Organic LETTERS

Letter

pubs.acs.org/OrgLett

The Aryne [2,3] Stevens Rearrangement

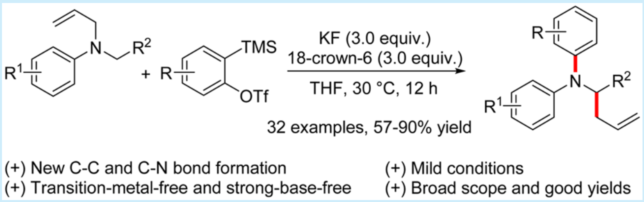
Tony Roy,[†,§] Manikandan Thangaraj,[†,§] Trinadh Kaicharla,[†,§] Rupa V. Kamath,[†] Rajesh G. Gonnade,[‡] and Akkattu T. Biju*[,†,§]

[†]Organic Chemistry Division, [‡]Centre for Materials Characterization, CSIR-National Chemical Laboratory (CSIR-NCL), Dr. Homi Bhabha Road, Pune 411008, India

[§]Academy of Scientific and Innovative Research (AcSIR), New Delhi 110020, India

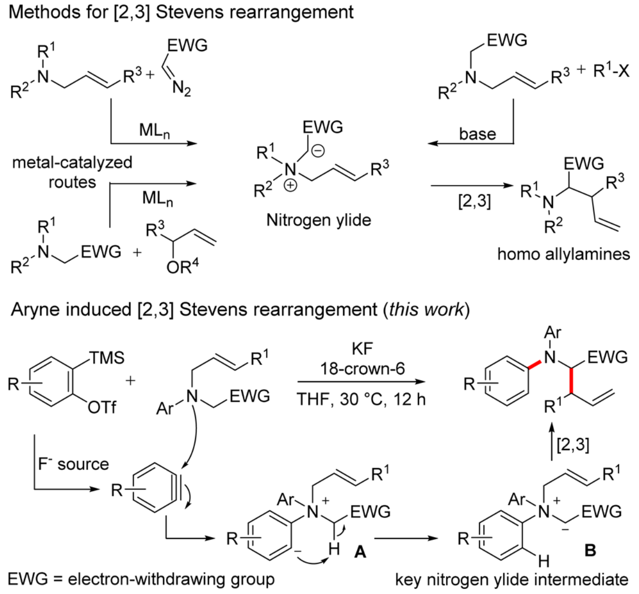
S *Supporting Information*

ABSTRACT: Arynes are employed in the transition-metal-free and mild [2,3] Stevens rearrangement of tertiary allylic amines for the synthesis of functionalized homoallylic amines in moderate to good yield with a broad substrate scope. The key nitrogen ylide intermediate was generated by the *N*-arylation of allyl amines using arynes. Moreover, the reaction of chiral allyl amines with arynes resulted in the enantiospecific synthesis of homoallylic amines. In addition, preliminary studies on the [1,2] Stevens rearrangement is also presented.



The Stevens rearrangement involves the conversion of ammonium/sulfonium salts into complex nitrogen/sulfur containing products, usually taking place in the presence of a strong base.[1,2] The reaction proceeds via either [1,2] or [2,3] sigmatropic rearrangement, and the key intermediate is a nitrogen ylide.[3] Traditionally, the nitrogen ylides for this rearrangement are generated from the corresponding ammonium salts (prepared from tertiary amines and alkyl halides) by treatment with a base (Scheme 1).[4] However, the harsh reaction conditions needed for the synthesis of many ammonium salt precursors and use of a strong base limit the broad application of this method.[5] Consequently, studies toward the mild and general methods for the [1,2], and [2,3] rearrangements are highly desirable. Transition-metal-catalyzed methods have been utilized for the generation of nitrogen ylides. The metal-catalyzed cross-coupling of tertiary allyl amines with diazoesters is a convenient method for the direct access to nitrogen ylides.[6] In 2011, the Tambar group demonstrated the Pd-catalyzed allylic amination strategy using tertiary amino esters and allyl carbonates for the nitrogen ylide generation, and the method was applied in a tandem ylide generation/[2,3] rearrangement.[7]

Scheme 1. [2,3] Stevens Rearrangement



In this context, we envisioned the generation of nitrogen ylide intermediates by the reaction of tertiary amino esters/ketones with arynes[8] followed by the [2,3] Stevens rearrangement for the synthesis of functionalized homoallylic amines. The addition of a tertiary amine to the aryne generated from the 2-(trimethylsilyl) aryl triflate[9] could generate the 1,3-zwitterionic intermediate **A**, which could undergo an intramolecular proton transfer to form the key nitrogen ylide intermediate **B**.[10] The ylide **B** could undergo a [2,3] Stevens rearrangement to afford the homoallylic amines (Scheme 1). Herein, we report the mild and transition-metal-free [2,3] Stevens rearrangement induced by arynes for the synthesis of functionalized homoallylic amines.[11] It may be noted in this context that the aryne induced [3,3] sigmatropic rearrangements of tertiary allyl amines for the synthesis of 2-allyl aniline derivatives are reported by Greaney and co-workers.[12,13]

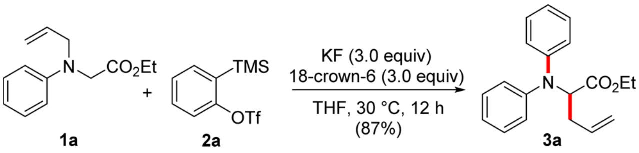
Inspired by our previous work on generating the nitrogen ylides from arynes and electron-deficient aziridines,[10a] the present study was commenced with the treatment of ethyl *N*-allyl-*N*-phenylglycinate **1a** with the aryne generated from the 2-

Received: September 18, 2016

DOI: 10.1021/acs.orglett.6b02809
Org. Lett. XXXX, XXX, XXX−XXX

(trimethylsilyl)aryl triflate precursor **2a**[9] using KF in the presence of an 18-crown-6 as additive in THF at 30 °C. To our delight, under these reaction conditions, the homoallylic amine **3a** derived from the [2,3] Stevens rearrangement of the initially generated nitrogen ylide was formed in 87% yield (Scheme 2).

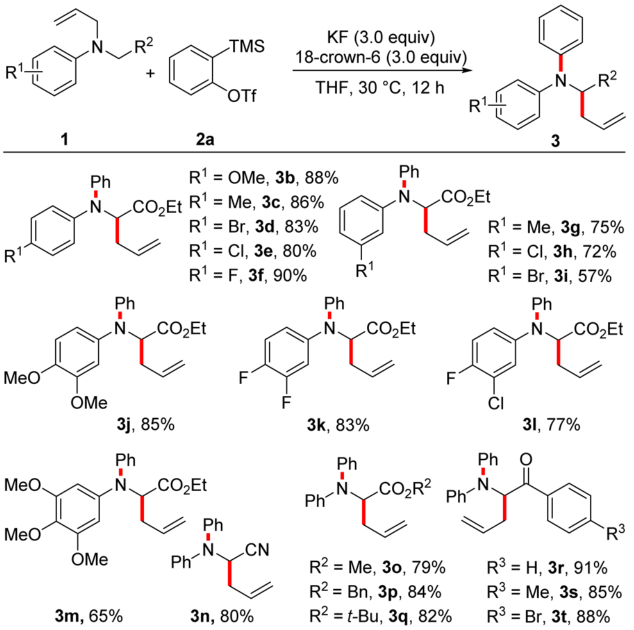
Scheme 2. Aryne Induced [2,3] Stevens Rearrangement



Notably, the aza-Claisen product reported by Greaney and coworkers was not formed under the present reaction conditions.[12] The use of CsF as the fluoride source (in CH_3CN as solvent) afforded **3a** in 68% yield only. The use of tetrabutyl ammonium fluoride (TBAF) resulted in a reduced yield of **3a**.

With the optimized reaction conditions in hand, we evaluated the scope of amines in this reaction (Scheme 3).[14]

Scheme 3. Scope of Amines in the Aryne Induced [2,3] Stevens Rearrangement[a]

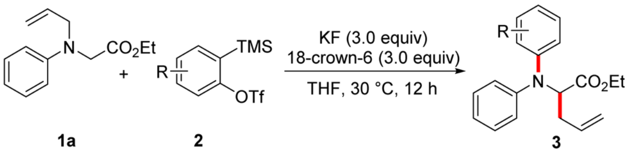


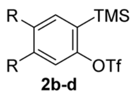
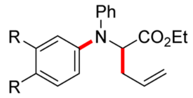
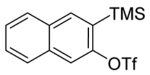
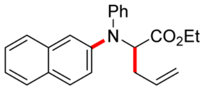
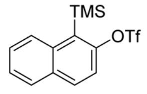
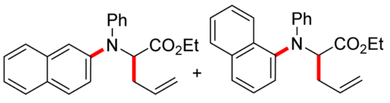
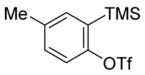
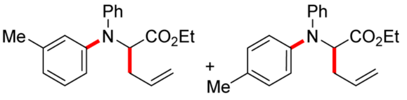
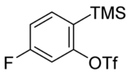
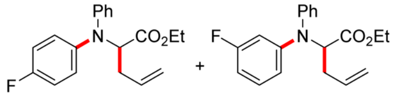
[a]General conditions: **1** (0.50 mmol), **2a** (0.75 mmol), KF (3.0 equiv), 18-crown-6 (3.0 equiv), THF (2.0 mL), 30 °C and 12 h. Yields of the isolated products are given.

Interestingly, various electronically different *para*-substituted allylic anilines underwent smooth rearrangement under the present reaction conditions to afford the *N*,*N*-diaryl homoallylic amines in good yields (**3b**–**3f**). Moreover, *meta*-substituted anilines were well tolerated furnishing the desired products in good yields (**3g**–**3i**). Disappointingly, *ortho*-substituted anilines afforded only traces of the expected product. Notably, various 3,4-disubstituted allylic anilines worked well under the present reaction conditions giving the rearranged products in good yields (**3j**–**3l**). It is noteworthy that the allylic amine derived from 3,4,5-trimethoxy aniline also afforded the desired product **3m** in 65% yield. When the electron-withdrawing ester group was replaced by a nitrile group, the reactivity was unaltered and the α-amino cyano compound **3n** was formed in 80% yield. In addition, different alkoxy carbonyl groups including methyl, benzyl, and *tert*-butyl as the electron-withdrawing group were well tolerated in this rearrangement reaction (**3o**–**3q**). Furthermore, use of differently substituted benzoyl groups as the electron-withdrawing group was feasible under the present conditions and the corresponding rearranged products are formed in good yields (**3r**–**3t**). In the case of compound **3r**, the structure was further confirmed by X-ray analysis.[15]

The feasibility of this [2,3] Stevens rearrangement was then examined with differently substituted arynes (Table 1).

Table 1. Variation of the Aryne Moiety[a]



entry	aryne precursor	product(s), yield (%)
1 2 3	 2b-d	 3u, R = Me, 79% 3v, R = $O(CH_2)O$, 73% 3w, R = F, 70%
4	 2e	 3x, 72%
5	 2f	 3x, 69%, (>20:1)[b] 3x'
6	 2g	 3y, 80%, (1:1)[b] 3y'
7	 2h	 3z, 78%, (2:1)[b] 3z'

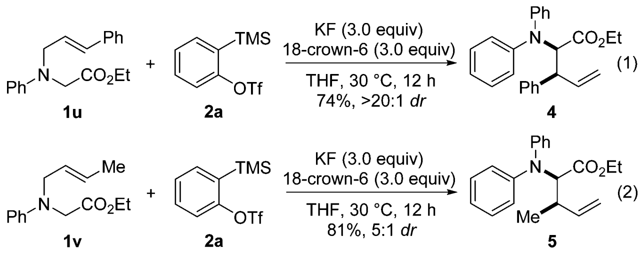
[a]General conditions: **1a** (0.50 mmol), **2** (0.75 mmol), KF (3.0 equiv), 18-crown-6 (3.0 equiv), THF (2.0 mL), 30 °C and 12 h. Yields of the isolated products are given. [b]The regioisomer ratio was determined by ^1H NMR analysis of crude reaction mixture.

Electronically dissimilar 4,5-disubstituted symmetrical arynes generated from the corresponding triflate precursors **2b**–**d** readily furnished the respective homoallylic amines in good yields (**3u**–**3w**). Moreover, the reaction of **1a** with symmetrical and unsymmetrical naphthalyne generated from the precursors **2e** and **2f** resulted in the formation of 2-naphthyl substituted homoallyl amine **3x** in good yield. In the case of unsymmetrical naphthalyne, **3x** was formed in high regioselectivity. In addition, the unsymmetrical 4-methyl aryne generated from **2g** afforded the mixture of regioisomers **3y** and **3y′** in 80% yield and a 1:1 ratio. Furthermore, the reaction of **1a** with 4-fluoroaryne resulted in the mixture of regioisomers **3z** and **3z′** in 78% yield and a 2:1 ratio thereby further expanding the scope of this aryne [2,3] rearrangement reaction.

Next, we examined the outcome of this rearrangement with allyl amines having a substituent at the allylic position.

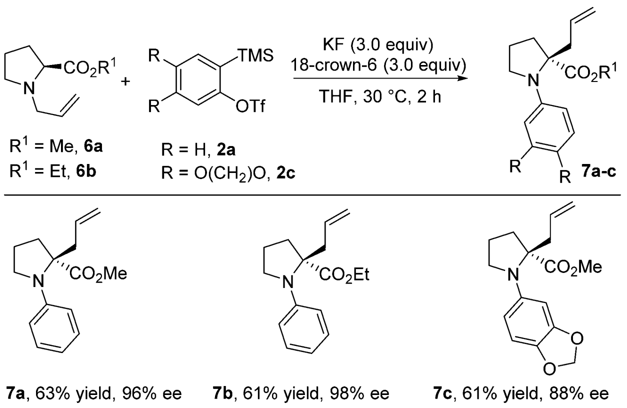
Gratifyingly, the reaction of arynes with the tertiary cinnamyl amine **1u** under the present conditions afforded the diastereoselective synthesis of functionalized homoallylic amine **4** in 74% yield and a >20:1 ratio (determined by ^{1}H NMR) for the *syn* isomer (Scheme 4, eq 1). Moreover, the reaction of an aryne with the crotyl substituted substrate **1v** resulted in the formation of the desired product **5** in 81% yield and 5:1 *dr* (eq 2).

Scheme 4. Aryne Induced Diastereoselective [2,3] Stevens Rearrangement



This aryne induced [2,3] rearrangement was also applied to enantiomerically pure proline-derived allyl amines. Treatment of the chiral methyl ester **6a** (>99% ee) with the aryne generated from **2a** under the optimized reaction conditions for 2 h resulted in the formation of the *N*-aryl proline derivative **7a** bearing a quaternary stereocenter in 63% yield and 96% ee (Scheme 5). The reaction proceeds via the retention of enantiopurity as well as the inversion of configuration.[16] It is noteworthy that the transfer of chirality from carbon to nitrogen (up on *N*-arylation of **6** using arynes) and then back to carbon (via the nitrogen ylide formation and subsequent [2,3] Stevens rearrangement) has been observed.[17] Moreover, the ethyl ester **6b** afforded the desired product **7b** in 61% yield and 98% ee. Additionally, 4,5-disubstituted aryne generated from the triflate precursor **2c** also afforded the corresponding proline derivative **7c** in 61% yield and 88% ee.

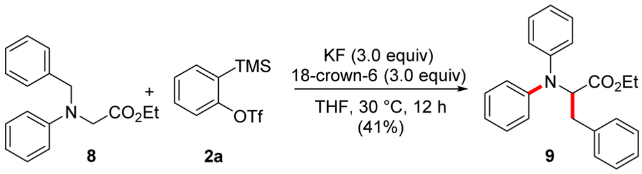
Scheme 5. Aryne Induced Enantiospecific [2,3] Stevens Rearrangement[a]



[a] General conditions: **6** (0.50 mmol), **2** (0.75 mmol), KF (3.0 equiv), 18-crown-6 (3.0 equiv), THF (2.0 mL), 30 °C, and 2 h. Yields of the isolated products are given, and the ee was determined by HPLC analysis on a chiral column.

We have also performed a preliminary study on the [1,2] Stevens rearrangement. Treatment of *N*-benzyl aniline derivative **8** with the aryne generated from **2a** using KF in the presence of 18-crown-6 as an additive in THF at 30 °C resulted in the formation of the functionalized tertiary amine **9** in 41% yield (Scheme 6). Increasing the concentration of aryne did not improve the yield of **9** under the present conditions. It is likely that the reaction proceeds via the initial generation of nitrogen ylide from aryne and **8**, which undergoes a [1,2] rearrangement to afford the desired product **9**.

Scheme 6. Aryne Induced [1,2] Stevens Rearrangement



In conclusion, we have developed a mild and transition-metal-free procedure for the [2,3] Stevens rearrangement induced by arynes for the synthesis of functionalized homoallylic amines. The reaction proceeds via the generation of the nitrogen ylide intermediate from arynes and tertiary allyl amines. A variety of tertiary allyl amines were well tolerated under the present reaction conditions. Formation of a new carbon−carbon and carbon−nitrogen bond under mild and strong-base-free reaction conditions, a broad substrate scope, and high yields of products are the notable features of the present reaction. The reaction of arynes with chiral allyl amines afforded chiral homoallylic amines with retention of enantiopurity and inversion in configuration. Further studies on related sigmatropic rearrangements induced by arynes are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02809.

Experimental procedures, characterization data of the products, copies of the ^{1}H and ^{13}C NMR spectra of products, and HPLC data (PDF)

Crystallographic data for compound **3r** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: at.biju@ncl.res.in.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support for this work has been generously provided by the CSIR-New Delhi (as part of the 12th Five-Year plan program under ORIGIN-CSC0108). T.R. thanks DST for an Inspire fellowship, and M.T. and T.K. thank CSIR for the research fellowships. We thank Mr. Santigopal Mondal for the HPLC analysis, Dr. P. R. Rajamohanan for the excellent NMR support, and Dr. B. Santhakumari (all CSIR-NCL) for the HRMS data.

■ REFERENCES

(1) Stevens, T. S.; Creighton, E. M.; Gordon, A. B.; MacNicol, M. *J. Chem. Soc.* **1928**, 3193.

(2) For reviews, see: (a) West, T. H.; Spoehrle, S. S. M.; Kasten, K.; Taylor, J. E.; Smith, A. D. *ACS Catal.* **2015**, *5*, 7446. (b) Bach, R.; Harthong, S.; Lacour, J. In *Comprehensive Organic Synthesis II*, 2nd ed.; Knochel, P., Ed.; Elsevier: Amsterdam, 2014; Vol. 3, pp 992−1037. (c) Lahm, G.; Pacheco, J. C. O.; Opatz, T. *Synthesis* **2014**, *46*, 2413. (d) Sweeney, J. B. *Chem. Soc. Rev.* **2009**, *38*, 1027. (e) Somfai, P.; Panknin, O. *Synlett* **2007**, 1190. (f) Vanecko, J. A.; Wan, H.; West, F. G. *Tetrahedron* **2006**, *62*, 1043. (g) Li, A.-H.; Dai, L.-X.; Aggarwal, V. K. *Chem. Rev.* **1997**, *97*, 2341.

(3) (a) Xu, B.; Tambar, U. K. *J. Am. Chem. Soc.* **2016**, *138*, 12073. (b) Biswas, B.; Collins, S. C.; Singleton, D. A. *J. Am. Chem. Soc.* **2014**, *136*, 3740.

(4) For selected reports, see: (a) West, T. H.; Daniels, D. S. B.; Slawin, A. M. Z.; Smith, A. D. *J. Am. Chem. Soc.* **2014**, *136*, 4476. (b) Gawley, R. E.; Moon, K. *Org. Lett.* **2007**, *9*, 3093. (c) Sweeney, J. B.; Tavassoli, A.; Workman, J. A. *Tetrahedron* **2006**, *62*, 11506. (d) Workman, J. A.; Garrido, N. P.; Sançon, J.; Roberts, E.; Wessel, H. P.; Sweeney, J. B. *J. Am. Chem. Soc.* **2005**, *127*, 1066. (e) Aggarwal, V. K.; Fang, G.-Y.; Charmant, J. P. H.; Meek, G. *Org. Lett.* **2003**, *5*, 1757. (f) Coldham, I.; Middleton, M. L.; Taylor, P. L. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2951. (g) Gulea-Purcarescu, M.; About-Jaudet, E.; Collignon, N.; Saquet, M.; Masson, S. *Tetrahedron* **1996**, *52*, 2075.

(5) For selected reports on Lewis acid mediated reports, see: (a) Everett, R. K.; Wolfe, J. P. *J. Org. Chem.* **2015**, *80*, 9041. (b) Blid, J.; Panknin, O.; Tuzina, P.; Somfai, P. *J. Org. Chem.* **2007**, *72*, 1294. (c) Blid, J.; Panknin, O.; Somfai, P. *J. Am. Chem. Soc.* **2005**, *127*, 9352. (d) Blid, J.; Brandt, P.; Somfai, P. *J. Org. Chem.* **2004**, *69*, 3043. (e) Coldham, I.; Middleton, M. L.; Taylor, P. L. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2817.

(6) For selected reports, see: (a) Honda, K.; Shibuya, H.; Yasui, H.; Hoshino, Y.; Inoue, S. *Bull. Chem. Soc. Jpn.* **2008**, *81*, 142. (b) Roberts, E.; Sançon, J. P.; Sweeney, J. B. *Org. Lett.* **2005**, *7*, 2075. (c) Zhou, C.-Y.; Yu, W.-Y.; Chan, P. W. H.; Che, C.-M. *J. Org. Chem.* **2004**, *69*, 7072. (d) Padwa, A.; Beall, L. S.; Eidell, C. K.; Worsencroft, K. J. *J. Org. Chem.* **2001**, *66*, 2414. (e) Doyle, M. P.; Tamblyn, W. H.; Bagheri, V. *J. Org. Chem.* **1981**, *46*, 5094.

(7) (a) Soheili, A.; Tambar, U. K. *J. Am. Chem. Soc.* **2011**, *133*, 12956. See also: (b) Nash, A.; Soheili, A.; Tambar, U. K. *Org. Lett.* **2013**, *15*, 4770. (c) Soheili, A.; Tambar, U. K. *Org. Lett.* **2013**, *15*, 5138.

(8) For recent reviews on arynes, see: (a) Dubrovskiy, A. V.; Markina, N. A.; Larock, R. C. *Org. Biomol. Chem.* **2013**, *11*, 191. (b) Wu, C.; Shi, F. *Asian J. Org. Chem.* **2013**, *2*, 116. (c) Pérez, D.; Peña, D.; Guitián, E. *Eur. J. Org. Chem.* **2013**, 5981. (d) Tadross, P. M.; Stoltz, B. M. *Chem. Rev.* **2012**, *112*, 3550. (e) Gampe, C. M.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2012**, *51*, 3766. (f) Bhunia, A.; Yetra, S. R.; Biju, A. T. *Chem. Soc. Rev.* **2012**, *41*, 3140. (g) Okuma, K. *Heterocycles* **2012**, *85*, 515. (h) Bhojgude, S. S.; Biju, A. T. *Angew. Chem., Int. Ed.* **2012**, *51*, 1520. (i) Yoshida, H.; Ohshita, J.; Kunai, A. *Bull. Chem. Soc. Jpn.* **2010**, *83*, 199. For a review on hetarynes, see: (j) Goetz, A. E.; Shah, T. K.; Garg, N. K. *Chem. Commun.* **2015**, *51*, 34. For a recent account, see: (k) Bhojgude, S. S.; Bhunia, A.; Biju, A. T. *Acc. Chem. Res.* **2016**, *49*, 1658.

(9) (a) Himeshima, Y.; Sonoda, T.; Kobayashi, H. *Chem. Lett.* **1983**, *12*, 1211. See also: (b) Peña, D.; Cobas, A.; Pérez, D.; Guitián, E. *Synthesis* **2002**, 1454.

(10) For reports on generation on nitrogen ylides using arynes, see: (a) Roy, T.; Thangaraj, M.; Gonnade, R. G.; Biju, A. T. *Chem. Commun.* **2016**, *52*, 9044. (b) Swain, S. P.; Shih, Y.-C.; Tsay, S.-C.; Jacob, J.; Lin, C.-C.; Hwang, K. C.; Horng, J.-C.; Hwu, J. R. *Angew. Chem., Int. Ed.* **2015**, *54*, 9926.

(11) While this manuscript was under preparation, Gu, Tian and co-workers reported a closely related aryne-mediated [2,3] sigmatropic rearrangement. For details, see: Zhang, J.; Chen, Z.-X.; Du, T.; Li, B.; Gu, Y.; Tian, S.-K. *Org. Lett.* **2016**, *18*, 4872.

(12) Cant, A. A.; Bertrand, G. H. V.; Henderson, J. L.; Roberts, L.; Greaney, M. F. *Angew. Chem., Int. Ed.* **2009**, *48*, 5199.

(13) For related aryne reactions triggered by tertiary amines proceeding via Smiles rearrangement, see: (a) Holden, C. M.; Sohel, S. M. A.; Greaney, M. F. *Angew. Chem., Int. Ed.* **2016**, *55*, 2450. (b) Bhojgude, S. S.; Baviskar, D. R.; Gonnade, R. G.; Biju, A. T. *Org. Lett.* **2015**, *17*, 6270. For related reports from our group, see: (c) Roy, T.; Bhojgude, S. S.; Kaicharla, T.; Thangaraj, M.; Garai, B.; Biju, A. T. *Org. Chem. Front.* **2016**, *3*, 71. (c1) Roy, T.; Baviskar, D. R.; Biju, A. T. *J. Org. Chem.* **2015**, *80*, 11131. (d) Bhojgude, S. S.; Kaicharla, T.; Biju, A. T. *Org. Lett.* **2013**, *15*, 5452.

(14) For details, see the Supporting Information

(15) CCDC 1504535 (**3r**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(16) For reports on retention of enantiopurity and inversion of configuration in related [2,3] rearrangement involving proline derivatives, see: (a) Arboré, A. P. A.; Cane-Honeysett, D. J.; Coldham, I.; Middleton, M. L. *Synlett* **2000**, 236. (b) Glaeske, K. W.; West, F. G. *Org. Lett.* **1999**, *1*, 31. (c) Gawley, R. E.; Zhang, Q.; Campagna, S. *J. Am. Chem. Soc.* **1995**, *117*, 11817.

(17) Seebach, D.; Boes, M.; Naef, R.; Schweizer, W. B. *J. Am. Chem. Soc.* **1983**, *105*, 5390.