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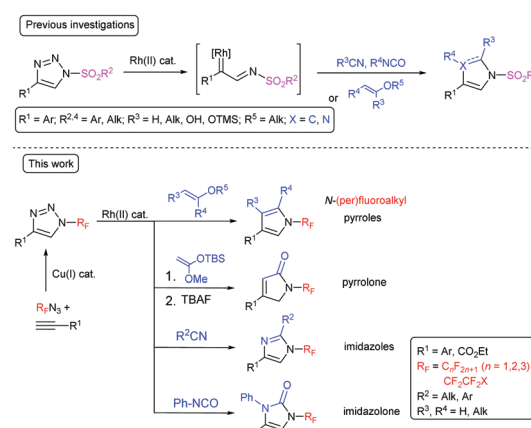
A rhodium-catalyzed transannulation of *N*-(per)fluoroalkyl-1,2,3-triazoles under microwave conditions – a general route to *N*-(per)fluoroalkyl-substituted five-membered heterocycles†

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A rhodium-catalyzed transannulation via ring-opening of *N*-(per)fluoroalkyl-substituted 1,2,3-triazoles followed by cycloaddition with different nitriles, enol ethers, isocyanates and silyl ketene acetals under microwave heating provided a highly efficient route to previously unreported *N*-(per)fluoroalkyl-substituted imidazoles, pyrroles, imidazolones and pyrrolones, respectively. These reactions were found to be applicable to the synthesis of a variety of 5-membered heterocycles bearing different (per)fluoroalkyl substituents as well as both electron-donating and electron-withdrawing groups attached to the heterocyclic core.

Substituted imidazoles and pyrroles are widely used as different biologically active compounds, agrochemicals and pharmaceuticals including anticancer, antimicrobial, fungicidal and antiviral drugs.^{1–3} Fluorinated and in particular trifluoromethyl-containing compounds also have a broad spectrum of applications ranging from drug candidates to novel materials.^{4–9} However, *N*-CF₃ and *N*-R_F (R_F = perfluoroalkyl) motifs are relatively rare^{10–13} and imidazoles or pyrroles with perfluoroalkyl groups attached to the nitrogen atom are almost unknown.^{14,15} Some azoles were trifluoromethylated in an electrophilic way but generally a mixture of regioisomers in low or moderate yields was obtained.¹⁶ Recently, we have reported the synthesis of azido-perfluoroalkanes (R_FN₃) by the reaction of the precursors of fluorinated carbanions with an electrophilic azide source which allowed access to *N*-(per)fluoroalkyl-1,2,3-triazoles by Cu(I)-catalyzed azide-alkyne cycloaddition.^{17,18}

N-Sulfonyl-substituted 1,2,3-triazoles are known to undergo a rhodium-catalyzed ring-opening and nitrogen elimination to form a rhodium iminocarbene and subsequent insertion of the carbene or cycloaddition with different 2π-components.^{19–21} This transannulation reaction is a highly efficient, atom-economical method for the synthesis of five-membered heterocycles, such as imidazoles,²² pyrroles,^{23–25} imidazolones,²⁶ pyrrolones,²⁷ and others.^{28,29} Fused pyridotriazoles, which exist in equilibrium with the diazoform, also undergo transannulation.^{30,31} Transannulation was reported to be limited to *N*-sulfonyl triazoles with one exception being *N*-(1,2,4-triazolyl)-substituted triazoles which undergo transannulation with nitriles (Scheme 1).³² Both the abovementioned groups exhibit a strong –M effect, which facilitates triazole ring opening. We have proposed that the rhodium-catalyzed transannulation of *N*-(per)fluoroalkyl-1,2,3-triazoles might lead to a range of structurally diverse five-membered nitrogen heterocycles with (per)fluoroalkyl groups attached to the nitrogen atom and herein we report our findings in this direction (Scheme 1).



Scheme 1 Transannulation reactions with 1,2,3-triazoles.

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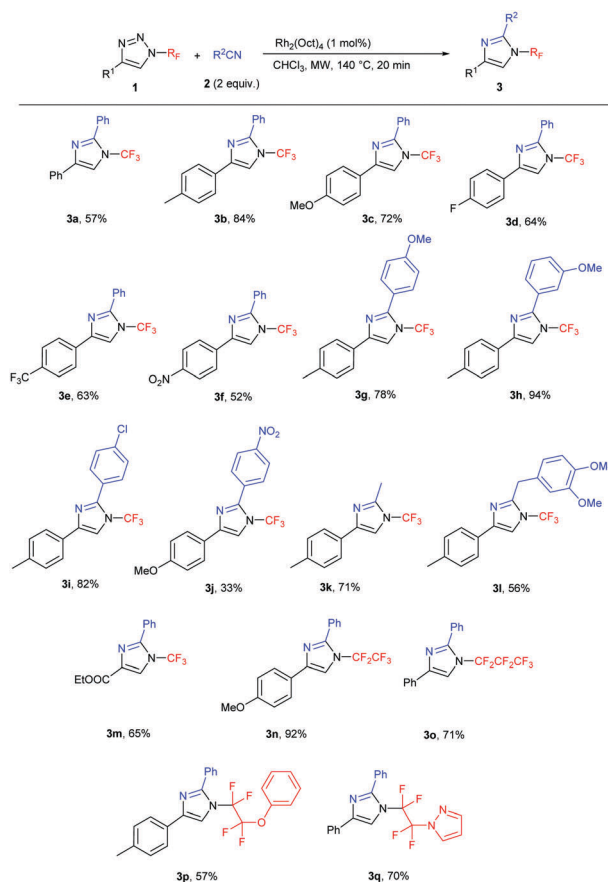
We initiated our studies using the reaction between 4-methoxyphenyl-substituted 1-trifluoromethyl-1,2,3-triazole **1c** and benzonitrile with a rhodium(II) acetate dimer as a catalyst. While conventional heating of the mixture in 1,2-dichloroethane (DCE) gave poor conversion to product **3c** (Table 1, entry 1), full conversion of **1c** and moderate isolated yield of **3c** were achieved by microwave heating (entry 2). Use of a two-fold excess of benzonitrile led to an increase in the yield to 51% (entry 3). Reaction temperature and time optimization revealed that 140 °C and 20 min were optimal. Finally, switching to Rh₂(Oct)₄ and using chloroform as the solvent afforded the optimized 72% isolated yield of **3c** (entry 7). Importantly, the reaction did not take place without the rhodium catalyst or with CuTC (entry 8).

Subsequently, the scope of the reaction was studied under the optimized conditions (Table 2). We tested the transannulation reaction with nitriles on variously substituted aromatic *N*-perfluoroalkyl-triazoles (Scheme 3). Electron-rich substrates such as 4-methoxy- and 4-methyl-substituted triazoles (**1b**, **1c**) were found to be more reactive and produced higher yields than electron-poor substrates (such as **1f**). It is worth noting that this reaction is applicable for the synthesis of the ethoxycarbonyl-substituted aliphatic triazole **3m** as well, presumably due to the ability of the CO₂Et group to stabilize the forming rhodium carbenoid intermediate similarly to the aryl group despite the reported lower stability of electron-poor carbenoids.¹⁹

We found the reaction to be rather insensitive to the electronic nature of the nitrile. The yields were excellent in the case of electron-rich, neutral and mildly electron-poor aromatic nitriles and aliphatic nitriles. Only highly electron-poor 4-nitrobenzonitrile reacted much slower under the conditions, thus providing the product in moderate yield.

Longer carbon chain *N*-perfluoroalkyl triazoles participated in the transannulation reaction with equal efficiency to their CF₃ analogues and high yields of pentafluoroethyl- and perfluoropropyl-substituted imidazoles (**3n** and **3o**, respectively) were obtained. Moreover, tetrafluoroethylene-containing substrates with phenoxy or pyrazolyl functional groups were tolerated,

Table 2 Synthesis of *N*-(per)fluoroalkyl imidazoles by transannulation^a



^a Isolated yields.

Table 1 Optimization of reaction conditions^a

Entry	Catalyst	PhCN ^b	Solvent, temp., time	Yield ^c (%)
1	Rh ₂ (OAc) ₄	1.3	DCE, 80 °C, 17 h	3
2	Rh ₂ (OAc) ₄	1.3	DCE, 150 °C MW, 1 h	100 (40)
3	Rh ₂ (OAc) ₄	2	DCE, 150 °C MW, 1 h	100 (51)
4	Rh ₂ (OAc) ₄	2	DCE, 100 °C MW, 20 min	40 (24)
5	Rh ₂ (OAc) ₄	2	DCE, 140 °C MW, 20 min	100 (44)
6	Rh ₂ (OAc) ₄	2	CHCl ₃ , 140 °C MW, 20 min	100 (59)
7	Rh ₂ (Oct) ₄	2	CHCl ₃ , 140 °C MW, 20 min	100 (72)
8	None or CuTC	2	CHCl ₃ , 140 °C MW, 20 min	0

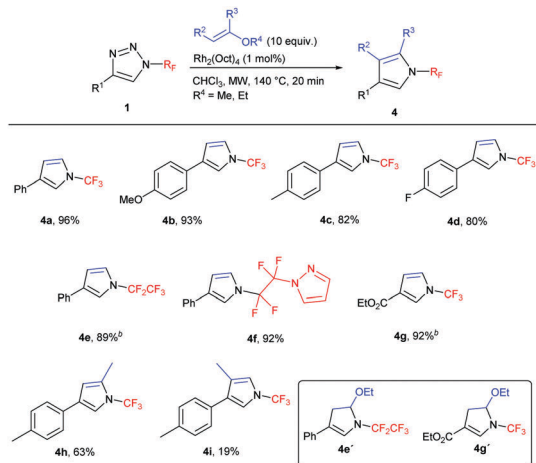
^a Reaction conditions: **1c** (0.10 mmol), PhCN (0.13–0.20 mmol), [Rh^{II}] (1 mol%), solvent (2 mL). ^b equiv. ^c Conversion of **1c** was determined by ¹⁹F NMR, in brackets isolated yields of **3c**.

providing a route to multifunctionalized *N*-fluoroalkylated imidazoles **3p** and **3q**.

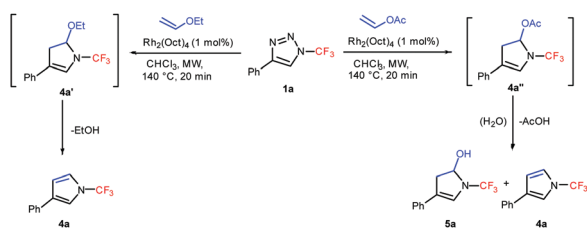
N-(Per)fluoroalkyl pyrroles are previously unreported and attractive targets, which might be accessible by the transannulation of triazoles **1** with vinyl ethers. First, the reaction with ethyl vinyl ether was tested in order to form 4,5-unsubstituted *N*-(per)fluoroalkyl pyrroles. Indeed, the transannulation in the presence of the Rh₂(Oct)₄ catalyst took place with concomitant ethanol elimination under the reaction conditions to afford pyrroles **4** in high yields (Table 3). In the case of **4e**, a mixture of **4e** and **4e'** (1 : 1.2) formed; in the case of **4g**, only compound **4g'** was observed. In both cases, the treatment of the crude reaction mixture with TsOH resulted in the formation of the desired pyrroles **4e** and **4g**, respectively. 2,4-Disubstituted pyrrole **4h** was successfully prepared by the reaction with 2-methoxypropene. The only limitation of the methodology was observed in the preparation of 3,4-disubstituted pyrrole in the reaction with 1-ethoxypropene, where **4i** was isolated in low yield.

A comparison of the reactivity of **1a** with ethyl vinyl ether and vinyl acetate revealed that while in the case of ethyl vinyl ether ethanol elimination from intermediate **4a'** proceeded smoothly under the reaction conditions, whereas in the case of vinyl acetate intermediate **4a''** preferentially undergoes hydrolysis and a mixture of the desired **4a** and **5a** was obtained (Scheme 2).



Table 3 Synthesis of pyrroles by transannulation with vinyl ethers^a

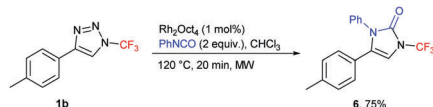
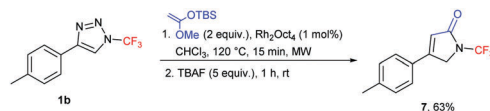
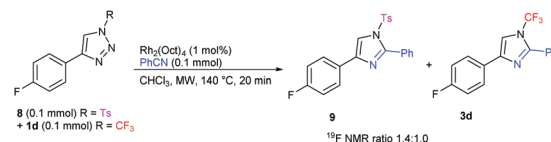
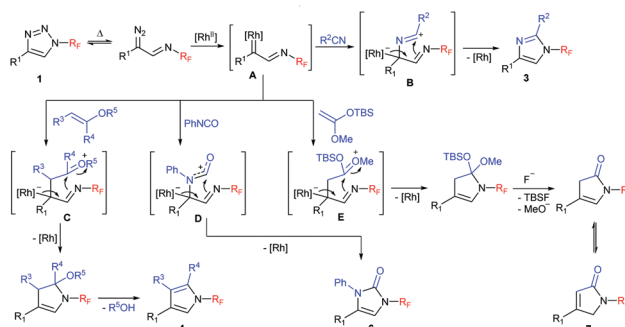
^a Isolated yields. ^b After treatment of intermediates **4e'** and **4g'** with TsOH (2 equiv.), rt, 2 h.

Scheme 2 A comparison of the reactivity of **1a** with ethyl vinyl ether and vinyl acetate.

After having developed an efficient strategy for the preparation of unknown *N*-(per)fluoroalkylated imidazoles and pyrroles, we set to investigate the application of the methodology for the preparation of other unreported classes of compounds – *N*-perfluoroalkyl imidazolones and pyrrolones. Gratifyingly, *N*-trifluoromethyl-substituted imidazolone **6** was prepared by transannulation of **1b** with phenylisocyanate (Scheme 3). For the preparation of *N*-trifluoromethyl pyrrolone **7**, one-pot two-step synthesis with silyl ketene acetal, followed by the treatment with TBAF, was used (Scheme 4).

In order to compare the reactivities of previously described *N*-tosyl and our *N*-perfluoroalkyl triazoles in the Rh-catalyzed transannulation reaction, a competitive experiment was performed between equimolar amounts of **1d** and *N*-tosyl triazole **8**. From the composition of the reaction mixture analyzed by ^{19}F NMR, it is clear that **1d** reacted somewhat slower than **8**, however, the reactivity difference is small (Scheme 5).

A plausible mechanism for the transannulation process mirrors the one proposed for *N*-Ts triazoles. Triazole **1** upon

Scheme 3 Synthesis of *N*-trifluoromethyl imidazolone **6**.Scheme 4 Synthesis of *N*-trifluoromethyl pyrrolone **7**.Scheme 5 Transannulation competition experiment revealing comparative reactivity of *N*-trifluoromethyl and *N*-tosyl triazoles with benzonitrile.Scheme 6 Proposed simplified mechanism for the transannulation of *N*-perfluoroalkyl-1,2,3-triazoles.

treatment with the Rh^{II} catalyst at elevated temperature is transformed into the key rhodium iminocarbene intermediate **A** (Scheme 6). Formal [3+2] cycloadditions with 2π components provide zwitterionic species **B-E** (the actual mechanism might be more complex and can involve the formation of ylides and metallacyclobutenes or in the cases of pyrroles and pyrrolones the formation of cyclopropanes followed by the Cloke rearrangement).^{20,22,24} The subsequent elimination of the rhodium catalyst (and optional group deprotection or elimination) affords the final products.

The stability of *N*-perfluoroalkyl imidazoles and pyrroles under acidic or basic conditions at ambient temperature (18 h reaction time) was also investigated. Imidazole **3g** was treated with 0.5 M NaOH in CD_3OD . Proton-deuterium exchange (H/D 81 : 19) of the aromatic hydrogen was observed, suggesting its considerable C–H acidity. When the solution of **3g** was treated with 1.2 M sulfuric acid in CD_3OD , a shift of the aromatic hydrogen signal in ^1H NMR spectrum from 7.90 ppm to 8.45 ppm was observed. Treatment of **4b** with 0.5 M NaOH or 1.2 M sulfuric acid in CD_3OD led to no significant change in the NMR spectra. In all the cases, no decomposition or hydrolysis of **3g** or **4b** was observed by NMR, showing good stability of these *N*-trifluoromethylated nitrogen heterocycles in acidic and basic media.

In conclusion, we have developed a highly efficient method for the synthesis of a broad range of previously unreported



N-fluoroalkyl-substituted five-membered heterocycles based on a microwave heating-assisted rhodium-catalyzed transannulation of *N*-fluoroalkyl-substituted triazoles. This way, a variety of structurally diverse *N*-fluoroalkyl pyrroles, pyrrolones, imidazoles and imidazolones have been prepared in a straightforward manner. These novel classes of fluorinated compounds should be attractive for discovery programs. It was found that transannulations are not only limited to *N*-tosyl triazoles but also work with *N*-CF₃ triazoles and proceed with benzonitrile with a comparable reactivity. *N*-Trifluoromethyl imidazoles and pyrroles are hydrolytically stable in both acidic and basic media.

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Conflicts of interest

There are no conflicts to declare.

Notes and references

- 1 L. D. Luca, *Curr. Med. Chem.*, 2006, **13**, 1–23.
- 2 M. Boiani and M. Gonzalez, *Mini-Rev. Med. Chem.*, 2005, **5**, 409–424.
- 3 J. T. Gupton, *Heterocyclic Antitumor Antibiotics. Topics in Heterocyclic Chemistry*, Springer, Berlin, Heidelberg, 2006, vol. 2.
- 4 P. V. Reddy, *Organofluorine Compounds in Biology and Medicine*, Elsevier, Amsterdam, Netherlands, 2015.
- 5 I. Ojima, *Fluorine in Medicinal Chemistry and Chemical Biology*, Wiley-Blackwell, New York, 2009.
- 6 P. Kirsch, *Modern Fluoroorganic Chemistry*, Wiley-VCH, Weinheim, 2nd edn, 2013.
- 7 J. Wang, M. Sanchez-Rosello, J. L. Acena, C. Del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok and H. Liu, *Chem. Rev.*, 2014, **114**, 2432–2506.
- 8 Y. Zhou, J. Wang, Z. Gu, S. Wang, W. Zhu, J. L. Acena, V. A. Soloshonok, K. Izawa and H. Liu, *Chem. Rev.*, 2016, **116**, 422–518.
- 9 S. Purser, P. R. Moore, S. Swallow and V. Gouverneur, *Chem. Soc. Rev.*, 2008, **37**, 320–330.
- 10 A. F. Baxter, K. O. Christe and R. Haiges, *Angew. Chem., Int. Ed.*, 2015, **54**, 14535–14538.
- 11 W. J. Middleton, *J. Org. Chem.*, 1984, **49**, 4541–4543.
- 12 J. Yu, J. H. Lin and J. C. Xiao, *Angew. Chem., Int. Ed.*, 2017, **56**, 16669–16673.
- 13 T. Scattolin, K. Deckers and F. Schoenebeck, *Angew. Chem., Int. Ed.*, 2017, **56**, 221–224.
- 14 T. M. Sokolenko, K. I. Petko and L. M. Yagupolskii, *Chem. Heterocycl. Compd.*, 2009, **45**, 430–435.
- 15 G. Bissky, G.-V. Rösenthaller, E. Lork, J. Barten, M. Médebielle, V. Staninets and A. A. Kolomeitsev, *J. Fluorine Chem.*, 2001, **109**, 173–181.
- 16 K. Niedermann, N. Fruh, R. Senn, B. Czarniecki, R. Verel and A. Togni, *Angew. Chem., Int. Ed.*, 2012, **51**, 6511–6515.
- 17 Z. E. Blastik, S. Voltrova, V. Matousek, B. Jurasek, D. W. Manley, B. Klepetarova and P. Beier, *Angew. Chem., Int. Ed.*, 2017, **56**, 346–349.
- 18 S. Voltrova, M. Muselli, J. Filgas, V. Matousek, B. Klepetarova and P. Beier, *Org. Biomol. Chem.*, 2017, **15**, 4962–4965.
- 19 H. M. L. Davies and A. M. Walji, Rhodium(II)-Stabilized Carbenoids Containing Both Donor and Acceptor Substituents, in *Modern Rhodium-Catalyzed Organic Reactions*, ed. P. A. Evans, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, 2005.
- 20 B. Chattopadhyay and V. Gevorgyan, *Angew. Chem., Int. Ed.*, 2012, **51**, 862–872.
- 21 H. M. Davies and J. S. Alford, *Chem. Soc. Rev.*, 2014, **43**, 5151–5162.
- 22 T. Horneff, S. Chuprakov, N. Chernyak, V. Gevorgyan and V. V. Fokin, *J. Am. Chem. Soc.*, 2008, **130**, 14972–14974.
- 23 B. Chattopadhyay and V. Gevorgyan, *Org. Lett.*, 2011, **13**, 3746–3749.
- 24 S. Rajasekar and P. Anbarasan, *J. Org. Chem.*, 2014, **79**, 8428–8434.
- 25 J. Feng, Y. Wang, Q. Li, R. Jiang and Y. Tang, *Tetrahedron Lett.*, 2014, **55**, 6455–6458.
- 26 S. Chuprakov, S. W. Kwok and V. V. Fokin, *J. Am. Chem. Soc.*, 2013, **135**, 4652–4655.
- 27 R. Q. Ran, J. He, S. D. Xiu, K. B. Wang and C. Y. Li, *Org. Lett.*, 2014, **16**, 3704–3707.
- 28 T. Miura, Y. Funakoshi and M. Murakami, *J. Am. Chem. Soc.*, 2014, **136**, 2272–2275.
- 29 J. E. Spangler and H. M. Davies, *J. Am. Chem. Soc.*, 2013, **135**, 6802–6805.
- 30 S. Chuprakov, F. W. Hwang and V. Gevorgyan, *Angew. Chem., Int. Ed.*, 2007, **46**, 4757–4759.
- 31 V. Helan, A. V. Gulevich and V. Gevorgyan, *Chem. Sci.*, 2015, **6**, 1928–1931.
- 32 M. Zibinsky and V. V. Fokin, *Org. Lett.*, 2011, **13**, 4870–4872.

