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Rhodium(II)-catalyzed transannulation approach to *N*-fluoroalkylated indoles†

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Copper(I)-catalyzed cycloaddition of substituted cyclohexenyl acetylenes with azido(per)fluoroalkanes afforded 4-cyclohexenyl-substituted *N*-(per)fluoroalkylated 1,2,3-triazoles. Their rhodium(II)-catalyzed transannulation led to fused *N*-(per)fluoroalkyl pyrroles and subsequent oxidation provided *N*-(per)fluoroalkyl indoles.

Indole heterocyclic system is an important pharmacophore displaying a broad spectrum of biological activities, such as antiviral, anti-inflammatory, anticancer, antimicrobial, antimalarial, antidiabetic, and antioxidant activities.[1] Furthermore, the indole scaffold is present in the amino acid tryptophan, biogenic amine tryptamine, neurotransmitter serotonin, and numerous alkaloids.[2] While the free NH group of the indole moiety is present in many bioactive indoles, several *N*-alkylated indole drugs became commercially successful (Fig. 1).

Introduction of fluorine atoms and fluorinated groups (such as the trifluoromethyl group) is an established strategy to improve medicinal properties of drug candidates, including bioactivity, bioavailability, influencing pK_a of neighbouring groups, and protein binding affinity.[3–6]

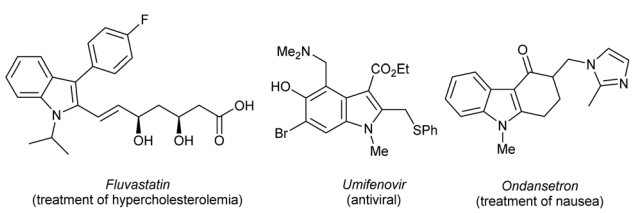
Fluorinated and trifluoromethylated indole derivatives are known. Radical trifluoromethylation of indole and its derivatives takes place in position 2 or 3 of the indole ring[7,8] and electrophilic trifluoromethylation is not a viable strategy for the preparation of trifluoromethylated indoles (Scheme 1), although it works on indolides with the Togni reagents[9,10] or Umemoto's oxonium reagents.[11] Similarly, oxidative desulfurization of dithiocarbamates to *N*-CF_3 motifs is known to proceed on indolines but not on indoles.[12]

N-Trifluoromethylated azoles (imidazoles, benzimidazoles, pyrazoles) have promising medicinal chemistry properties;[13] however, *N*-trifluoromethylated indole derivatives are very rare. The only known access to them is a multistep synthesis starting from aryl isothiocyanates which are transformed into key intermediates *N*-CF_3-hydrazines using an excess of AgF and triphosgene. Under acidic conditions, these hydrazines participate in a Fisher indole synthesis (Scheme 1).[14] This synthetic strategy is limited to *N*-trifluoromethylated 2,3-disubstituted indoles. Furthermore, only three examples of this kind are known.

Our alternative synthetic methodology to *N*-CF_3 and *N*-(per)fluoroalkyl indoles **3** utilizes 4-cyclohexenyl substituted 1,2,3-triazoles **1** with fluoroalkyl groups on nitrogen. They are easily prepared from fluorinated azidoalkanes developed in our group[15,16] using copper(I)-catalyzed azide–alkyne cycloaddition (CuAAC). Taking inspiration from Rh(II)-catalyzed reaction of analogous *N*-sulfonyl triazoles,[17] transannulation (4π cyclization) of triazoles **1** would give fused pyrroles **2**. Their oxidation would provide target indoles **3** (Scheme 1).

Substituted cyclohexenyl acetylenes[17] underwent CuAAC with a variety of fluorinated azidoalkanes under previously reported conditions[18] using copper(I) 3-methylsalicylate (CuMeSal) catalyst in THF under ambient temperature (Scheme 2). The method allows for the generation of diversity on the cyclohexenyl moiety as well as substitution on the nitrogen with substrate-dependent yields ranging from good to high.

Triazole **1a** was subjected to Rh(II)-catalyzed transannulation reaction. Optimization of the reaction conditions revealed that $Rh_2(esp)_2$ catalyst was more efficient than $Rh_2(Oct)_4$ or $Rh_2(AcO)_4$ catalysts (Table 1, entries 1–3). The minimal reaction temperature and time were 100 °C and 10 min, respect-



Fluvastatin (treatment of hypercholesterolemia) — *Umifenovir* (antiviral) — *Ondansetron* (treatment of nausea)

Fig. 1 Examples of *N*-alkylated indole-containing drugs.

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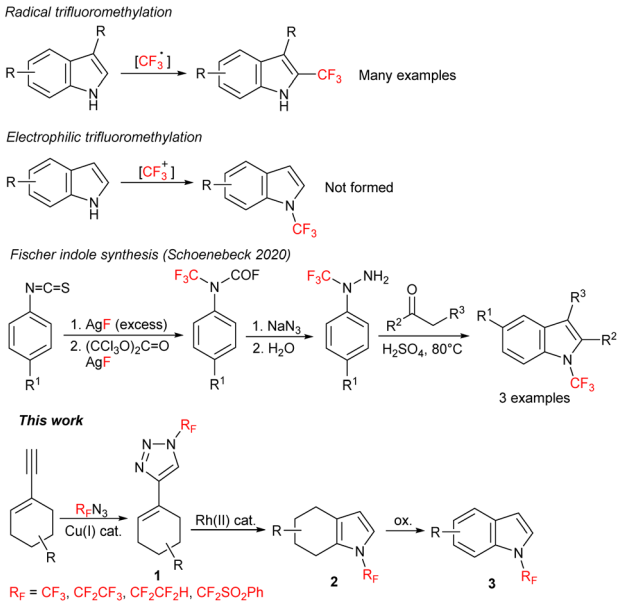
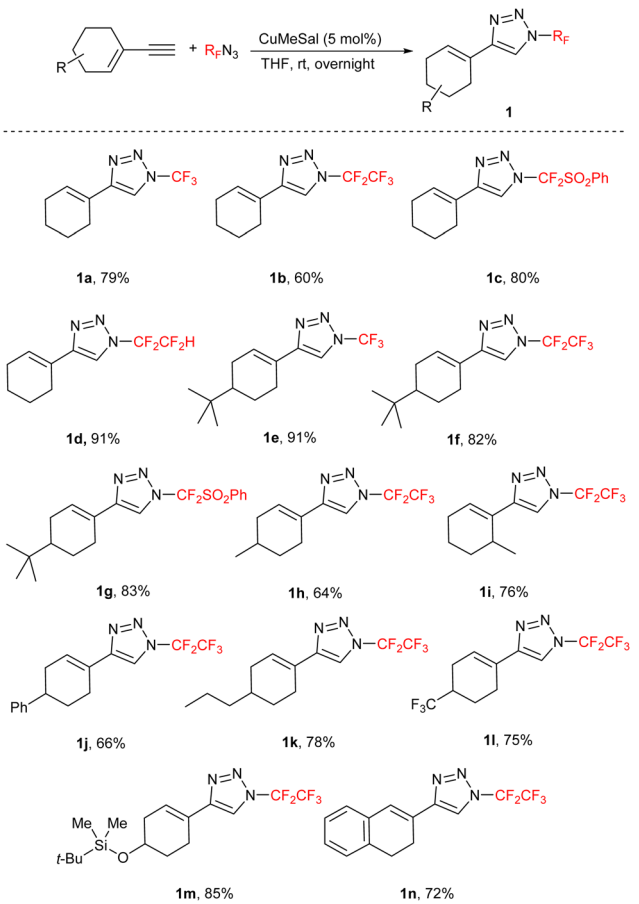
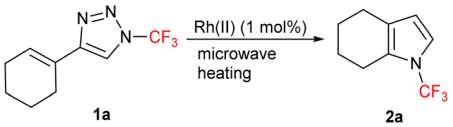


Scheme 1 Approaches to trifluoromethylated and fluoroalkylated indoles.



Scheme 2 Preparation of triazoles **1**.

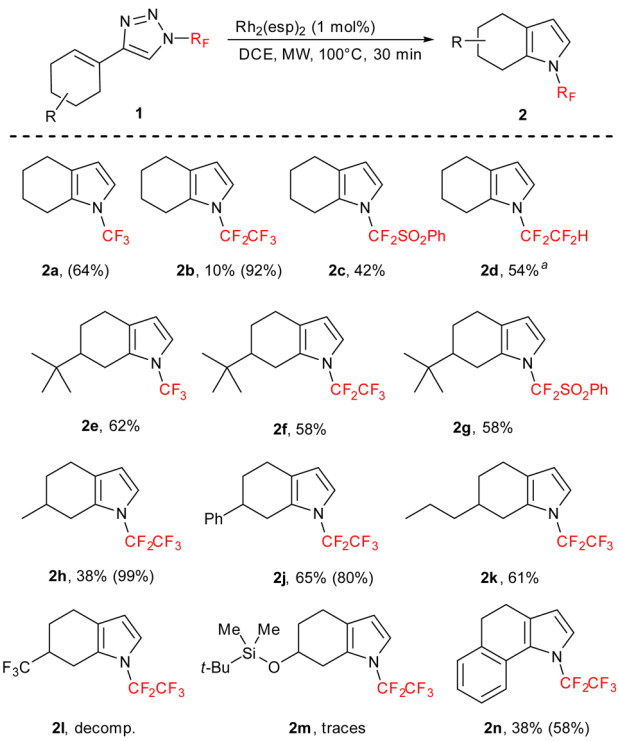
Table 1 Optimization of fused pyrrole **2a** formation[a]



Entry	Rh(II)	Solvent	Temp. (°C)	Time (min)	**2a** yield[b] (%)
1	$Rh_2(Oct)_4$	$CHCl_3$	100	10	4[c]
2	$Rh_2(OAc)_4$	$CHCl_3$	100	10	22[c]
3	$Rh_2(esp)_2$	$CHCl_3$	100	10	50
4	$Rh_2(esp)_2$	$CHCl_3$	100	5	47[c]
5	$Rh_2(esp)_2$	$CHCl_3$	80	10	38[c]
6	$Rh_2(esp)_2$	DCE	100	10	50
7	$Rh_2(esp)_2$	Toluene	100	30	51
8	$Rh_2(esp)_2$	DCM	100	30	55
9	$Rh_2(esp)_2$	THF	100	30	nr
10	$Rh_2(esp)_2$	DMF	100	30	nr
11	**$Rh_2(esp)_2$**	**DCE**	**100**	**30**	**64**
12	$Rh_2(esp)_2$	Hexane	100	30	30

[a] Reaction conditions: **1a** (0.2 mmol), solvent (2 ml). [b] ^{19}F NMR yield. [c] Full conversion of **1a** was not achieved. nr – no reactivity.

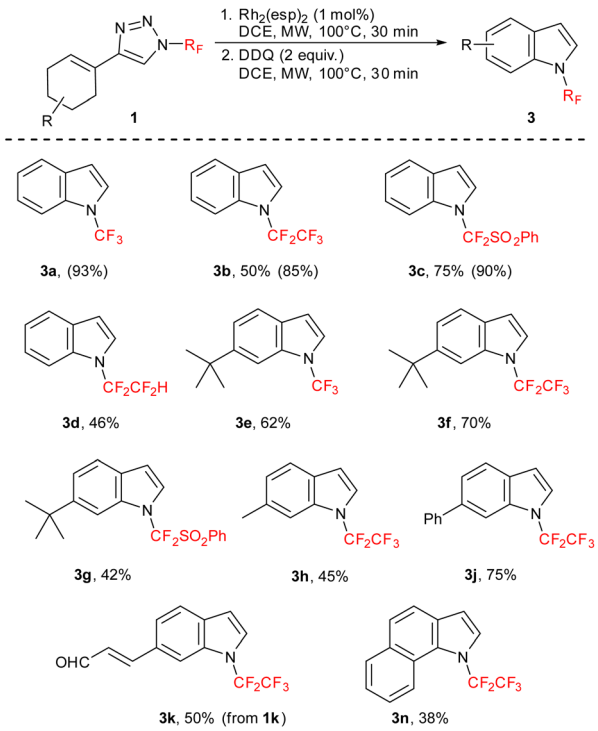
ively (entries 3–5). Several solvents were tested and the best product yield was obtained using 1,2-dichloroethane (entries 6–8). Under optimized conditions (entry 9) product **2a** was obtained in 64% ^{19}F NMR yield. High product volatility significantly reduced the isolated yield, nevertheless optimized conditions for the synthesis of compounds **2** were identified.



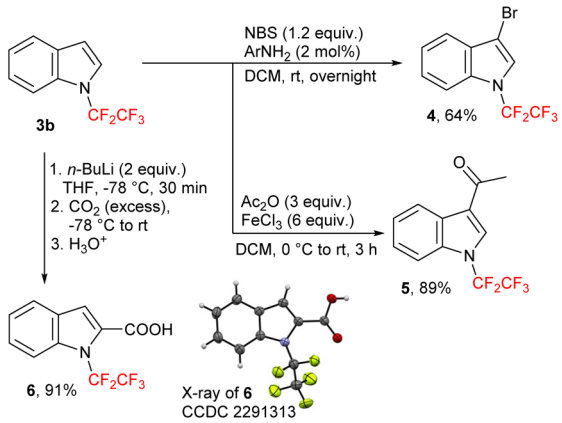
Scheme 3 Preparation of fused pyrroles **2** (^{19}F NMR yields in parentheses). [a] Using microwave heating to 140 °C for 30 min.

Application of optimized conditions to triazoles **1** afforded fused pyrroles **2** (Scheme 3). Product **2b** was highly volatile and was not isolated, but it formed in a high NMR yield. The presence of *t*-Bu, *n*-Pr or Ph groups on the fused ring reduced the volatility and allowed the product isolation in good yields. The presence of electron-acceptor trifluoromethyl group on the cyclohexenyl moiety caused the decomposition of product **2l**. The silyl-containing substrate **1m** was not a competent substrate in this reaction. Pyrroles **2** were stable at −20 °C under inert atmosphere but decomposed on air or at ambient temperature. We established that the addition of DDQ to the reaction mixture of **2a** led to full oxidation to indole **3a** under microwave heating to 100 °C for 30 min. This enabled to perform a one-pot reaction of triazoles **1** directly to indoles **3** (Scheme 4). Again, **3a** was too volatile for isolation, but other indoles formed with moderate to good efficiency. Triazole **1k** underwent successful transannulation and oxidation to the desired *N*-fluoroalkylated indole, accompanied by the side-product **3k**. The use of 6 equiv. of DDQ afforded cleanly the α,β-unsaturated aldehyde **3k** arising from the oxidation of the pendant *n*-propyl group. All of the reported *N*-trifluoromethyl-, *N*-pentafluoroethyl, *N*-tetrafluoroethyl-, and *N*-difluoromethylphenylsulfonyl indoles are new compounds.

To demonstrate the synthetic utility of the prepared *N*-fluoroalkyl indoles, derivatization of the primary product **3b** was conducted. *N*-Fluoroalkylated indoles should be strongly deactivated towards electrophilic aromatic substitution compared to NH or *N*-Me indoles. Nevertheless, efficient electrophilic bromination and acylation took place selectively in position three to afford brominated or acylated indoles, **4** and **5**, respectively (Scheme 5). Lithiation with *n*-BuLi and carboxylation was also regioselective and gave indole-2-carboxylic acid **6**. Crystallographic analysis of acid **6** confirmed the product structure.



Scheme 4 One-pot synthesis of indoles **3** from triazoles **1** (^{19}F NMR yields in parentheses).



Scheme 5 Derivatization of *N*-pentafluoroethyl indole **3b**. Ar = 2,4,6-trimethylphenyl.

In summary, 4-cyclohexenyl-substituted *N*-fluoroalkylated-1,2,3-triazoles **1** obtained by CuAAC undergo rhodium(II)-catalyzed transannulation reaction to fused *N*-fluoroalkylated pyrroles **2** which are oxidized to *N*-fluoroalkylated indoles **3**. The two-step process can be conveniently performed in one pot. This methodology represents an alternative synthetic pathway to *N*-CF_3-indoles, previously prepared *via* *N*-CF_3-hydrazines, and is applicable to the synthesis of indoles, substituted with various fluoroalkyl groups on nitrogen and having a substitution on the benzene ring. Follow-up derivatizations of one example of *N*-perfluoroalkyl indole by electrophilic aromatic acylation, bromination, and lithiation/carboxylation expand the diversity of accessible *N*-fluoroalkylated indole structures.

Author contributions

OB conceived the idea, performed synthetic experiments and partially wrote the manuscript, BK performed crystallographic measurements, and PB conceived the idea and wrote the manuscript.

Conflicts of interest

There are no conflicts to declare.

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