How to cite: *Angew. Chem. Int. Ed.* **2021**, *60*, 21708–21712
International Edition: doi.org/10.1002/anie.202107898
German Edition: doi.org/10.1002/ange.202107898

C–H Functionalization

Asymmetric Synthesis of Enantiopure Pyrrolidines by C(sp^3)–H Amination of Hydrocarbons

Yanis Lazib, Pascal Retailleau, Tanguy Saget, Benjamin Darses,* and Philippe Dauban**

In memory of Viktor Snieckus

Abstract: *The asymmetric synthesis of enantiopure pyrrolidines is reported via a streamlined strategy relying on two sequential C–H functionalizations of simple hydrocarbons. The first step is a regio- and stereoselective catalytic nitrene C–H insertion. Then, a subsequent diastereoselective cyclization involving a 1,5-hydrogen atom transfer (HAT) from a N-centered radical leads to the formation of pyrrolidines that can then be converted to their free NH-derivatives.*

Pyrrolidines are synthetic targets of choice for organic chemists.[1] 2,5-Substituted derivatives, particularly, are important motifs with relevant applications in many areas of chemistry. In addition to be at the core of the recently approved antiviral Ombistavir **1** (Figure 1),[2] they are privileged scaffolds in asymmetric catalysis. For example, they have been used as C_2-symmetrical ligands for metal complexes **2**,[3] organocatalysts **3**,[4] or chiral auxiliaries **4**.[5] This paramount importance has translated to the design of innovative methods for the synthesis of pyrrolidines,[6] including stereoselective methods based on enantioselective functional group transformations.[7,8]

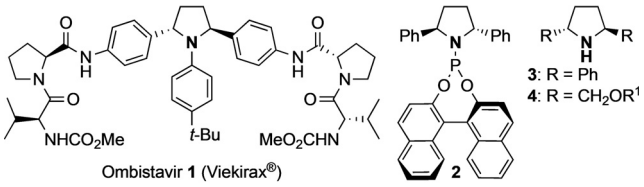
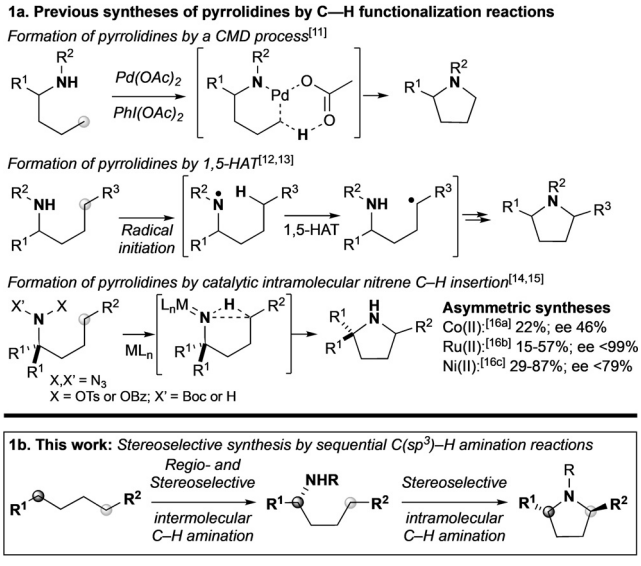


Figure 1. Relevant examples of 2,5-substituted pyrrolidines.

The emergence of catalytic C–H functionalization reactions in the last twenty years has revolutionized the art of retrosynthesis. C–H bonds are now considered as functional groups that allow the conception of efficient synthetic strategies with improved step- and atom-economy.[9] This new paradigm in organic synthesis has found applications in heterocyclic chemistry with the use of new bond disconnections for the synthesis of nitrogen heterocycles.[10] With respect of pyrrolidines, three main strategies have been developed for their preparation (Scheme 1 a). Daugulis and Chen first reported the application of C–H activation reactions to the formation of pyrrolidines. The latter involves a catalytic C–H/N–H coupling via a concerted metallation–deprotonation process that mainly occurs at primary C–H bonds.[11] Inspired by the Hofmann–Löffler–Freytag reaction,[12] stoichiometric approaches relying on intramolecular H-atom transfer have been designed. Because the 1,5-pathway is highly favored, the formation of pyrrolidines via the intermediacy of *N*-centered radicals is often exclusively observed.[13] The last strategy is based on metal-catalyzed intramolecular C(sp^3)–H insertion of nitrenes generated from either azides[14] or hydroxylamine derivatives.[15] Contrary to the other approaches, enantioselective versions of these nitrene transfers have recently been reported.[16] These are rare examples of asymmetric pyrrolidines syntheses via a C–



Scheme 1. C–H functionalization reactions for the syntheses of pyrrolidines.

[*] Y. Lazib, Dr. P. Retailleau, Dr. T. Saget, Dr. B. Darses, Dr. P. Dauban
Université Paris-Saclay, CNRS, Institut de Chimie des Substances Naturelles, UPR 2301
Av. de la Terrasse, 91198 Gif-sur-Yvette (France)
E-mail: tanguy.saget@cnrs.fr
benjamin.darses@univ-grenoble-alpes.fr
philippe.dauban@cnrs.fr
Dr. B. Darses
Université Grenoble Alpes, Département de Chimie Moléculaire, CNRS UMR-5250
38058 Grenoble (France)
E-mail: benjamin.darses@univ-grenoble-alpes.fr
Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under: https://doi.org/10.1002/anie.202107898.

H activation process that, however, display limitations in terms of yield[16b] or enantioselectivity.[16a,c]

With the aim to develop an efficient access to substituted pyrrolidines, we envisioned the design of a novel strategy that would preclude the presence of a pre-installed nitrogen function. Thus, we wondered whether enantiopure pyrrolidines could be accessible from simple hydrocarbons via a streamlined two-step sequence. The latter consists in an asymmetric regioselective intermolecular nitrene C(sp^3)–H insertion with an enantiopure sulfonimidamide as a chiral auxiliary, followed by a diastereoselective cyclization involving a 1,5-HAT (Scheme 1b). In this manuscript, we wish to report the results of our studies.[17]

The first step of our approach relies on a catalytic intermolecular C(sp^3)–H amination reaction mediated by iodine(III) oxidants.[18] Several methods have been developed to this end, but the use of rhodium(II) complexes in combination with sulfamates generally affords the best conversion in intermolecular C–H amination.[19] However, their application to 1,4-diarylbutane derivatives did not prove efficient both in terms of yields and selectivity (see Scheme S1, supporting information). Far more efficient was the stereoselective version developed with sulfonimidamides (Figure 2).[20] Whereas the method has been applied mostly to ethylarene derivatives so far,[21] we were pleased to obtain the expected products from various complex substrates generally formed as single stereoisomers (See Table S1, supporting information).

The reaction was first applied to symmetrical derivatives **7a–e**. The yields in the 40–99% range underscore the influence of electronic factors on the course of the reaction. We capitalized on this observation to perform the regioselective functionalization of non-symmetrical analogs. The differentiation of both aromatic rings via the introduction of electron-donating or -withdrawing substituents led to selectively functionalize a single benzylic site. Accordingly, compounds **7i–k** were converted in high yields (78–84%) and excellent levels of regio- and stereocontrol. Moreover, similar results were obtained with substrates **7f–h** for which steric factors—the presence of an *ortho*-substituent—are responsible for the complete regioselectivity.[21] It is noteworthy that the reaction also efficiently applies to various butyl or hexyl derivatives (products **8l**,**m**) as well as to simple alkanes (**8o** and **8p**). In the end, the stereoselective intermolecular C(sp^3)-H functionalization afforded >15 different precursors awaiting the second amination step to deliver enantiopure pyrrolidines.

Initial tests of cyclization from product **8a** relied on light irradiation-based protocols reported by Suárez,[22] Muñiz,[13a] and Nagib.[13f] However, they only gave 1:1 mixtures of *cis:trans* pyrrolidine **9a** isolated in ≈20% yield in the presence of stoichiometric amounts of iodine sources. By contrast, the thermal conditions described by Nagib[13f] proved more efficient as **9a** was isolated in 58% yield but with a low d.r. of 1.2:1 (entry 1, Table 1). Optimization of the conditions was envisaged with the aim to address the issue of diastereoselectivity, since diastereoselective Hofmann-Löffler-Freytag reactions are still rare in the literature.

A screening of solvents (See Table S2, supporting information) revealed that the best yields were obtained in aromatic solvents and toluene was selected for the rest of the study (entry 2). We then investigated the influence of the hypervalent iodine reagent on the cyclization outcome.[23] Several iodine(III) oxidants prepared from various iodoarene precursors or having different carboxylate ligands were tested (See Table S3, supporting information). The use of the reagent derived from 3-chloro-1-iodobenzene and having *m*CBA ligands (*m*CBA: *meta*-chlorobenzoate) led us to isolate compound **9a** with a higher d.r. of 4.6:1 while preserving a good reactivity (entry 3). A similar observation was then made after the screening of the iodide source (See Table S4, supporting information). Indeed, we found that the stereoselectivity of the iodine-mediated cyclization was boosted in the presence of silver(I) iodide. The pyrrolidine **9a** was obtained with a d.r. of 8:1 albeit with a lower yield of 30% (entry 4). Finally, optimal conditions were obtained by

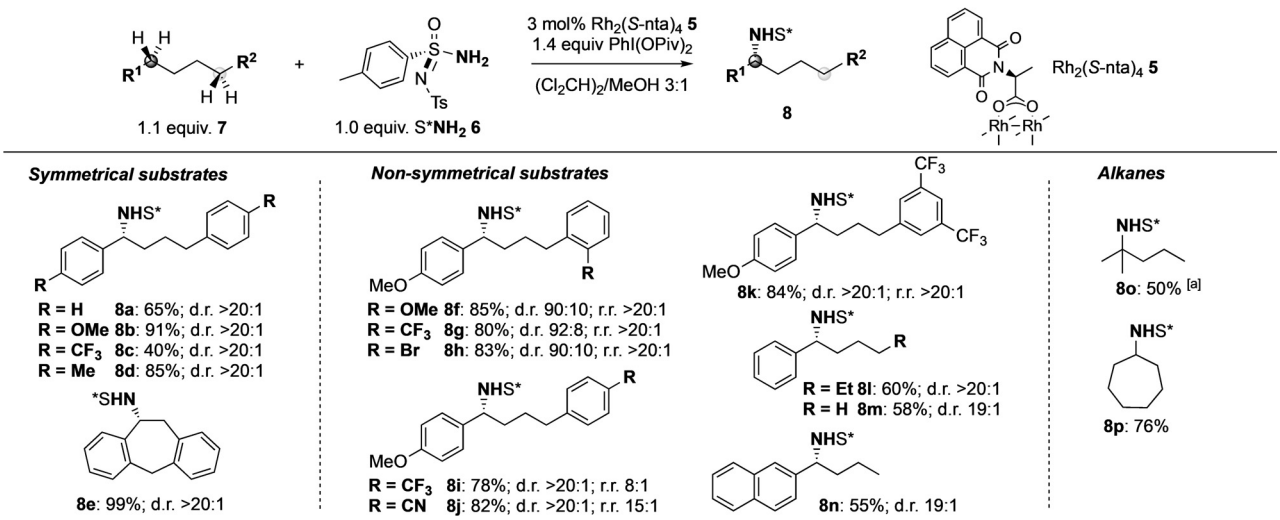
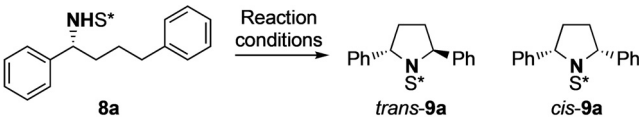


Figure 2. Regio- and stereoselective intermolecular C(sp^3)–H amination of hydrocarbons; d.r. and r.r. are reported for isolated compounds. [a] 5.0 equiv of substrate.

Table 1: Screening of conditions for the stereoselective cyclization.[a]



Entry	Iodine source (equiv)	Hypervalent iodine (equiv)	Solvent	Yield[b]	d.r.[c]
1	NaI (4.0)	$PhI(OAc)_2$ (4.0)	MeCN	58	1.2:1
2	NaI (4.0)	$PhI(OAc)_2$ (4.0)	Toluene	75	2:1
3	NaI (4.0)	3-ClC_6H_4I(*m*CBA)$_2$ (4.0)	Toluene	76	4.6:1
4	AgI (4.0)	3-ClC_6H_4I(*m*CBA)$_2$ (4.0)	Toluene	30	8:1
5[d]	AgI (4.0)	3-ClC_6H_4I(*m*CBA)$_2$ (4.0)	Toluene	61	8:1
6[d]	AgI (4.3)	3-ClC_6H_4I(*m*CBA)$_2$ (4.3)	Toluene	65	8:1
7[d,e]	**AgI (4.3)**	**3-ClC_6H_4I(*m*CBA)$_2$ (4.3)**	**Toluene**	**71**	**8:1**
8[d,e]	AgI (5.0)	3-ClC_6H_4I(*m*CBA)$_2$ (5.0)	Toluene	72	8:1
9[d,e]	AgI (3.0)	3-ClC_6H_4I(*m*CBA)$_2$ (5.0)	Toluene	46	7.5:1
7[d,e]	AgI (4.3)	3-ClC_6H_4I(*m*CBA)$_2$ (3.0)	Toluene	39	7:1

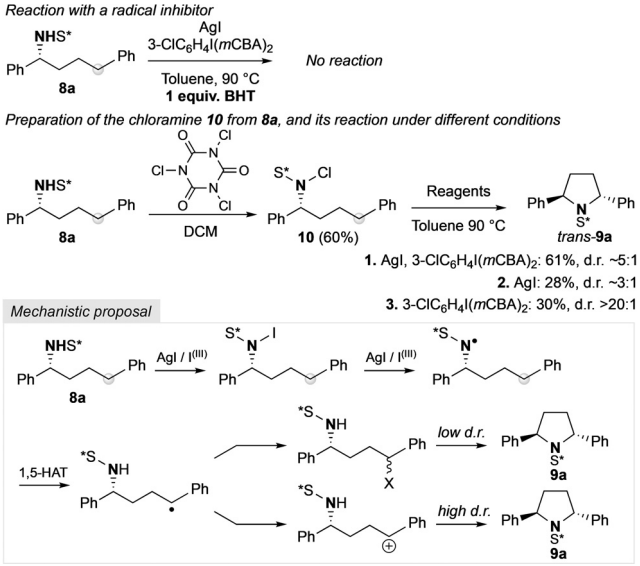
[a] Reaction conditions: A mixture of **8a** (0.10 mmol), iodine source and hypervalent iodine reagent in toluene is stirred (1 mL) at 65 °C for 48–72 h. [b] After flash chromatography. [c] Determined by ^{1}H NMR of crude reaction mixture. [d] Run at 90 °C. [e] $c = 0.05$ M.

increasing the temperature (90 °C, entry 5), tuning the amount of hypervalent iodine reagent and silver iodide to 4.3 equiv (entry 6 vs. entries 8–10), and working at a higher dilution ($c = 0.05$ M, entry 7).

These conditions were then successfully applied to all the compounds depicted in Figure 2 to deliver the corresponding pyrrolidines **9a–p** with good d.r. (Figure 3). Importantly, the *trans* and *cis* isomers, in the relevant cases, were separated and isolated as enantiopure products after chromatography on silica gel, the *trans* derivative being always predominantly formed with yields ranging from 41% to 70%. This was corroborated by careful NMR experiments, and by the X-ray structures of the *trans*-products **9f** and **9j**.

Importantly, this sequence of two consecutive stereoselective C(sp^3)–H amination reactions led us to synthesize a variety of new 2,5-disubstituted pyrrolidines for which the preparative methods are scarce. These methods rely on the lengthy elaboration of 1,4-dicarbonyl compounds,[24] the derivatization of pyroglutamic acid,[25] or the direct functionalization of preformed pyrrolidines.[26] Also worth of mention are the bridged nitrogen heterocycles **9e** and **9p** accessible in two steps from dibenzosuberane and cycloheptane, which are simplified analogues of the NMDA receptor antagonist MK-801 and tropane alkaloids, respectively. Finally, compound **9o** highlights that a simple alkane such as 2-methylpentane can be used as starting materials for the synthesis of heterocycles.

Several test experiments were performed to investigate the mechanism of the intramolecular C(sp^3)–H amination reaction of amides **8** (Scheme 2). First, the starting material was recovered unreacted in the presence of the radical inhibitor BHT, a result that supports the involvement of a radical pathway. Then, we studied the reactivity of haloamines that are generated in the reaction.[13] Because *N*-iodoamides are too unstable to be isolated, we decided to



Scheme 2. Mechanistic investigations.

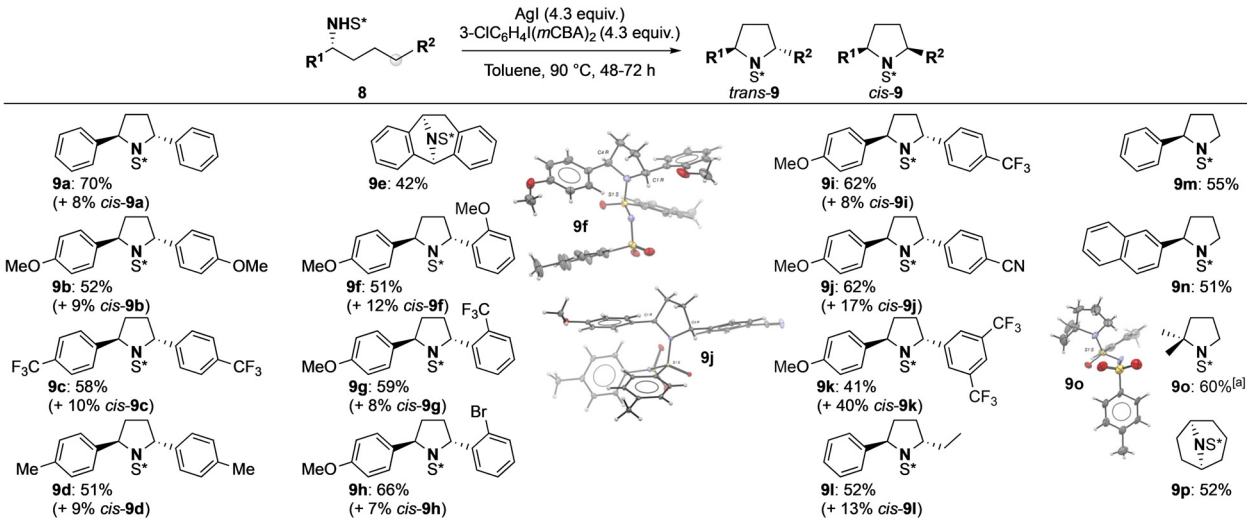
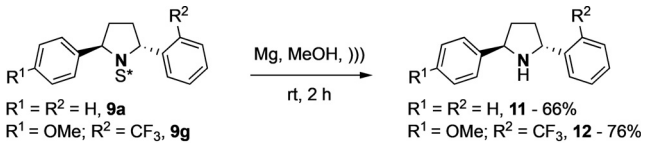


Figure 3. Stereoselective intramolecular C(sp^3)–H amination for the formation of pyrrolidines. [a] AgI was replaced by CuI.

prepare the analogous chloroamine **10** that could be obtained from **8a** by reaction with trichloroisocyanuric acid. Pleasingly, compound **10** was transformed to the expected pyrrolidine **9a** in good yield by combining AgI with 3-$ClC_6H_4I(mCBA)_2$ in toluene at 90 °C. Additional experiments revealed that moderate conversions and lower yields are obtained in the sole presence of AgI or the hypervalent iodine reagent. These results clearly highlight a synergistic effect of both reagents on the efficiency of the overall process. Surprisingly, the reaction with the hypervalent iodine reagent alone afforded the *trans* isomer with full selectivity, whereas a much lower d.r. was obtained in its absence. These significant changes in the diastereoselectivity depending on the conditions suggest that several competing mechanisms might operate during the cyclization. These observations led to a mechanistic proposal that involves the initial formation of a *N*-centered radical from the iodoamine, followed by a 1,5-Hydrogen Atom Transfer. From the resulting benzylic radical, two scenarios could operate. It could be trapped to afford the corresponding iodide. Then, a stereospecific S_N2-type cyclization would deliver the pyrrolidine **9a** with a low d.r. because the trapping of the benzylic radical remote from the stereogenic center is expected to proceed with a low diastereocontrol. Alternatively, the radical could be oxidized by the hypervalent iodine reagent to a carbocation that could undergo a S_N1-type cyclization proceeding with high diastereocontrol.[27] Thus, the overall d.r. would be the result of the simultaneous occurrence of both mechanisms for the cyclization, and the use of highly soluble 3-$ClC_6H_4I(mCBA)_2$ is key to achieve good selectivity.[28]

Final experiments were aimed at removing the sulfonimidoyl group to isolate the free *NH*-pyrrolidines (Scheme 3). Use of magnesium in dry methanol under sonication allowed us to isolate pyrrolidines **11** and **12** in 66 % and 76 % yields, respectively.[29]



Scheme 3. Deprotection of the *N*-(sulfonimidoyl)pyrrolidines.

In conclusion, chiral disubstituted pyrrolidines are accessible in only two steps in an enantiopure form from simple hydrocarbons used as the limiting component.[30] The strategy relies on two consecutive C(sp^3)–H amination reactions involving a catalytic stereoselective nitrene insertion then a diastereoselective HLF-type cyclization. Worthy of note is the straightforward access to non-symmetrical disubstituted products that could provide new scaffolds for the design of chiral organocatalysts or organometallic complexes. This sequence was ultimately applied to alkanes making these broadly available compounds useful building blocks for the synthesis of heterocycles. Work is in progress to investigate application of our strategy to the synthesis of new pyrrolidines as useful tools in catalysis.

Acknowledgements

We wish to thank the French National Research Agency (program no ANR-11-IDEX-0003-02 and CHARMMMAT ANR-11-LABX-0039; fellowship to Y.L.), the COMUE Université Paris-Saclay (program IDEX Paris/Saclay CDE-2018–002093; fellowship to Y.L.), and the ICSN for their support.

Conflict of Interest

The authors declare no conflict of interest.

Keywords: C–H amination · haloamine · nitrene · pyrrolidine · stereoselectivity

[1] Pyrrolidines belong to the top 5 most frequent nitrogen heterocycles in the U.S. FDA approved drugs. E. Vitaku, D. T. Smith, J. T. Njardarson, *J. Med. Chem.* **2014**, *57*, 10257.
[2] J. J. Feld, K. V. Kowdley, E. Coakley, S. Sigal, D. R. Nelson, D. Crawford, O. Weiland, H. Aguilar, J. Xiong, T. Pilot-Matias, B. DaSilva-Tillmann, L. Larsen, T. Podsadecki, B. Bernstein, *N. Engl. J. Med.* **2014**, *370*, 1594.
[3] a) Y. H. Choi, J. Y. Choi, H. Y. Yang, Y. H. Kim, *Tetrahedron: Asymmetry* **2002**, *13*, 801; b) M. Fañanás-Mastral, M. Pérez, P. H. Bos, A. Rudolph, S. R. Harutyunyan, B. L. Feringa, *Angew. Chem. Int. Ed.* **2012**, *51*, 1922; *Angew. Chem.* **2012**, *124*, 1958.
[4] E. K. Kemppainen, G. Sahoo, A. Piisola, A. Hamza, B. Kotai, I. Papai, P. M. Pikho, *Chem. Eur. J.* **2014**, *20*, 5983.
[5] J. K. Whitesell, *Chem. Rev.* **1989**, *89*, 1581.
[6] S. Lee, H. Lei, T. Rovis, *J. Am. Chem. Soc.* **2019**, *141*, 12536. See reference [3].
[7] P.-Q. Huang in *Asymmetric Synthesis of Nitrogen Heterocycles* (Ed.: J. Royer), Wiley-VCH, Weinheim, **2009**, pp. 51 – 94.
[8] For some recent asymmetric strategies, see: a) K. R. Campos, A. Klapars, J. H. Waldman, P. G. Dormer, C. Y. Chen, *J. Am. Chem. Soc.* **2006**, *128*, 3538; b) G.-H. Hou, J.-H. Xie, P.-C. Yan, Q.-L. Zhou, *J. Am. Chem. Soc.* **2009**, *131*, 1366; c) B. M. Trost, S. M. Silverman, *J. Am. Chem. Soc.* **2012**, *134*, 4941; d) A. R. Brown, C. Uyeda, C. A. Brotherton, E. N. Jacobsen, *J. Am. Chem. Soc.* **2013**, *135*, 6747; e) M. Jäkel, J. Qu, T. Schnitzer, G. Helmchen, *Chem. Eur. J.* **2013**, *19*, 16746; f) X.-J. Dai, O. D. Engl, T. Léon, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2019**, *58*, 3407; *Angew. Chem.* **2019**, *131*, 3445.
[9] a) K. Godula, D. Sames, *Science* **2006**, *312*, 67; b) J. Yamaguchi, A. D. Yamaguchi, K. Itami, *Angew. Chem. Int. Ed.* **2012**, *51*, 8960; *Angew. Chem.* **2012**, *124*, 9092; c) D. J. Abrams, P. A. Provencher, E. N. Sorensen, *Chem. Soc. Rev.* **2018**, *47*, 8925; d) O. Baudoin, *Angew. Chem. Int. Ed.* **2020**, *59*, 17798; *Angew. Chem.* **2020**, *132*, 17950.
[10] M. Zhang, Q. Wang, Y. Peng, Z. Chen, C. Wan, J. Chen, Y. Zhao, R. Zhang, A. Q. Zhang, *Chem. Commun.* **2019**, *55*, 13048.
[11] a) E. T. Nadres, O. Daugulis, *J. Am. Chem. Soc.* **2012**, *134*, 7; b) G. He, Y. Zhao, S. Zhang, C. Lu, G. Chen, *J. Am. Chem. Soc.* **2012**, *134*, 3; c) M. Yang, B. Su, Y. Wang, K. Chen, X. Jiang, Y.-F. Zhang, X.-S. Zhang, G. Chen, Y. Cheng, Z. Cao, Q.-Y. Guo, L. Wang, Z.-J. Shi, *Nat. Commun.* **2014**, *5*, 4707.
[12] a) A. W. Hofmann, *Ber. Dtsch. Chem. Ges.* **1883**, *16*, 558; b) K. Löffler, C. Freytag, *Ber. Dtsch. Chem. Ges.* **1909**, *42*, 3427.
[13] a) C. Martínez, K. Muñiz, *Angew. Chem. Int. Ed.* **2015**, *54*, 8287; *Angew. Chem.* **2015**, *127*, 8405; b) P. Becker, T. Duhamel, C. J. Stein, M. Reiher, K. Muñiz, *Angew. Chem. Int. Ed.* **2017**, *56*, 8004; *Angew. Chem.* **2017**, *129*, 8117; c) P. Becker, T. Duhamel,

C. Martinez, K. Muñiz, *Angew. Chem. Int. Ed.* **2018**, *57*, 5166; *Angew. Chem.* **2018**, *130*, 5262; d) T. Duhamel, C. J. Stein, C. Martinez, M. Reiher, K. Muñiz, *ACS Catal.* **2018**, *8*, 3918; e) N. R. Paz, D. Rodríguez-Sosa, H. Valdés, R. Marticorena, D. Melián, M. Belén Copano, C. C. Gonzalez, A. J. Herrera, *Org. Lett.* **2015**, *17*, 2370; f) E. A. Wappes, S. C. Fosu, T. C. Chopko, D. A. Nagib, *Angew. Chem. Int. Ed.* **2016**, *55*, 9974; *Angew. Chem.* **2016**, *128*, 10128; g) F. Wang, S. S. Stahl, *Angew. Chem. Int. Ed.* **2019**, *58*, 6385; *Angew. Chem.* **2019**, *131*, 6451; h) D. Meng, Y. Tang, J. Wei, X. Shi, M. Yang, *Chem. Commun.* **2017**, *53*, 5744; i) M. C. Lux, J. Jurczyk, Y.-H. Lam, Z. J. Song, C. Ma, J. B. Roque, J. S. Ham, N. Sciammetta, D. Adpressa, R. Sarpong, C. S. Yeung, *Org. Lett.* **2020**, *22*, 6578; j) R.-X. Jin, J.-C. Dai, Y. Li, X.-S. Wang, *Org. Lett.* **2021**, *23*, 421; For reviews, see: k) M. Nechab, S. Mondal, M. P. Bertrand, *Chem. Eur. J.* **2014**, *20*, 16034; l) L. M. Stateman, K. M. Nakafuku, D. A. Nagib, *Synthesis* **2018**, *50*, 1569.

[14] a) E. T. Hennessy, T. A. Betley, *Science* **2013**, *340*, 5915; b) D. A. Iovan, M. J. T. Wilding, Y. Baek, E. T. Hennessy, T. A. Betley, *Angew. Chem. Int. Ed.* **2017**, *56*, 15599; *Angew. Chem.* **2017**, *129*, 15805; c) Y. Dong, R. M. Clarke, G. J. Porter, T. A. Betley, *J. Am. Chem. Soc.* **2020**, *142*, 10996; d) N. C. Thacker, Z. Lin, T. Zhang, J. C. Gilhula, C. W. Abney, W. Lin, *J. Am. Chem. Soc.* **2016**, *138*, 3501; e) B. Bagh, D. L. J. Broere, V. Sinha, P. F. Kuijpers, N. P. Van Leest, B. de Bruin, S. Demeshko, M. A. Siegler, J. I. van der Vlugt, *J. Am. Chem. Soc.* **2017**, *139*, 5117; f) I. T. Alt, C. Guttroff, B. Plietker, *Angew. Chem. Int. Ed.* **2017**, *56*, 10582; *Angew. Chem.* **2017**, *129*, 10718; g) K.-P. Shing, Y. Liu, B. Cao, X.-Y. Chang, T. You, C.-M. Che, *Angew. Chem. Int. Ed.* **2018**, *57*, 11947; *Angew. Chem.* **2018**, *130*, 12123; h) K.-P. Shing, Y. Liu, B. Cao, X.-Y. Chang, C.-M. Che, *Org. Lett.* **2019**, *21*, 895.

[15] a) S. Munnuri, A. M. Adebesin, M. P. Paudyal, M. Yousufuddin, A. Dalipe, J. R. Falck, *J. Am. Chem. Soc.* **2017**, *139*, 18288; b) H. Noda, Y. Asuda, M. Shibasaki, *Org. Lett.* **2020**, *22*, 8769.

[16] a) P. F. Kuijpers, M. J. Tiekink, W. B. Breukelaar, D. L. J. Broere, N. P. Van Leest, J. I. van der Vlugt, J. N. H. Reek, B. de Bruin, *Chem. Eur. J.* **2017**, *23*, 7945; b) J. Qin, Z. Zhou, T. Cui, M. Hemming, E. Meggers, *Chem. Sci.* **2019**, *10*, 3202; c) Y. Dong, C. J. Lund, G. J. Porter, R. M. Clarke, S.-L. Zheng, T. R. Cundari, T. A. Betley, *J. Am. Chem. Soc.* **2021**, *143*, 817; For a different strategy based on the asymmetric α-C–H arylation of pyrrolidines, see: d) P. Jain, P. Verma, G. Xia, J.-Q. Yu, *Nat. Chem.* **2017**, *9*, 140.

[17] A two-step synthesis of pyrrolidines from alkylbenzenes has recently been reported by application of radical chemistry. The reactions afford racemic products as mixtures of diastereoisomers. See: a) F. Wu, J. P. Ariyarathna, N. Kaur, M. L. Kennell, O. H. Bassiouni, W. Li, *Org. Lett.* **2020**, *22*, 2135; b) A. E. Bosnidou, K. Muñiz, *Angew. Chem. Int. Ed.* **2019**, *58*, 7485; *Angew. Chem.* **2019**, *131*, 7564.

[18] For reviews, see: a) P. Müller, C. Fruit, *Chem. Rev.* **2003**, *103*, 2905; b) J. W. W. Chang, T. M. U. Ton, P. W. H. Chan, *Chem. Rec.* **2011**, *11*, 331; c) J. L. Roizen, M. E. Harvey, J. Du Bois, *Acc. Chem. Res.* **2012**, *45*, 911; d) J. Buendia, G. Grelier, P. Dauban, *Adv. Organomet. Chem.* **2015**, *64*, 77; e) J. M. Alderson, J. R. Corbin, J. M. Schomaker, *Acc. Chem. Res.* **2017**, *50*, 2147; f) D. Hazelard, P.-A. Nocquet, P. Compain, *Org. Chem. Front.* **2017**, *4*, 2500.

[19] For relevant studies, see: a) K. W. Fiori, J. Du Bois, *J. Am. Chem. Soc.* **2007**, *129*, 562; b) J. L. Roizen, D. N. Zalatan, J. Du Bois, *Angew. Chem. Int. Ed.* **2013**, *52*, 11343; *Angew. Chem.* **2013**, *125*, 11553; c) N. D. Chiappini, J. B. C. Mack, J. Du Bois, *Angew. Chem. Int. Ed.* **2018**, *57*, 4956; *Angew. Chem.* **2018**, *130*, 5050; d) A. Nasrallah, V. Boquet, A. Hecker, P. Retailleau, B. Darses, P. Dauban, *Angew. Chem. Int. Ed.* **2019**, *58*, 8192; *Angew. Chem.* **2019**, *131*, 8276; e) A. Nasrallah, Y. Lazib, V. Boquet, B. Darses, P. Dauban, *Org. Process Res. Dev.* **2020**, *24*, 724; f) E. Brunard, V. Boquet, E. Van Elslande, T. Saget, P. Dauban, *J. Am. Chem. Soc.* **2021**, *143*, 6407.

[20] a) C. Liang, F. Robert-Peillard, C. Fruit, P. Müller, R. H. Dodd, P. Dauban, *Angew. Chem. Int. Ed.* **2006**, *45*, 4641; *Angew. Chem.* **2006**, *118*, 4757; b) C. Liang, F. Collet, F. Robert-Peillard, P. Müller, R. H. Dodd, P. Dauban, *J. Am. Chem. Soc.* **2008**, *130*, 343; c) F. Collet, C. Lescot, C. Liang, P. Dauban, *Dalton Trans.* **2010**, *39*, 10401; d) B. Darses, A. G. Jarvis, A.-K. Mafroud, G. Estenne-Bouhtou, G. Dargazanli, P. Dauban, *Synthesis* **2013**, *45*, 2079.

[21] a) J. Buendia, B. Darses, P. Dauban, *Angew. Chem. Int. Ed.* **2015**, *54*, 5697; *Angew. Chem.* **2015**, *127*, 5789; b) J. Buendia, G. Grelier, B. Darses, A. G. Jarvis, F. Taran, P. Dauban, *Angew. Chem. Int. Ed.* **2016**, *55*, 7530; *Angew. Chem.* **2016**, *128*, 7656.

[22] P. De Armas, R. Carrau, J. I. Concepción, C. G. Francisco, R. Hernández, E. Suárez, *Tetrahedron Lett.* **1985**, *26*, 2493.

[23] An initial experiment with $PhI(OPiv)_2$ led to a lower yield of 35% while no reaction occurred in the presence PhIO or $PhI(OCOCF_3)_2$.

[24] a) J. M. Chong, I. S. Clarke, I. Koch, P. C. Olbach, N. J. Taylor, *Tetrahedron: Asymmetry* **1995**, *6*, 409; b) D. J. Aldous, W. M. Dutton, P. G. Steel, *Tetrahedron: Asymmetry* **2000**, *11*, 2455.

[25] a) B. M. Trost, D. A. Thaisrivongs, E. J. Donckele, *Angew. Chem. Int. Ed.* **2013**, *52*, 1523; *Angew. Chem.* **2013**, *125*, 1563; b) A. Claraz, G. Sahoo, D. Berta, A. Madarász, I. Pápai, P. M. Pikho, *Angew. Chem. Int. Ed.* **2016**, *55*, 669; *Angew. Chem.* **2016**, *128*, 679; c) S. Kortet, A. Claraz, P. M. Pikho, *Org. Lett.* **2020**, *22*, 3010.

[26] B. M. Trost, S. M. Silverman, J. P. Stambuli, *J. Am. Chem. Soc.* **2011**, *133*, 19483.

[27] This mechanistic proposal does not apply to non-benzylic radicals, as in the case of compound **91** for which a lower d.r. is observed.

[28] This proposal is in line with an additional experiment performed from haloamine **10** in the presence of AgCl and the iodine(III) oxidant. The resulting *trans*-pyrrolidine **9a** was isolated in 49% and an excellent d.r. of >20:1. We believe that these conditions induce the formation of a benzylic chloride from which the S_N2-type cyclization would be disfavored, hence the sole S_N1-type mechanism would operate.

[29] The racemic *trans*-pyrrolidine **11** was prepared according to the protocol reported by Seidel et al. (See: W. Chen, L. Ma, A. Paul, D. Seidel, *Nat. Chem.* **2018**, *10*, 165). Then, application of the method reported by Pihko et al. (see ref. [25b]) that involves the derivatization of 2,5-diarylpyrrolidines to phosphoramidites, led us to determine that the (*R*,*R*)-pyrrolidine **11** was obtained with an e.r. of >98:2.

[30] Deposition Numbers 2051915, 2051916, and 2081923 contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures.

Manuscript received: June 14, 2021
Accepted manuscript online: July 30, 2021
Version of record online: August 27, 2021

