. Price, W. W. Prior, L. Salphati, S. Sideris, S. T. Staben, S. Steinbacher, V. Tsui, J. Wallin, D. Sampath, A. G. Olivero, *J. Med. Chem.* **2016**, *59*, 985 – 1002; c) K. M. Boy, J. M. Guernon, Y.-J. Wu, Y. Zhang, J. Shi, W. Zhai, S. Zhu, S. W. Gerritz, J. H. Toyn, J. E. Meredith, D. M. Barten, C. R. Burton, C. F. Albright, A. C. Good, J. E. Grace, K. A. Lentz, R. E. Olson, J. E. Macor, L. A. Thompson III, *Bioorg. Med. Chem. Lett.* **2015**, *25*, 5040 – 5047; d) A. J. Duraiswamy, M. A. Lee, B. Madan, S. H. Ang, E. S. W. Tan, W. W. V. Cheong, Z. Ke, V. Pendharkar, L. J. Ding, Y. S. Chew, V. Manoharan, K. Sangthongpitag, J. Alam, A. Poulsen, S. Y. Ho, D. M. Virshup, T. H. Keller, *J. Med. Chem.* **2015**, *58*, 5889 – 5899.

[5] For reviews, see: a) C. Sambiagio, S. P. Marsden, A. J. Blacker, P. C. McGowan, *Chem. Soc. Rev.* **2014**, *43*, 3525 – 3550; b) F. Monnier, M. Taillefer, *Angew. Chem. Int. Ed.* **2009**, *48*, 6954 – 6971; *Angew. Chem.* **2009**, *121*, 7088 – 7105.

[6] Pd-catalysed *N*-arylation of amino acid derivatives: a) S. Sharif, D. Mitchell, M. J. Rodriguez, J. L. Farmer, M. G. Organ, *Chem. Eur. J.* **2016**, *22*, 14860 – 14863; b) H. Hammoud, M. Schmitt, E. Blaise, F. Bihel, J. J. Bourguignon, *J. Org. Chem.* **2013**, *78*, 7930; c) F. Ma, X. Xie, L. Ding, J. Gao, Z. Zhang, *Tetrahedron* **2011**, *67*, 9405; d) R. Surasani, D. Kalita, A. V. Dhanunjaya Rao, K. B. Chandrasekhar, *Beilstein J. Org. Chem.* **2012**, *8*, 2004.

[7] For recent reports, see: a) C. Jing, D. Xing, L. Gao, J. Li, W. Hu, *Chem. Eur. J.* **2015**, *21*, 19202 – 19207; b) S. M. Nicolle, W. Lewis, C. J. Hayes, C. J. Moody, *Angew. Chem. Int. Ed.* **2016**, *55*, 3749 – 3753; *Angew. Chem.* **2016**, *128*, 3813 – 3817; c) W. Li, Y. Duan, M. Zhang, J. Cheng, C. Zhu, *Chem. Commun.* **2016**, *52*, 7596 – 7599; d) I. Aparici, M. Guerola, C. Dialer, A. Simón-Fuentes, M. Sánchez-Roselló, C. del Pozo, S. Fustero, *Org. Lett.* **2015**, *17*, 5412 – 5415; e) J. J. Medvedev, O. S. Galkina, A. A. Klinkova, D. S. Giera, L. Hennig, C. Schneider, V. A. Nikolaev, *Org. Biomol. Chem.* **2015**, *13*, 2640 – 2651; f) C. Jing, D. Xing, Y. Qian, T. Shi, Y. Zhao, W. Hu, *Angew. Chem. Int. Ed.* **2013**, *52*, 9289 – 9292; *Angew. Chem.* **2013**, *125*, 9459 – 9462.

[8] For recents report of non-ammonium ylide-forming reaction of anilines in the presence of metal carbenoids, see: T.-S. Zhang, W.-J. Hao, N. N. Wang, G. Li, D.-F. Jiang, S.-J. Tu, B. Jiang, *Org. Lett.* **2016**, *18*, 3078 – 3081; S. Jia, D. Xing, D. Zhang, W. Hu, *Angew. Chem. Int. Ed.* **2014**, *53*, 13098 – 13101; *Angew. Chem.* **2014**, *126*, 13314 – 13317.

[9] A. Zaki, H. Fahim, *J. Chem. Soc.* **1942**, 270; H. A. Fahim, M. Galaby, *J. Chem. Soc.* **1950**, 3529.

[10] A. A. Cant, G. H. V. Bertrand, J. L. Henderson, L. Roberts, M. F. Greaney, *Angew. Chem. Int. Ed.* **2009**, *48*, 5199 – 5202; *Angew. Chem.* **2009**, *121*, 5301 – 5304; *idem. Angew. Chem. Int. Ed.* **2012**, *51*, 10214; *Angew. Chem.* **2012**, *124*, 10360.

[11] Y. Kobayashi, T. Kutsama, K. Morinaga, M. Fujita, Y. Hanzawa, *Chem. Pharm. Bull.* **1970**, *18*, 2489 – 2498.

[12] For reviews of the use of arynes in synthesis, see: a) S. S. Bhojgude, A. Bhunia, A. T. Biju, *Acc. Chem. Res.* **2016**, *49*, 1658 – 1670; b) A. Panossian, F. R. Leroux, *Chimia* **2016**, *70*, 43 – 47; c) Y. Zeng, J. Hu, *Synthesis* **2016**, *48*, 2137 – 2150; d) S. Yoshida, T. Hosoya, *Chem. Lett.* **2015**, *44*, 1450 – 1460; e) R. Karmakar, D. Lee, *Chem. Soc. Rev.* **2016**, *45*, 4459 – 4470; f) A. Bhunia, A. T. Biju, *Synlett* **2014**, *25*, 608 – 614; g) A. E. Goetz, N. K. Garg, *J. Org. Chem.* **2014**, *79*, 846 – 851; h) H. Yoshida, K. Takaki, *Synlett* **2012**, *23*, 1725 – 1732; i) H. Yoshida, K. Takaki, *Heterocycles* **2012**, *85*, 1333 – 1349; j) K. Okuma, *Heterocycles* **2012**, *85*, 515 – 544; k) P. M. Tadross, B. M. Stoltz, *Chem. Rev.* **2012**, *112*, 3550 – 3577; l) S. S. Bhojgude, A. T. Biju, *Angew. Chem. Int. Ed.* **2012**, *51*, 1520 – 1522; *Angew. Chem.* **2012**, *124*, 1550 – 1552; m) S. A. Worlikar, R. C. Larock, *Curr. Org. Chem.* **2011**, *15*, 3214 – 3232; n) T. L. Gilchrist, *Sci. Synth.* **2008**, *43*, 151 – 224; o) R. Sanz, *Org. Prep. Proced Int.* **2008**, *40*, 215 – 291.

[13] For recent reports of the use of arynes in synthesis, see: a) Y. Li, D. Qiu, R. Gu, J. Wang, J. Shi, Y. Li, *J. Am. Chem. Soc.* **2016**, *138*, 10814 – 10817; b) M. Pérez-Gómez, J.-A. García-López, *Angew. Chem. Int. Ed.* **2016**, *55*, 14389 – 14393; c) Y. Li, C. Mück-Lichtenfeld, A. Studer, *Angew. Chem. Int. Ed.* **2016**, *55*, 3254 – 3254; *Angew. Chem.* **2016**, *128*, 3310 – 3310; d) S. K. Sundalam, A. Nilova, T. L. Seidl, D. R. Stuart, *Angew. Chem. Int. Ed.* **2016**, *55*, 8431 – 8434; e) E. Gorobets, M. Parvez, D. J. Derksen, B. A. Keay, *Chem. Eur. J.* **2016**, *22*, 8479 – 8482; f) C. M. Holden, S. M. A. Sohel, M. F. Greaney, *Angew. Chem. Int. Ed.* **2016**, *55*, 2450 – 2453; *Angew. Chem.* **2016**, *128*, 2496 – 2499; g) J. Shi, D. Qiu, J. Wang, H. Xu, Y. Li, *J. Am. Chem. Soc.* **2015**, *137*, 5670 – 5673; h) P. J. Milner, T. Kinzel, Y. Zhang, S. L. Buchwald, *J. Am. Chem. Soc.* **2014**, *136*, 15757 – 15766; i) T. Truong, M. Mesgar, K. K. A. Le, O. Daugulis, *J. Am. Chem. Soc.* **2014**, *136*, 8568 – 8576; j) A. E. Goetz, A. L. Silberstein, M. A. Corsello, N. K. Garg, *J. Am. Chem. Soc.* **2014**, *136*, 3036 – 3039; k) Y. Dong, B. Liu, P. Chen, Q Liu, M. Wang, *Angew. Chem. Int. Ed.* **2014**, *53*, 3442 – 3446; *Angew. Chem.* **2014**, *126*, 3510 – 3514; l) S. Y. Yun, K.-P. Wang, N.-K. Lee, P. Mamidipalli, D. Lee, *J. Am. Chem. Soc.* **2013**, *135*, 4668 – 4671; n) D. A. Candito, D. Dobrovolsky, M. Lautens, *J. Am. Chem. Soc.* **2012**, *134*, 15572 – 15580; o) T. Truong, O. Daugulis, *J. Am. Chem. Soc.* **2011**, *133*, 4243 – 4245.

[14] See, for instance: A. F. Gasiecki, J. L. Cross, R. F. Henry, V. Gracias, S. W. Djuric, *Tetrahedron Lett.* **2008**, *49*, 6286 – 6288; B. Burns, B. Coates, S. J. Neeson, P. J. Stevenson, *Tetrahedron Lett.* **1990**, *31*, 4351 – 4354; S. J. Neeson, P. J. Stevenson, *Tetrahedron Lett.* **1988**, *29*, 3993 – 3996.

[15] W. D. Ollis, I. O. Sutherland, Y. Thebtaranonth, *J. Chem. Soc. Perkin Trans. 1* **1981**, 1953 – 1962.

[16] For seminal exemplars, see: a) A. Nash, A. Soheili, U. K. Tambar, *J. Am. Chem. Soc.* **2011**, *133*, 12956; b) A. Nash, A. Soheili, U. K. Tambar, *Org. Lett.* **2013**, *15*, 4770; c) A. Soheili, U. K. Tambar, *Org. Lett.* **2013**, *15*, 5138; d) R. W. Jemison, T. Laird, W. D. Ollis, I. O. Sutherland, *J. Chem. Soc. Perkin Trans. 1* **1980**, 1436 – 1449; R. W. Jemison, T. Laird, W. D. Ollis, I. O. Sutherland, *J. Chem. Soc. Perkin Trans. 1* **1980**, 1450 – 1457.

[17] For an example of an attempt to construct this motif, see: U. Sankar, C. V. S. Kumar, V. Subramanian, K. K. Balasubramanian, S. Mahalakshimi, *J. Org. Chem.* **2016**, *81*, 2340 – 2354.

[18] J. M. Medina, J. L. Mackey, N. K. Garg, K. N. Houk, *J. Am. Chem. Soc.* **2014**, *136*, 15798 – 15805; A. E. Goetz, S. M. Bronner, J. D. Cisneros, J. M. Melamed, R. S. Paton, K. N. Houk, N. K. Garg, *Angew. Chem. Int. Ed.* **2012**, *51*, 2758 – 2762; *Angew. Chem.* **2012**, *124*, 2812 – 2816.

[19] S. J. Stachel, T. G. Steele, A. Petrocchi, S. J. Haugabook, G. McGaughey, M. K. Holloway, T. Allison, S. Munshi, P. Zuck, D. Colussi, K. Tugasheva, A. Wolfe, S. L. Graham, J. P. Vacca, *Bioorg. Med. Chem. Lett.* **2012**, *22*, 240 – 244.

[20] Whilst this manuscript was in submission, two reports of aryne-induced [2,3]-sigmatropic rearrangement of acyclic allyl amines were published: a) T. Roy, M. Thangaraj, T. Kaicharla, R. V. Kamath, R. G. Gonnade, A. T. Biju, *Org. Lett.* **2016**, *18*, 5428 – 5431; b) J. Zhang, Z.-X. Chen, T. Du, B. Li, Y. Gu, S.-K. Tian, *Org. Lett.* **2016**, *18*, 4872 – 4875.

[21] Stereochemistry deduced from ^{1}H NMR spectra.

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