

Stereoselective Direct *N*-Trifluoropropenylation of Heterocycles with a Hypervalent Iodonium Reagent

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Abstract: The availability and synthesis of fluorinated enamine derivatives such as *N*-(3,3,3-trifluoropropenyl) heterocycles are challenging, especially through direct functionalization of the heterocyclic scaffold. Herein, a stereoselective *N*-trifluoropropenylation method based on the use of a bench-stable trifluoropropenyl iodonium salt is described. This reagent enables the straightforward trifluoropropenylation of various *N*-heterocycles under mild reaction conditions, providing trifluoromethyl enamine type moieties with high stereoselectivity and efficiency.

Nitrogen heterocycles are one of the most common and important molecular motifs in nature,^[1] and a significant portion of biologically active molecules are based on this framework.^[2] Among the subclasses of nitrogen heterocycles, *N*-alkenylated molecules are an important class from a synthetic aspect due to the transformability of the double bond^[3] and several derivatives are used in the field of medicinal chemistry.^[4] *N*-alkenylations can be achieved with hydroamination of alkynes^[5] or the functionalization of vinylic species equipped with leaving groups via metal-catalyzed^[6] or metal-free reactions.^[7] The key aspect of these direct functionalizations is the stereoselectivity, thus the development of *E*- or *Z*-selective methods are desirable, however this is challenging.

Fluorine-containing molecules are more and more desired compounds in pharmaceutical, agrochemical and material sciences.^[8] The strategic incorporation of fluorine atoms in organic compounds is a valuable tool for researchers to satisfy the developing needs and expectations for new APIs.^[9] Therefore, versatile synthetic methodologies were developed for the installation of different fluorous functional groups into organic scaffolds.^[10] Among these fluorous motifs, the 3,3,3-trifluoro-

propen-1-yl group is relatively rare and methods which enable its incorporation into heterocycles through the formation of new C–N bond are hardly available and mostly limited to some specific substrates, such as cyclic amides.^[11] The *N*-trifluoropropenylation of enamides such as pyrrolidin-2-one can be achieved through the palladium-^[11a] or copper-catalyzed^[11b] trifluoromethylation of *N*-vinylpyrrolidin-2-one with CF₃I or under photocatalytic conditions (Figure 1a),^[11c–e] while the same product can be obtained with trifluoropropionaldehyde (Figure 1b).^[11f] The use of 3,3,3-trifluoropropyne gas as a C₂-CF₃ surrogate requires the handling of gaseous reagent, but it was successfully applied as Michael acceptor in its reaction with 2'-deoxyiodouridine used for iodinated DNA bases (Figure 1c).^[11g] The NH functionalities in uracil and thymine can be trifluoropropenylated with 2-bromo-3,3,3-trifluoropropene with moderate stereoselectivity (Figure 1c).^[11h]

However, the applicability of the previous methods was demonstrated with only a few trifluoromethylated examples.


Recently, Meyer and Qacemi demonstrated the *N*-trifluoropropenylation of heterocycles such as pyrrole, pyrazole, triazole, and pyridone with the utilization of 2-chloro-3,3,3-trifluoroprop-1-ene (HCFO-1233xf) in a base-promoted transformation under mild reaction condition (Figure 1d).^[12] The reaction favors the formation of the *Z*-isomer, but the *Z/E* isomeric ratio of trifluoropropenyl heterocycles was between 6:4–7:3.


Taking into consideration the importance of the compound class and the limitations of their versatile and selective synthesis, we aimed to develop a novel procedure which enables the direct introduction of trifluoropropenyl functional groups into heterocycles through the formation of new C–N bond in a selective and efficient manner under mild reaction conditions enabled by hypervalent iodonium species.^[13]

In our laboratory, we recently designed and synthesized a bench stable trifluoroisopropenyl iodonium salt (**1**) and studied its reactivity toward nitrogen nucleophiles. Primary amines provided trifluoromethylaziridines,^[14] while the utilization of secondary amines ensured the synthesis of trifluoroalkyl amines and diamines through aziridinium intermediate.^[15] To complete the spectrum of applicable nitrogen nucleophiles, we studied the reaction of nitrogen heterocycles with the trifluoropropenyl-iodonium salt to discover new synthetic possibilities and develop a stereoselective, versatile, and efficient methodology to the access of *N*-trifluoropropenyl heterocyclic species through a one-step direct functionalization (Figure 2).

We choose benzotriazole (**2**) as model substrate for the reactivity and optimization studies, focusing on the effect of base and solvent. To our delight, in dichloromethane with

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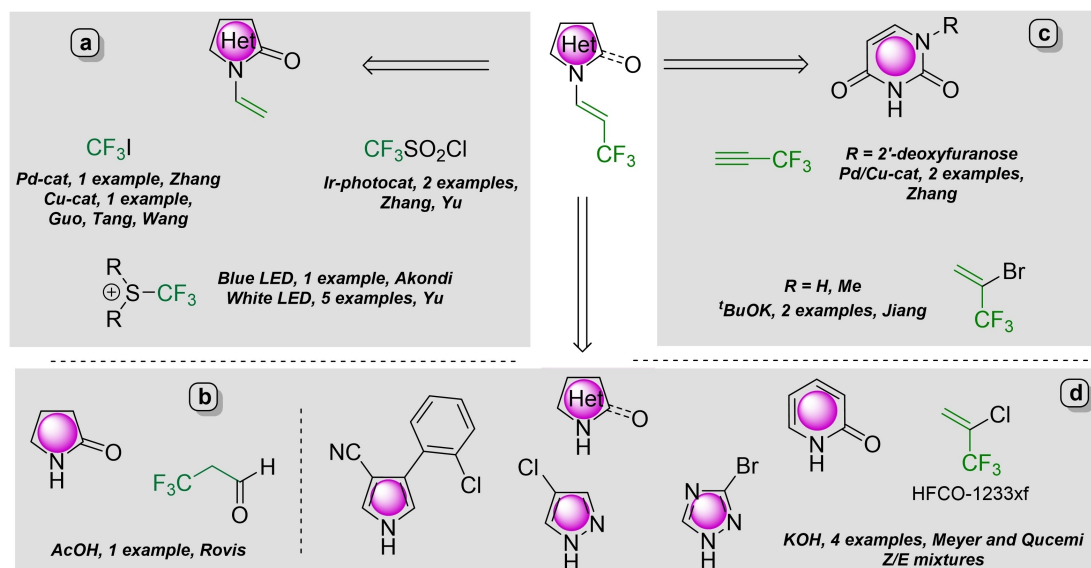
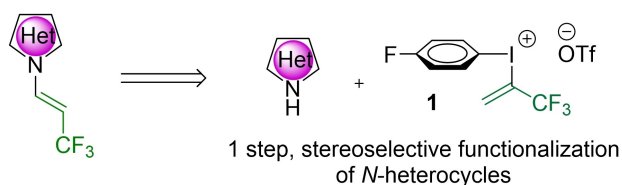
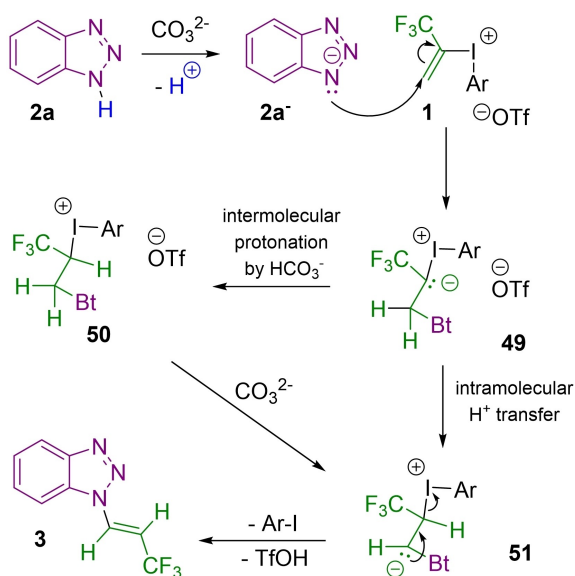
Figure 1. Full spectrum of synthetic approaches to *N*-trifluoropropenyl heterocyclesFigure 2. Research goal: new method for direct trifluoropropenylation of *N*-heterocycles with iodonium reagent.

Figure 3. Proposed reaction mechanism.

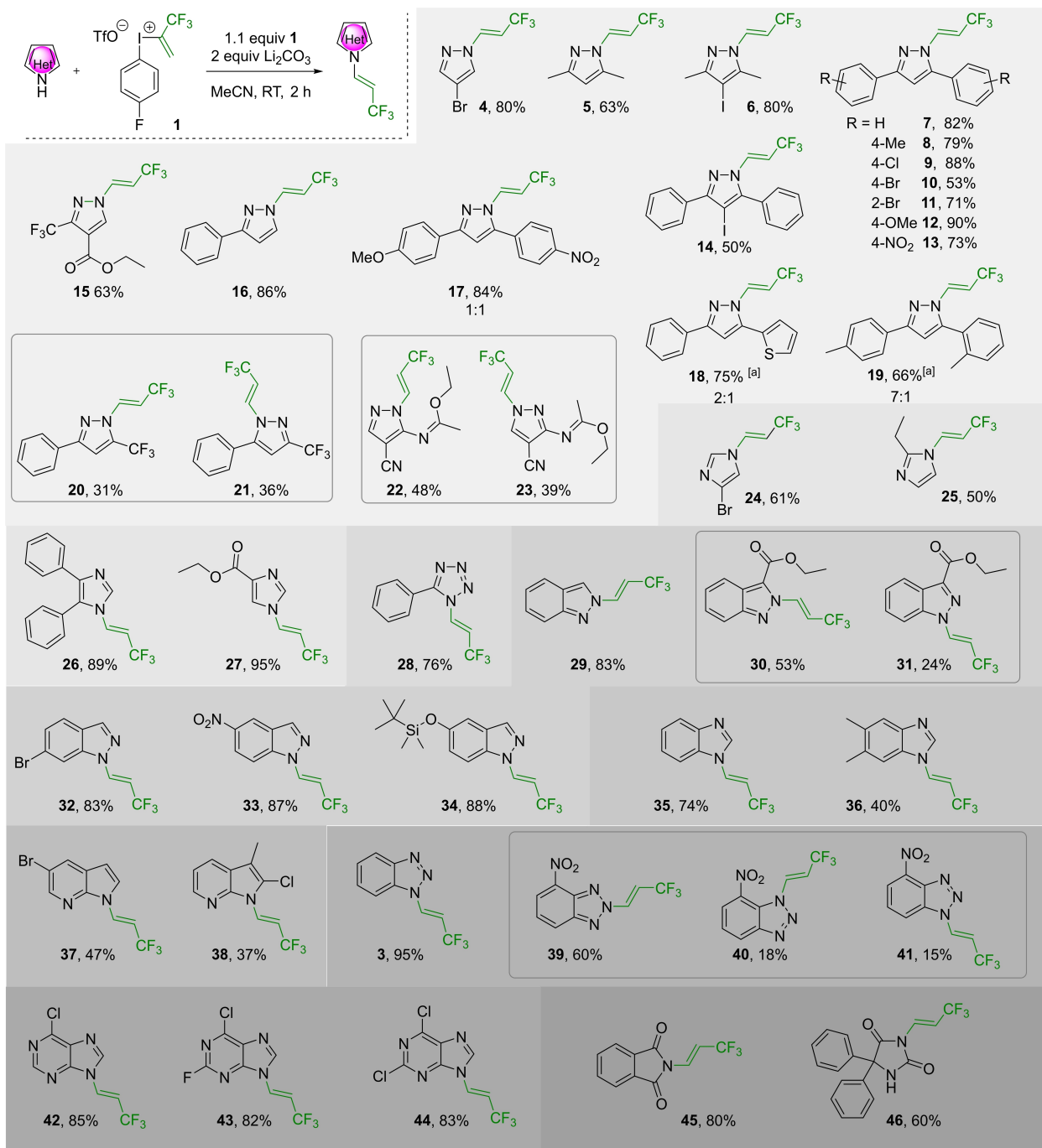
Li_2CO_3 base the desired trifluoropropenylation of benzotriazole with 1.2 equivalent of iodonium reagent 1 the trifluoropropenylation took place on *N*-1 resulting 3 in 83% conversion in 2 h at

25°C (Table 1, Entry 1). However, formation of constitutional isomers was also observed as minor products.^[16] In further optimization, we aimed to improve both the selectivity and the efficiency of the trifluoropropenylation. In this regard, the use of other carbonates such as sodium and potassium resulted lower conversions (80% and 60% respectively, Table 1, Entry 2 and 3). In the presence of NaH, product 3 formed in 75% conversion, while collidine could be used effectively as simple organic base with complete reaction, providing the major product 3 in 85% conversion. Next, we studied some solvent-base pairs including EtOAc, THF, and MeCN as solvents and Li_2CO_3 , Na_2CO_3 , and collidine as bases to find the best

Table 1. Trifluoropropenylation of benzotriazole.^[a]

Entry	Solvent ^[b]	Base	Conversion ^[c]
1	DCM	Li_2CO_3	83
2	DCM	Na_2CO_3	80
3	DCM	K_2CO_3	60
4	DCM	$\text{NaH}^{[d]}$	75
5	DCM	Collidine	85
6	EtOAc	Li_2CO_3	80
7	THF	Li_2CO_3	85 (76)
8	THF	Na_2CO_3	80 (73)
9	MeCN	Collidine	66
10	MeCN	Na_2CO_3	83 (76)
11	MeCN	Li_2CO_3	96 (95)

[a] Reaction conditions: 0.20 mmol benzotriazole, 1.2 equiv. iodonium salt, 2.0 mL solvent, 2.0 equiv. base, room temp. 2 h [b] dry solvents [c] conversion to the main product determined by GC (isolated yield of 3) [d] 1.1 equiv. NaH



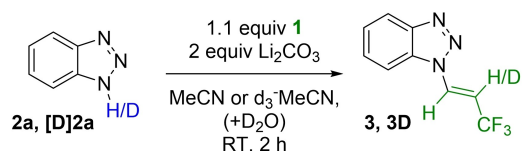
Scheme 1. Substrate scope. N–H heterocycles (0.30–1.00 mmol, 1.0 equiv), Li_2CO_3 (0.60–2.00 mmol, 2.0 equiv), trifluoroisopropenyl idonium salt **1** (0.33–1.10 mmol, 1.1 equiv) and 3–10 mL of MeCN, room temperature, 2 h. [a] the major regioisomer is depicted on the scheme

combination for the selective trifluoropropenylation (Table 1, entries 6–11). We found that the combination of MeCN and Li_2CO_3 provided the best conditions for the reaction, which took place in full regio- and stereoselectivity and the *E*-trifluoropropenylated benzotriazole **3** was isolated in 95% yield after workup.

After finding the optimal solvent-base pair for the transformation (we performed the same solvent-base optimization with indazole, and obtained the same result),^[16] we were also

able to lower the idonium salt loading to 1.1 equivalents without any diminution of isolated yield. Increasing the temperature had no effect on reaction time or yield.^[16]

With the optimized conditions in hand, we aimed to explore the scope of the reaction with the *E*-selective *N*-trifluoropropenylation of various heterocycles bearing NH functionality. In this regard, reactions of pyrazoles provided the desired products under the optimized reaction conditions. Although the parent compound 1*H*-pyrazole could be trifluoropropenylated with full



Substrate	Solvent	D ₂ O	Yield of 3+3D	3D %
2a	MeCN	0	95%	0%
2a	d ₃ -MeCN	0	87%	0%
[D]2a	MeCN	0	93%	19%
[D]2a	d ₃ -MeCN	0	92%	24%
2a	MeCN	1 equiv	95%	25%
[D]2a	MeCN	1 equiv	90%	53%
[D]2a	d ₃ -MeCN	1 equiv	81%	40%

Scheme 2. Study of deuterium transfer.

conversion (not shown),^[16] the isolation of this product was problematic due to its volatility. The presence of Br substituent on the pyrazole ring enabled the isolation of **4** in 80% yield after the trifluoropropenylation.

Next, we examined a series of 3,5-symmetrically disubstituted pyrazoles such as 3,5 dimethyl-pyrazole and its 4-iodinated derivative and we were able to isolate the corresponding products **5** and **6** in 63 and 80% yield, respectively. Symmetric 3,5-diaryl pyrazoles were trifluoropropenylation without difficulties and the products **7–13** were isolated in 53–90% yield range, similarly to the 4-iodo derivative **14** which was isolated in 50% yield.

In case of non-symmetrically substituted pyrazoles, the 3-phenyl and 3-trifluoromethyl-4-carboxy substituted pyrazoles gave exclusively one constitutional isomer **15** and **16** in 86% and 63% yield, indicating the steric and electronic influence on the functionalization. Other non-symmetrically substituted 3,5-diaryl pyrazoles also reacted smoothly, however, only inseparable mixtures of constitutional isomers of **17**, **18**, and **19** could be isolated. In contrast, when 3-phenyl-5 trifluoromethylpyrazole was transformed, isomers **20** and **21** were isolable in 31 and 36% yield, respectively, similarly to products **22** and **23** which were separated and isolated with similar efficiency (48 and 39% yield, respectively).

In the 1*H*-imidazole series, 4-bromo, 2-ethyl, 4,5-diphenyl and 4-ethylcarboxylate derivatives underwent selective trifluoropropenylation and the corresponding enamines **24**, **25**, **26**, and **27** were isolated in 61%, 50%, 89% and 95% yield, respectively.

Among the five membered nitrogen heterocycles 5-phenyl-1*H*-tetrazole gave one constitutional isomeric product (**28**) which was isolated in 76% yield (Scheme 1).

Next, we studied the reactivity of the benzene-fused nitrogen heterocycles having a ring NH functionality. Indazoles were also successfully trifluoropropenylation with iodonium reagent under the optimized conditions.

The reaction of unsubstituted indazole framework provided *N*-2-trifluoropropenylation product **29** selectively in 83% yield.

Presence of ethylcarboxylate group in the pyrazole ring caused the formation of two isomers **30** and **31** which were

isolated after separation in 53% and 24%. Substituents such as Br, NO₂, and TBDMSO on the benzene ring of indazole selectively form *N*-1-trifluoropropenylation products **32**, **33**, and **34** with similar high efficiency (83%, 87% and 88% respectively). Beside the indazole derivatives, benzimidazoles were also successfully transformed and the desired products (**35**, **36**) were formed selectively and isolated in 74% and 40% yield.

In this series, we aimed for the transformation of indole, but we observed the formation of complex reaction mixture without the detection of the desired product.^[17] However, azaindoles were trifluoropropenylation successfully and enamine products **37** and **38** were isolated in 47% and 37% yields, respectively.

Although our model substrate benzotriazole used for the optimization studies, gave exclusively one product (**3**) under the optimized conditions in 95% isolated yield, the reaction with its 4-nitro-substituted derivative gave three regioisomers **39**, **40** and **41**, which were isolated in 60%, 18%, and 15% respectively after chromatographic purification.

Using the iodonium based functionalization protocol *N*-trifluoropropenylation purine derivatives **42**, **43**, and **44** were also isolated in high yields, giving the products in 85%, 82%, and 83%, respectively.

To our delight, not just aromatic heterocycles, but also heterocyclic imides were transformed efficiently using the developed methodology. Phthalimide reacted smoothly and the corresponding trifluoropropenyl-phthalimide **45** was isolated in 80% yield. Phenytoin was also a suitable substrate for the transformation, and we were able to isolate the *N*-trifluoropropenylation product **46** in 60% yield.

On the basis of our previous studies, we propose a mechanism for the trifluoropropenylation (Figure 3).

After the deprotonation step, the heterocyclic anion attacks to the terminal sp² carbon of the trifluoropropenyl moiety in a Michael addition type reaction, then the formed benzotriazolyl iodonium ylide (**49**) undergoes intramolecular proton transfer resulting anion **51**. Alternatively, the stabilized carbanion (**49**) can be protonated by the HCO₃[−] ion in an intermolecular fashion forming intermediate **50** which can be deprotonated by the base, with the resulting anion **51** undergoing *E*-selective elimination step to provide the final product **3**.

To support the mechanistic hypothesis, especially the relevance of intramolecular and intermolecular proton transfers, we performed the reactions with both [1*H*] and [1*D*] benzotriazole (**2a** and **[D]2a**) in MeCN and d₃-MeCN, and measured the deuterium incorporation in the product (Scheme 2). The [1*H*] substrate **2a** gave product **3** with 0% deuterium incorporation both in MeCN and d₃-MeCN (isolated yields 95% and 87%). Trifluoropropenylation of **[D]2a** in MeCN resulted 19% deuterium incorporation, while in d₃-MeCN the same reaction provided the product with 24% deuterium incorporation. In the presence of 1 equivalent of D₂O, the deuterium incorporation increased about 15–20% independently from the substrate and the applied solvent, showing the possibility of intermolecular protonation. These results support that both H-atoms of trifluoropropenyl group of the product are dominantly derived from the reagent **1** through intramolecular proton transfer, but

intermolecular base assisted proton transfer could also operate, beside some minor solvent effect on the proton transfer.

In summary, we developed a novel methodology for the direct *N*-trifluoropropenylation of heterocyclic molecules with the use of a trifluoropropenyl iodonium salt. The reaction enables the stereoselective synthesis of trifluoromethyl enamines having the potential in further transformations and adds to the synthetic applicability of trifluoropropenyl iodonium species toward versatile nitrogen nucleophiles.

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Conflict of Interest

The authors declare no conflict of interest.

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- [16] for details see Supporting Information.
- [17] the transformation of some additional heterocyclic systems was also unsuccessful. For details see Supporting Information.

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