

Rearrangement

The Benzyne Aza-Claisen Reaction**

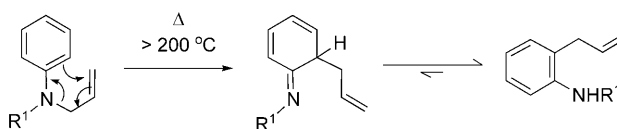
Alastair A. Cant, Guillaume H. V. Bertrand, Jaclyn L. Henderson, Lee Roberts, and Michael F. Greaney*

The aza-Claisen (or 3-aza-Cope) rearrangement of allylenamines is a powerful, atom-efficient method for the synthesis of functionalized amines.^[1] The scope of the reaction, however, has yet to be fully realized because of the forcing reaction conditions necessary to achieve rearrangement. Simple rearrangement of allylenamines requires very high reaction temperatures (> 200 °C) and is seldom used as a preparative method.^[2] Charge-accelerated aza-Claisen rearrangements, however, take place under milder reaction conditions and have been widely studied in terms of substrate range, stereocontrol, and application to the synthesis of complex molecules.^[3,4] The basic nitrogen atom provides the site for charge acceleration, usually through protonation, quaternization, or Lewis acid coordination. Even so, simple allylaniline aza-Claisen reactions require stoichiometric amounts of Lewis acids such as BF₃·OEt₂ and reaction temperatures well in excess of 100 °C (Scheme 1).^[5]

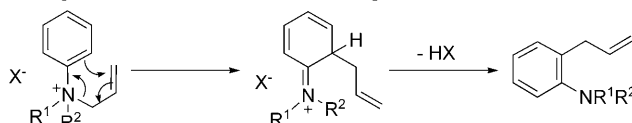
Our interest in aryne chemistry^[6] led us to speculate that the addition of benzyne to a tertiary allylamine could set up an aza-Claisen rearrangement pathway, thus creating a novel route to functionalized anilines. The electrophilic aryne would react rapidly with the nitrogen nucleophile to afford the zwitterion **2**. This key intermediate could undergo direct rearrangement through a 6-endo intramolecular S_N2' reaction to produce aniline **3** (path A). Alternatively, protonation of **2** by the solvent would afford the ammonium salt **4**, which could rearrange via the conventional charge-accelerated aza-Claisen pathway to produce the same aniline product **3** (path B). In one pot, we would take readily available tertiary allylamine and form one aryl C–N bond and one aryl C–C bond without recourse to metal catalysts or stoichiometric amounts of Lewis acid promoters.

Precedent for the addition of tertiary allylamine to benzyne can be found in seminal work from Wittig and Behnisch on the benzyne Diels–Alder (DA) reaction of pyrroles.^[7–9] When studying the DA reaction of *N*-methyl pyrroles with excess benzyne, Wittig isolated the novel

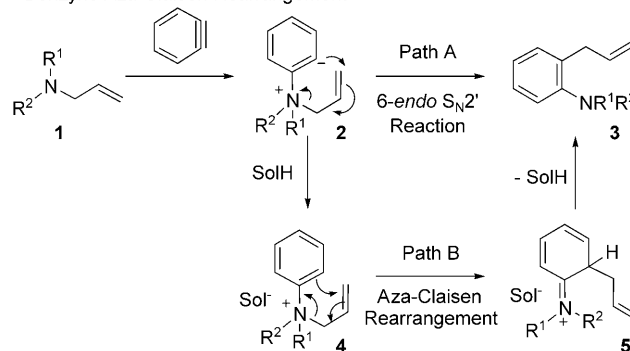
Aza-Claisen Rearrangement



Charge-accelerated Aza-Claisen Rearrangement

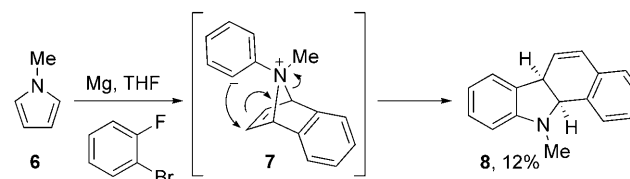


Benzyne Aza-Claisen Rearrangement



Scheme 1. The aza-Claisen rearrangement and proposed benzyne reaction. Sol = solvent.

benzocarbazole **8** in 12% yield (Scheme 2). Initial DA reaction and subsequent *N*-arylation gave the intermediate zwitterion **7**, which undergoes rearrangement in a manner



Scheme 2. Wittig's pyrrole Diels–Alder reaction and subsequent rearrangement. THF = tetrahydrofuran.

that is exactly analogous to path A in Scheme 1. Although the yield of the transformation was low, we were encouraged by this early precedent which accounts for three sequential reactions in one pot, and which was achieved in an era predating purification involving chromatographic methods.

We began our investigations into the aryne aza-Claisen rearrangement using benzyne precursor **9a**^[10] and *N*-allylpi-

[*] A. A. Cant, G. H. V. Bertrand, J. L. Henderson, Dr. M. F. Greaney
School of Chemistry, University of Edinburgh
King's Buildings, West Mains Road, Edinburgh, EH9 3JJ (UK)
Fax: (+44) 131-650-4743
E-mail: michael.greaney@ed.ac.uk

Dr. L. Roberts
Discovery Chemistry, Pfizer Global R&D, Sandwich (UK)

[**] We thank Pfizer, CRUK, and the University of Edinburgh for funding as well as the EPSRC mass spectrometry service at the University of Swansea. Jordi Rull and Fabien Ehret are thanked for preliminary work in the area.

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.200901410>.

peridine **10a** as substrates, with cesium fluoride used to generate the key aryne reactive intermediate. After a screen of the reaction solvents and temperatures, we were pleased to observe that heating in a toluene/acetonitrile mixture at 110 °C afforded the desired aza-Claisen product **11a** in an excellent 92 % yield (Table 1, entry 1). The reaction was

Table 1: Aryne aza-Claisen rearrangement using benzyne precursor **9a** and amines **10**.^[a] Tf = triflate, Tol = toluene.

Entry	Amine	Product	Yield [%] ^[b]
1			92
2			62
3 ^[c]			65
4			91
5			74
6 ^[d]			31

[a] Reaction conditions: *o*-trimethylsilylphenyl triflate (1 equiv), amine (1.5 equiv), and CsF (3 equiv) in toluene (0.75 mL) and MeCN (0.25 mL). Reactions were carried out on a 0.2 mmol scale and heated to 110 °C for 48 hours in a sealed tube. [b] Yield of isolated product. [c] Prestirred at room temperature for 24 hours. [d] Reaction was performed in DME at reflux.

viable for a range of simple tertiary allyl amines, with the morpholine, diethyl, and aniline derivatives **10b–d** undergoing smooth rearrangement in good to excellent yields (Table 1, entries 2–4). We examined a substituted allyl substrate with the cyclohexenyl amine **10e**, which afforded the tricyclic aniline **11e** in 74 % yield (Table 1, entry 5). The crotyl derivative **10f** likewise underwent successful rearrangement, albeit in low yield owing to significant deallylation taking place to produce *N*-phenylpiperidine (Table 1, entry 5). The methyl group did, however, act as a marker to prove that the reaction was taking place as envisioned in path A or B in

Scheme 1. Alternative mechanisms of allyl transfer corresponding to overall σ insertion could be discounted.^[11,12]

We next examined the scope of the reaction with respect to the aryne structure. Methylenedioxy benzyne and naphthyne derivatives were both good substrates, and produced the aza-Claisen products in 57 % and 79 % yield (Table 2,

Table 2: Investigation of the reaction scope with respect to the aryne **9**.^[a]

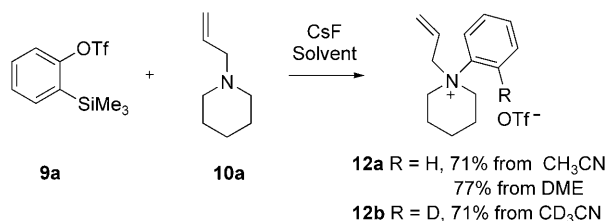
Entry	Aryne precursor	Product	Yield [%] ^[b]
1			57
2			79
3			76
4			79 ^[c]
5			40

[a] Reaction conditions: aryne precursor (1 equiv), 1-allylpiperidine (1.5 equiv), and CsF (3 equiv) in toluene (0.75 mL) and MeCN (0.25 mL). Reactions were carried out on a 0.2 mmol scale and heated at reflux for 48 hours in a sealed tube. [b] Yield of isolated product. [c] Products isolated as a 2.3:1 ratio of **11k**/**11k'**.

entries 1 and 2). The naphthyne substrate showed good regiocontrol, with the nucleophilic addition of amine occurring cleanly at the more sterically accessible β position. The electron-rich dimethoxy aryne substrate **9d** provided valuable insight into the mechanism of the benzyne aza-Claisen rearrangement (Table 2, entry 3). Whilst the Claisen product was isolated in good yield, the position of both allyl and amine groups was incommensurate with the position of the aryne triple bond. The regioselectivity of amine addition is exclusively distal to the methoxy group, as expected,^[13] but the subsequent rearrangement to the 1,2,4,5-tetrasubstituted arene **11j** indicates that the incipient anion is being quenched prior to aza-Claisen rearrangement (path B in Scheme 1).

Similar behavior was observed for the methoxyaryne substrate **9e**, which produced a mixture of aniline products **11k** and **11k'** in a ratio of 2.3:1 (Table 2, entry 4). The 2,3-pyridyne precursor **9f** was not viable in the reaction; initial nucleophilic addition of the amine was observed but the subsequent aza-Claisen rearrangement did not take place under the reaction conditions. Instead, deallylation occurred and a moderate yield of 2-(piperidin-1-yl)pyridine **11l** was isolated after 48 hours.

To shed further light on the aza-Claisen rearrangement/ S_N2' reaction dichotomy we examined the reaction of **9a** and **10a** at room temperature. Stirring the reaction for 24 hours in the presence of CsF and subsequent filtration, concentration, and chromatography afforded the triflate salt **12a** in 71% yield (Scheme 3). As suspected, the zwitterion **2** is being



Scheme 3. Salt formation from benzyne and tertiary allylamine. DME = 1,2-dimethoxyethane.

protonated by the acetonitrile component of the reaction solvent, which was verified by conducting the reaction in CD_3CN and observing deuterium incorporation in the salt **12b**. The triflate salt **12a** was productive in the aza-Claisen rearrangement, and produced high yields of aniline **11a** when heated under the established reaction conditions. Salt **12a** is likewise formed in non-acidic solvents such as DME, although subsequent aza-Claisen rearrangement in ethereal solvents was found to be less efficient.

We extended the benzyne aza-Claisen reaction to cyclic tertiary amines of the type **13** (Table 3). This strategy, which has been demonstrated for stable alkynes such as dimethylacetylene dicarboxylate,^[14] affords benzannulated medium-ring amines in a single step, and would complement published ring-closing metathesis (RCM) routes to these biologically active motifs.^[15] In the event, the proline derivatives **13a** and **b** were treated with benzyne precursor **9a** to successfully produce the corresponding nine-membered ring compounds **14a** and **b** in moderate yield (Table 3, entries 1 and 2). It was possible in the case of **13b** to start with the secondary amine and generate the tertiary amine in situ using two equivalents of benzyne precursor, which then rearranged to the *N*-phenyl benzazonine product **14b** in 40% overall yield.

Nicotinic acid precursors to ten-membered rings proved more recalcitrant substrates, with the *N*-benzyl substrate **13c** affording a 28% yield of benzazecine **14c** as a representative example (Table 3, entry 3). This inefficiency in the formation of ten-membered rings has also been observed in the RCM approach to benzazecines, with the *Z*-*N*-benzoyl analogue of

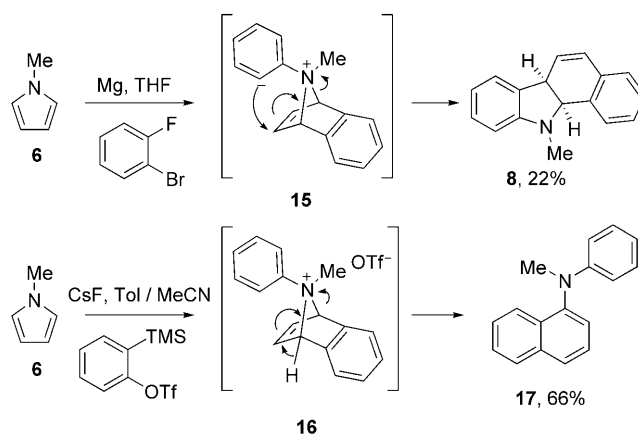
Table 3: Synthesis of medium-ring amines using the benzyne aza-Claisen rearrangement.^[a]

Entry	Amine	Product	Yield [%] ^[b]
1	13a	14a	41
2 ^[c]	13b	14b	40
3	13c	14c	28

[a] Reaction conditions: *o*-trimethylsilylphenyl triflate (1 equiv), amine (1.5 equiv), and CsF (3 equiv) in toluene (0.75 mL) and MeCN (0.25 mL). Reactions were carried out on a 0.2 mmol scale and were stirred for 24 hours at room temperature and then heated at reflux for 48 hours in a sealed tube. [b] Yield of isolated product. [c] 2 equivalents of *o*-trimethylsilylphenyl triflate to 1 equivalent of amine was used. Bn = benzyl.

14c being isolated in 17% yield after RCM with a reaction time of one week.^[15]

Finally, we were interested in reexamining Wittig's benzyne pyrrole DA system in light of our results on the aza-Claisen rearrangement. A repeat of Wittig's procedure using magnesium treatment of *o*-bromofluorobenzene as the benzyne source gave a complex product mixture from which the benzocarbazole product **8** could be isolated by column chromatography in 22% yield, along with a trace amount of the α -naphthylamine **17**.^[16] Repeating the reaction using the *O*-triflate silane method for benzyne generation developed by Kobayashi and co-workers^[10] unexpectedly produced the α -naphthylamine **17** in good yield (Scheme 4). The complete absence of any benzocarbazole product when using aryne precursor **9a** highlights the important role played by the reagents used to generate the aryne in the subsequent evolution of intermediates **15** and **16**. The increased basicity



Scheme 4. Diels-Alder benzyne aza-Claisen reaction.

of CsF relative to MgBrF in the latter reaction medium may promote the elimination from intermediate **16**; a full study of the reaction parameters that control this divergent behavior will form part of our future work in the area.

In conclusion, we have discovered a new benzyne aza-Claisen rearrangement of tertiary allylamines. The aryne simultaneously provides a π component for rearrangement as well as the quaternization event that enables the reaction to take place, thus affording a novel route to functionalized anilines.

Experimental Section

Synthesis of 1-(2-allylphenyl)piperidine **11a**: 2-(Trimethylsilyl)phenyl trifluoromethanesulfonate (90 mg, 0.30 mmol, 1 equiv) was then added to *N*-allylpiperidine (56 mg, 0.45 mmol, 1.5 equiv), cesium fluoride (137 mg, 0.9 mmol, 3 equiv), toluene (1.12 mL), and acetonitrile (0.38 mL) were placed in a sealed carousel tube under nitrogen. The reaction mixture was heated to 110 °C for 48 h. Filtration and concentration in vacuo gave a crude product that was purified by flash column chromatography on silica gel (hexanes, dry loaded) to afford **9a** (55 mg, 92%) as a colorless oil. ^1H NMR (360 MHz, CDCl_3): δ = 7.23–7.17 (2H, m), 7.08 (1H, dd, J = 1.3, 7.9 Hz), 7.03 (1H, dt, J = 1.3, 7.4 Hz), 6.01 (1H, tdd, J = 6.6, 10.0, 16.7 Hz), 5.16–5.07 (2H, m), 3.49 (2H, d, J = 6.6 Hz), 2.85–2.82 (4H, m), 1.75–1.69 (4H, m), 1.61–1.54 ppm (2H, m); ^{13}C NMR (90 MHz, CDCl_3): δ = 152.7 (Q), 138.0 (Q), 134.9 (CH), 129.8 (CH), 126.7 (CH), 123.1 (CH), 119.7 (CH), 115.4 (CH_2), 54.0 (2C, CH_2), 34.8 (CH_2), 26.5 (CH_2), 24.3 ppm (CH_2); IR (film): $\tilde{\nu}$ = 2933, 2853, 2800, 1489, 1450, 1226 cm^{-1} ; HRMS (EI^+) calc for $\text{C}_{14}\text{H}_{19}\text{N}$ ($[M]^+$): 201.15120; found: 201.15100.

Received: March 13, 2009

Revised: May 5, 2009

Published online: June 12, 2009

Keywords: allylamines · arynes · aza-Claisen rearrangement · medium-ring compounds

- [1] A. M. Martín Castro, *Chem. Rev.* **2004**, *104*, 2939–3002.
- [2] a) C. D. Hurd, W. W. Jenkins, *J. Org. Chem.* **1957**, *22*, 1418–1423; b) R. K. Hill, N. W. Gilman, *Tetrahedron Lett.* **1967**, *8*, 1421–1423.
- [3] U. Nubbemeyer, *Top. Curr. Chem.* **2005**, *244*, 149–213.
- [4] For recent examples of aza-Claisen rearrangements, see: a) K. L. Bridgwood, C. C. Tzschucke, M. O'Brien, S. Wittrock, J. M. Goodman, J. E. Davies, A. W. J. Logan, M. R. M. Huttl, S. V. Ley, *Org. Lett.* **2008**, *10*, 4537–4540; b) W. S. Bremner, M. G. Organ, *J. Comb. Chem.* **2008**, *10*, 142–147; c) F. M. Istrate, F. Gagosz, *Org. Lett.* **2007**, *9*, 3181–3184; d) A. Saito, A. Kanno, Y. Hanzawa, *Angew. Chem.* **2007**, *119*, 4005–4007; *Angew. Chem. Int. Ed.* **2007**, *46*, 3931–3933; e) J. Zhou, N. A. Magomedov, *J. Org. Chem.* **2007**, *72*, 3808–3815; f) D. Craig, N. P. King, D. M. Mountford, *Chem. Commun.* **2007**, 1077–1079; g) S. Yu, X. Pan, D. Ma, *Chem. Eur. J.* **2006**, *12*, 6572–6584; h) C. Kuhn, E. Roulland, J.-C. Madelmont, C. Monneret, J.-C. Florent, *Org. Biomol. Chem.* **2004**, *2*, 2028–2039; i) D. F. McComsey, B. E. Maryanoff, *J. Org. Chem.* **2000**, *65*, 4938–4943.
- [5] a) M. Alajarin, Á. Vidal, M.-M. Ortín, *Tetrahedron* **2005**, *61*, 7613–7621; b) A. Correa, I. Tellitu, E. Domínguez, R. SanMartín, *J. Org. Chem.* **2006**, *71*, 8316–8319; c) K.-T. Yip, M. Yang, K.-L. Law, N.-Y. Zhu, D. Yang, *J. Am. Chem. Soc.* **2006**, *128*, 3130–3131; d) S. Kotha, V. R. Shah, *Eur. J. Org. Chem.* **2008**, 1054–1064; e) I. Kiraly, G. Hornyanszky, K. Kupai, L. Novak, *Heterocycles* **2008**, *75*, 43–56.
- [6] a) J. L. Henderson, A. S. Edwards, M. F. Greaney, *Org. Lett.* **2007**, *9*, 5589–5592; b) J. L. Henderson, A. S. Edwards, M. F. Greaney, *J. Am. Chem. Soc.* **2006**, *128*, 7426–7427.
- [7] a) G. Wittig, W. Behnisch, *Chem. Ber.* **1958**, *91*, 2358–2365; b) G. Wittig, W. Behnisch, *Chem. Ber.* **1963**, *96*, 2851–2858.
- [8] See also: E. Wolthuis, W. Cady, R. Roon, B. Weidenaar, *J. Org. Chem.* **1966**, *31*, 2009–2011.
- [9] For other tertiary amine additions to arynes, see: a) A. R. Lepley, R. H. Becker, A. G. Giumanini, *J. Org. Chem.* **1971**, *36*, 1222–1227, and references therein; b) Y. Sato, T. Aoyama, H. Shirai, *J. Organomet. Chem.* **1974**, *82*, 21–27; c) J. P. N. Brewer, H. Heaney, S. V. Ley, T. J. Ward, *J. Chem. Soc. Perkin Trans. 1* **1974**, 2688–2693; d) Y. Sato, Y. Ban, T. Aoyama, H. Shirai, *J. Org. Chem.* **1976**, *41*, 1962–1965; e) Y. Sato, T. Toyooka, T. Aoyama, H. Shirai, *J. Org. Chem.* **1976**, *41*, 3559–3564.
- [10] Y. Himeshima, T. Sonoda, H. Kobayashi, *Chem. Lett.* **1983**, 1211–1214.
- [11] Review: D. Peña, D. Pérez, E. Guitián, *Angew. Chem.* **2006**, *118*, 3659–3661; *Angew. Chem. Int. Ed.* **2006**, *45*, 3579–3581.
- [12] For recent examples of σ -insertion reactions of arynes, see: a) S. Krishnan, J. T. Bagdanoff, D. C. Ebner, Y. K. Ramtohl, U. K. Tambar, B. M. Stoltz, *J. Am. Chem. Soc.* **2008**, *130*, 13745–13754; b) H. Yoshida, T. Kishida, M. Watanabe, J. Ohshita, *Chem. Commun.* **2008**, 5963–5965; c) H. Yoshida, T. Morishita, J. Ohshita, *Org. Lett.* **2008**, *10*, 3845–3847; d) C. Ni, L. Zhang, J. Hu, *J. Org. Chem.* **2008**, *73*, 5699–5713; e) T. Morishita, H. Fukushima, H. Yoshida, J. Ohshita, A. Kunai, *J. Org. Chem.* **2008**, *73*, 5452–5457; f) H. Yoshida, T. Morishita, H. Fukushima, J. Ohshita, A. Kunai, *Org. Lett.* **2007**, *9*, 3367–3370; g) H. Yoshida, Y. Mimura, J. Ohshita, A. Kunai, *Chem. Commun.* **2007**, 2405–2406; h) H. Yoshida, M. Watanabe, T. Morishita, J. Ohshita, A. Kunai, *Chem. Commun.* **2007**, 1505–1506; i) S. Beltran-Rodil, D. Peña, E. Guitián, *Synlett* **2007**, 1308–1310; j) F. T. Toledo, H. Marques, J. V. Comasseto, C. Raminelli, *Tetrahedron Lett.* **2007**, *48*, 8125–8127; k) H. Yoshida, H. Fukushima, J. Ohshita, A. Kunai, *J. Am. Chem. Soc.* **2006**, *128*, 11040–11041; l) M. Jeganmohan, C.-H. Cheng, *Chem. Commun.* **2006**, 2454–2456.
- [13] Z. Liu, R. C. Larock, *Org. Lett.* **2003**, *5*, 4673–4675.
- [14] a) M. H. Weston, K. Nakajima, M. Parvez, T. G. Back, *J. Org. Chem.* **2008**, *73*, 4630–4637; b) M. H. Weston, K. Nakajima, M. Parvez, T. G. Back, *Chem. Commun.* **2006**, 3903–3905; c) E. Vedejs, M. Gingras, *J. Am. Chem. Soc.* **1994**, *116*, 579–588; d) E. W. Baxter, D. Labaree, H. L. Ammon, P. S. Mariano, *J. Am. Chem. Soc.* **1990**, *112*, 7682–7692; e) A. L. Schwan, J. Warkentin, *Can. J. Chem.* **1988**, *66*, 1686–1694; f) K. A. Kandeel, J. M. Vernon, *J. Chem. Soc. Perkin Trans. 1* **1987**, 2023–2026; g) A. Hassner, R. D'Costa, A. T. McPhail, W. Butler, *Tetrahedron Lett.* **1981**, *22*, 3691–3694; for zwitterionic aza-Claisen ring expansion, see: h) A. Sudau, W. Muench, U. Nubbemeyer, J. W. Bats, *J. Org. Chem.* **2000**, *65*, 1710–1720; i) A. Sudau, U. Nubbemeyer, *Angew. Chem.* **1998**, *110*, 1178–1181; *Angew. Chem. Int. Ed.* **1998**, *37*, 1140–1143; j) M. Diederich, U. Nubbemeyer, *Angew. Chem.* **1995**, *107*, 1095–1098; *Angew. Chem. Int. Ed.* **1995**, *34*, 1026–1028.
- [15] M. Qadir, J. Cobb, P. W. Sheldrake, N. Whittall, A. J. P. White, K. K. (M.) Hii, P. N. Horton, M. B. Hursthouse, *J. Org. Chem.* **2005**, *70*, 1552–1557.
- [16] *N,N*-diphenyl- α -naphthylamine was reported as a side product (4%) of benzyne reaction with *N*-phenylpyrrole. See Ref. [7b].