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N-Trifluoromethyl Hydrazines, Indoles and Their Derivatives

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Abstract: Reported herein is the first efficient strategy to synthesize a broad range of unsymmetrical *N*-CF₃ hydrazines, which served as platform to unlock numerous currently inaccessible derivatives, such as tri- and tetra-substituted *N*-CF₃ hydrazines, hydrazones, sulfonyl hydrazines, and valuable *N*-CF₃ indoles. These compounds proved to be remarkably robust, being compatible with acids, bases, and a wide range of synthetic manipulations. The feasibility of *RN*(CF₃)-NH₂ to function as a directing group in C–H functionalization is also showcased.

Hydrazines (R₂N-NR₂) are ubiquitous motifs in materials,^[1] pharmaceuticals,^[2] agrochemicals,^[2d] dyes^[3] (Figure 1) as well as enabling functional groups in synthesis, being popular directing groups in catalysis^[4] and valuable precursors to heterocycles (such as indoles),^[5] or tetrazenes. Consequently, there is a significant interest in devising efficient synthetic strategies to novel hydrazine motifs. While mono-substituted hydrazines (i.e. R-NH-NH₂) are readily accessible via arylation of NH₂-NH₂ (and protected NH₂-NH-PG),^[6] the syntheses of higher substituted, and especially unsymmetrically substituted hydrazines as well as their fluorinated derivatives have been challenging to date.^[7] In this context, a straightforward method to generate trifluoromethylated and unsymmetrically substituted hydrazines would be particularly impactful, owing to the powerful effects of fluorination on the (metabolic) stabilities as well as physical properties of organic molecules.^[8] However, the current methodological repertoire to access *N*-CF₃ hydrazines is of limited scope^[9,10] (see Figure 1, middle), relying on harsh photolysis or unselective oxidations with XeF₂ (to yield **I**) as well as pyrolysis to yield polytrifluoromethylated hydrazines (**III**), or low-yielding trifluoromethylation of a single class of diazo compounds (to yield **II**), for which the feasibility of Boc deprotection and potential derivatizations has not been demonstrated however.^[10g]

In this context, we envisioned that if we could develop a general method to access pharmaceutically and agrochemically relevant aromatic *N*-CF₃ hydrazines, this might poten-

tially allow us to unlock valuable and currently inaccessible *N*-CF₃ derivatives, such as *N*-CF₃ hydrazones, sulfonyl hydrazines, or indoles. While the former have never been made, *N*-CF₃ indoles can currently only be synthesized with strongly basic or oxidizing conditions that limit generality and functional group tolerance, involving either deprotonation of the indole *N*-H and reaction with gaseous CF₃I (of unknown efficiency; no yield reported),^[11] or trifluoromethylation of the non-aromatic indoline precursor, followed by re-aromatization under highly oxidizing conditions.^[12] Interestingly, the *N*-deprotonation of indoles, followed by reaction with an electrophilic CF₃ source, such as Togni's reagent, does not yield *N*-CF₃ indoles.^[13]

We herein describe an efficient strategy to *N*-CF₃ hydrazines and showcase their robustness in follow-up transformations to yield *N*-CF₃ indoles, tri- and tetra-substituted hydrazines, sulfonyl hydrazines, acyl hydrazines, as well as their functionalizations via modern catalytic strategies (cross coupling, C–H activation, thiolation, cyanation and borylation).

Our group previously developed a strategy to trifluoromethylate secondary amines,^[14] however, we found that the application of the same protocol to *N*'-protected hydrazines was not a viable strategy to *N*-CF₃ hydrazines, as the key thiocarbonyl fluoride intermediate did not form. We therefore embarked on developing an alternative strategy: building

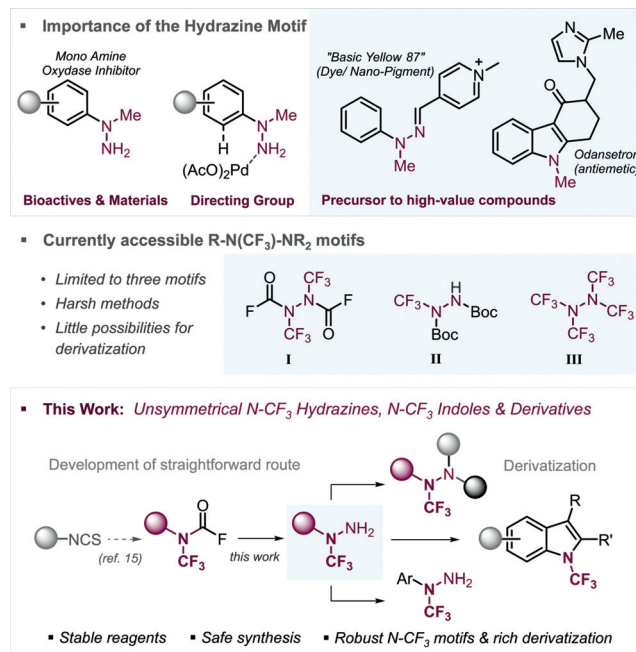


Figure 1. Importance of the hydrazine motif (top), current limited approaches to *N*-CF₃ hydrazines (middle) and this work (bottom).

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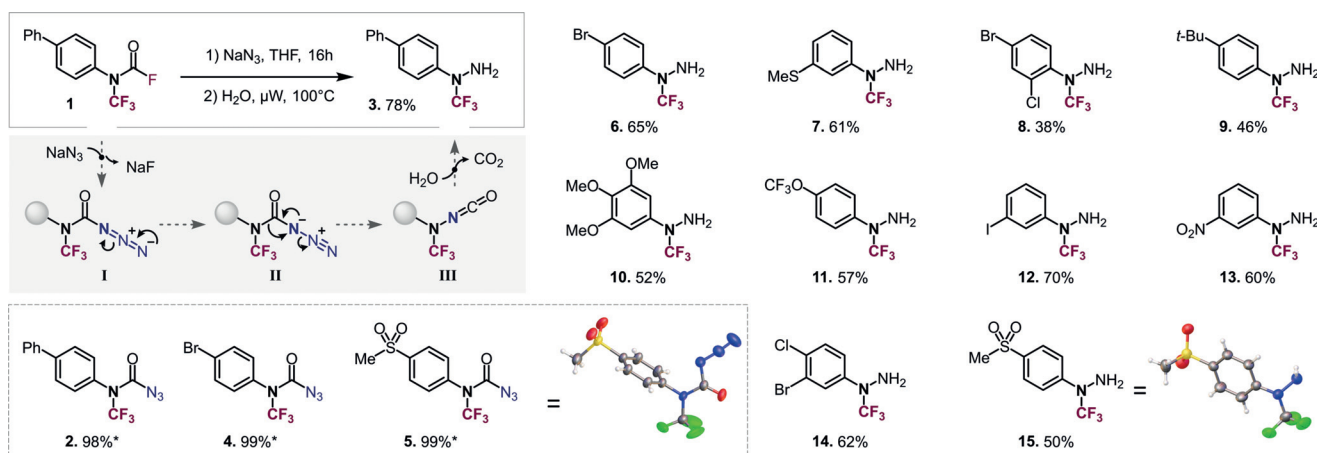


Figure 2. Proposed mechanism for the formation of hydrazines; *yield of carbamoyl azides after filtration; prepared *N*-CF₃ hydrazines (**3**–**15**) and X-ray structures.^[17]

instead on our previous development of a direct synthetic route to *N*-CF₃ carbamoyl fluorides from isothiocyanates (R-NCS),^[15] we set out to explore whether these *N*-CF₃ carbamoyl fluorides could be converted to the corresponding azides and would then potentially rearrange to the corresponding *N*-CF₃ hydrazines (see Figure 2). Such an envisioned Curtius-type rearrangement^[16] is unknown for *N*-CF₃ carbonyl compounds; certainly the key *N*-CF₃ migration (from **II** to **III**, see Figure 2) is not free of challenges, as fluoride elimination from the transient and partially negatively charged *N*-CF₃ could alternatively take place.

We initially set out to prepare the biphenyl carbamoyl fluoride **1** from the corresponding R-NCS compound. To our delight, when we subsequently subjected sodium azide to **1** in THF for 16 hours at room temperature, we successfully formed the corresponding carbamoyl azide **2**, which we isolated by filtration over celite in quantitative (98%) yield (see Figure 2). We unambiguously confirmed the structural integrity of the *N*-CF₃ carbamoyl azide by X-ray crystallographic analysis (see **5**, Figure 2). With the key precursor in hand, we subsequently tested its propensity to undergo the envisioned Curtius-type rearrangement. To our delight, after examining various conditions, we uncovered that *N*-CF₃ carbamoyl azide **2** forms the corresponding *N*-CF₃ hydrazine **3** after heating at 100 °C for 3 days in aqueous THF^[18] in 77% yield.

With the goal to potentially decrease the reaction time, we next turned to microwave-based heating and found that the application of constant temperature (100 °C) using power modulation led to a 24-fold rate increase, shortening the reaction time to only 3 h at 100 °C to reach the same yield of **3**. With this promising protocol in hand, we subsequently set out to explore the wider scope.

With a view towards potential follow-up diversifications, we next studied a derivative bearing an aromatic bromide (**4**). After reacting the corresponding bromo *N*-CF₃ carbamoyl fluoride with NaN₃ for 16 h at room temperature, we filtered and subsequently diluted the reaction mixture with THF and water, before subjecting to microwave irradiation. With this minimally disruptive reaction sequence free of any elaborate

work-up or column chromatography, we were able to obtain **6** in 65% yield. However, the *N*-CF₃ carbamoyl azides proved to be robust and can also be isolated and purified by column chromatography. Alternative halides other than C-Br, that is, iodide (**12**), chloride and polyhalogenated compounds (**8**, **14**) were similarly well tolerated (see Figure 2). Aside from being of value on their own to induce additional function via halogen bonding,^[19] which has become increasingly important in medicinal and material science,^[20] these halogen sites could serve as ideal handles for further diversification via established cross-coupling methodology. In our tests for compatibility of alternative functionalities, we found the protocol to be rather general, tolerating electron-rich as well as electron-deficient arenes. The electron-withdrawing nitro- (**13**), sulfone- (**15**) and even OCF₃ (**11**) groups were equally compatible as the donating methoxy (**10**), sulfide (**7**) or alkyl substituents (**9**). In this context, *meta*- and *para*-substitution were generally well tolerated, whereas the presence of *ortho*-substituents considerably slows the reaction, giving for example, **8** in only moderate yield (= 38%) after microwave irradiation for 36 h (along with unreacted carbamoyl azide). Non-aromatic carbamoyl fluorides, that is, alkyl derivatives, did not result in the corresponding hydrazines.

We envisioned that instead of exploring modified conditions to better tolerate *ortho*-substituents in the Curtius-type rearrangement, a more powerful strategy might potentially be to build on the established ability of hydrazines to function as the directing group in C–H functionalizations.^[21] If the novel *N*-CF₃ hydrazines were similarly able to direct transition metals and simultaneously tolerate modern C–H activation catalysis conditions (which is currently unknown), then this would be a powerful diversification strategy to access a number of different derivatives from a common hydrazine precursor.

Pleasingly, the application of Rh-catalyzed C–H activation^[21b] on hydrazines **6** and **9** allowed us to functionalize the *ortho* position upon reaction with an alkyne to give the corresponding olefins **20** and **21** (see Figure 3), showcasing that the CF₃ substituent does not impede the hydrazine's ability to function as a directing group. A strong feature of

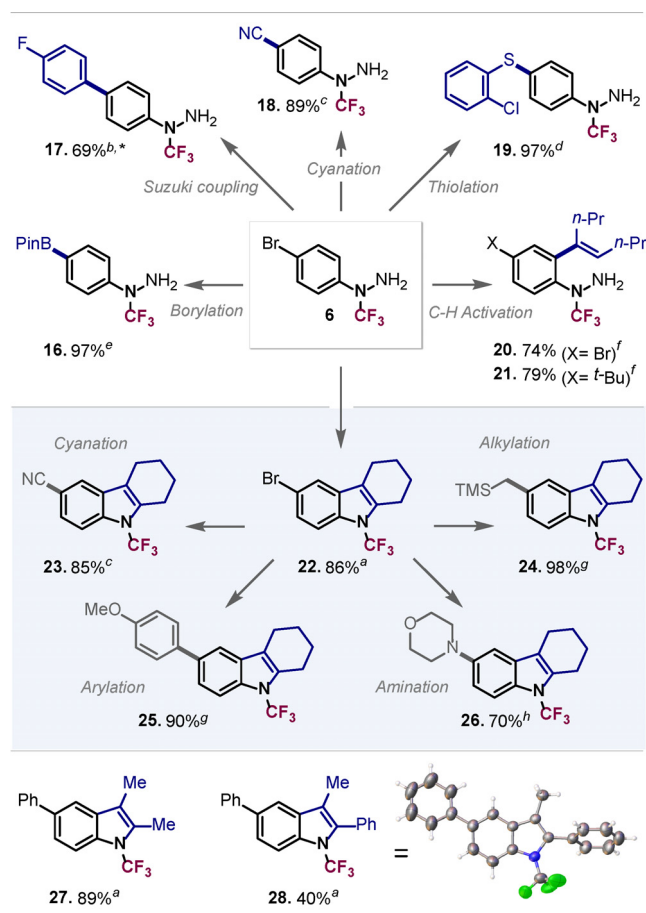


Figure 3. Derivatization of *N*-CF₃ hydrazines and indoles: a) ketone (2.0 equiv), H₂SO₄, MeOH, 80 °C, 4 h; b) ArBpin (1.2 equiv), KOAc (10.0 equiv), Pd(PPh₃)₄ (10 mol %), H₂O/toluene, 120 °C, 16 h; c) NaCN (1.1 equiv), Pd₂dba₃/P(t-Bu)₃ (1.0 mol %), THF/MeCN, 70 °C, 16 h; d) Na-thiolate (1.2 equiv), [Pd^I(μ-I)(PtBu₃)₂] (5 mol %), toluene, 70 °C, 16 h; e) (BPin)₂ (1.1 equiv), KOAc (3.0 equiv), PdCl₂(dppf)·DCM (3 mol %), H₂O/toluene, 100 °C, 16 h; f) alkyne (2.0 equiv), AcOH, AgSbF₆, [RhCp*Cl₂]₂ (2 mol %), MeOH, r.t., 72 h; g) Grignard reagent (1.5 equiv), [Pd^I(μ-I)(PtBu₃)₂] (2.5 mol %), toluene, r.t., 10 min; h) amine (1.2 equiv), Cs₂CO₃ (2.6 equiv), Pd(OAc)₂/BINAP (10 mol %), toluene 120 °C, 16 h.^[17] *Yield of **17** includes a small amount of inseparable impurity.

this transformation is the orthogonality of rhodium catalysis to typical palladium-catalyzed cross-coupling, as the C-Br moiety in **20** remained untouched, which leaves additional opportunities for diversification. With this in mind, we next examined the compatibility of the *N*-CF₃ motif with Pd-catalyzed cross-coupling conditions.

Typical Suzuki cross-coupling conditions were found to be well tolerated, giving arylated **17** in 69 % yield. Similarly, C–S bond formation under Pd^I dimer catalysis^[22] and even the usually sensitive cyanation^[23] proceeded efficiently and gave **19** and **18**, respectively, in high yields. To our delight, the introduction of B-Pin (**16**) was also possible, which offers additional opportunities for functionalization. As such, the *N*-CF₃ hydrazine moiety proved to be compatible with various reaction conditions, including strong base and elevated temperature, suggesting that it is a rather stable and robust motif.

Encouraged by these stability observations, we next set out to tackle the challenge of accessing *N*-CF₃ indoles, and explored whether the *N*-CF₃ hydrazines could also sustain highly acidic conditions and participate in a Fischer indole synthesis. The application of the standard Fischer indole conditions, that is, using H₂SO₄ as a catalyst, methanol as a solvent, and heating at 80 °C,^[24] indeed afforded the *N*-CF₃ indoles **22** and **27** in high yields (86–89 %) and phenylindole **28**, the X-ray crystallographic analysis of which unambiguously confirmed the structure (see Figure 3).

The *N*-CF₃ bond length of **28** in the solid state was determined to be 1.377 Å, which is slightly shorter than similar *N*-CH₃ indoles (1.457 Å). We reproduced this trend also computationally, that is, using DFT optimizations on a variety of compounds, we found fluorination to consistently shorten the N–C bond.^[25] Another noteworthy characteristic was the pyramidalization of the nitrogen, which caused the *N*-CF₃ bond to be 13° out-of-plane with respect to the indole ring. This is analogous to the stereo-electronic situation of other fluorinated motifs, for example, PhOCF₃ or *N*-CF₃ amides,^[8a,e,15,26] resulting in conformers usually inaccessible for the non-fluorinated analogs.

With the C-Br being also present in indole **22**, there is once again opportunity for diversification. Indeed, using dinuclear Pd^I catalysis^[27] it was possible to rapidly alkylate (**24**) and arylate (**25**) the indole core in less than 5 minutes at room temperature in excellent yields with the corresponding Grignard reagents as coupling partner (see Figure 3). The Pd⁰/Pd^{II}-catalyzed cyanation and Buchwald–Hartwig amination were also possible, giving **23** and **26**, respectively, in high yields. As such, the indole *N*-CF₃ motif seems to not only tolerate highly acidic (Fischer indole synthesis^[5e,28]) but also strongly nucleophilic and basic conditions (e.g. Grignard), suggesting that they are highly robust entities, which should enable widespread applications.

With the free NH₂ group in the newly synthesized ArN(CF₃)-NH₂ hydrazines, there is further potential to access higher substituted and unsymmetrical derivatives, and we next set out to also explore this chemical space. We successfully obtained hydrazone **30** in quantitative yield after heating at 80 °C for 3 h in acetic acid (see Figure 4). Hydrazones have uses in catalysis^[29] and material science^[1a,c] and are also useful synthetic intermediates, for example, in reductive aminations of amines to ultimately generate monoalkylated amines/hydrazines. Indeed, our mild reduction of **30** generated the *N*-alkylated hydrazine **31**, leaving the aromatic C-I and *N*-CF₃ groups fully untouched (see Figure 4). Alternatively, we found that the NH₂ could also be selectively coupled with 3-chlorobromobenzene via Pd-catalysis in a Buchwald–Hartwig amination to give **32**. Double arylation did not take place, which showcases that the RN(CF₃)-NH₂ motif can be selectively alkylated and arylated to generate the *N*-CF₃ analogs of higher substituted hydrazines. Straightforward carbonylation with a chloroformate gave carbamate **33**, which demonstrates the possibility for protecting the NH₂, if desired. For this transformation, the stoichiometry had to be carefully controlled to avoid double acylation of the chloroformate. Compound **33** was also further acylated to **34** in good yield using similar conditions to

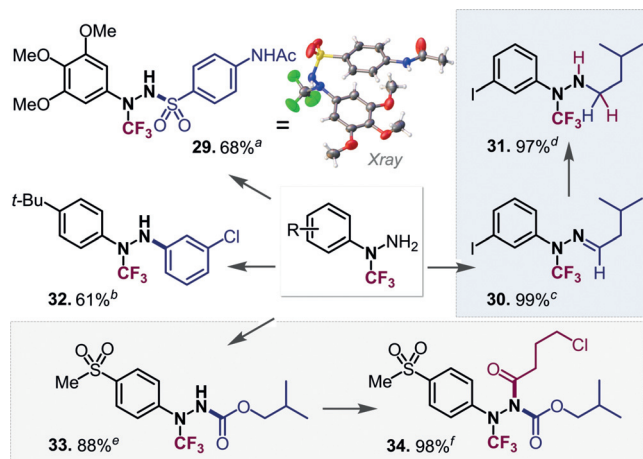


Figure 4. Derivatizations of N -CF₃ hydrazines on the free NH₂ moiety: a) sulfonyl-Cl (1.5 equiv), pyridine (1.5 equiv), DCM, r.t., 16 h; b) ArBr (1.5 equiv), Cs₂CO₃ (1.5 equiv), Pd(OAc)₂/tBu₃P (20 mol %), toluene, 120 °C, 16 h; c) aldehyde (2.0 equiv), AcOH, MeOH, 80 °C, 4 h; d) BH₃NMe₃ (1.0 equiv), HCl (gas), Et₂O; e) iso-butyl chloroformate (1.2 equiv), pyridine (1.5 equiv), DCM, r.t., 2 h; f) acylchloride (2.0 equiv), pyridine (2.0 equiv), DCM, r.t. 24 h.^[17]

generate a fully substituted N -CF₃ hydrazine with four different substituents. Since sulfonamides and their derivatives are also of significant interest in a medicinal and pharmaceutical context,^[30] we reacted **10** with sulfonyl chloride to prepare the sulfonyl hydrazide **29**, which was fully characterized by X-ray crystallographic analysis (see Figure 4).

In summary, a straightforward method was developed to readily access a wide range of N -CF₃ hydrazines. These compounds proved to be very stable under a broad range of conditions, including strong acids, bases, and high temperatures. The hydrazine core was also showcased to readily serve as a platform for the construction of more complex and unsymmetrically substituted N -CF₃ derivatives, including N -CF₃ hydrazones, sulfonyl hydrazines, and N -CF₃ indoles. The feasibility for downstream diversification via modern metal catalysis was also shown. We anticipate numerous applications of this methodology in synthesis, materials sciences, as well as the pharmaceutical and agrochemical arenas to unleash the currently untapped potential of these novel N -trifluoromethylated compounds.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: fluorine · N -CF₃ hydrazine · N -CF₃ indole · synthesis

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