

Regiospecific Synthesis of 1-Trifluoromethylisoquinolines Enabled by Photoredox Somophilic Vinyl Isocyanide Insertion

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Abstract: A strategy has been developed for the regiospecific synthesis of 1-trifluoromethylisoquinoline derivatives. This strategy is enabled by a photoredox vinyl isocyanide insertion with the help of Umemoto's reagent. The methodology presented here provides an access to highly functionalized 1-trifluoromethylisoquinolines regiospecifically under mild conditions in good-to-excellent chemical yields. A detailed mechanism is proposed, which is supported by experiments and theoretical calculations.

Keywords: iridium; isocyanides; isoquinolines; photochemistry; trifluoromethylation

Introduction of the trifluoromethyl (CF₃) group into organic compounds has attracted the attention of chemists for decades, due to the unique properties of trifluoromethylated molecules, such as elevated electronegativity, hydrophobicity, metabolic stability, and bioavailability.^[1] Aromatic and heterocyclic compounds bearing one or more CF₃ groups on the ring are important intermediates and building blocks for the synthesis of numerous modern pharmaceuticals, highly efficient crop protection agents, and specialty materials.^[2]

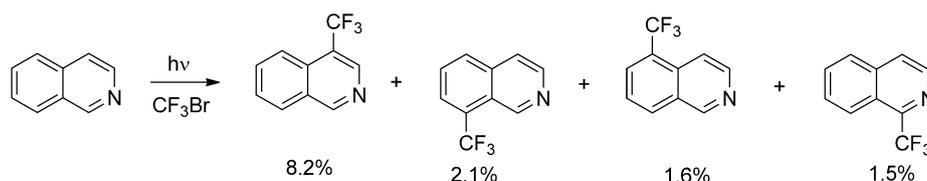
Recently, a variety of processes has been developed for the incorporation of the CF₃ group into diverse aromatic compounds.^[3] Particularly, transition metal-mediated or -catalyzed C–CF₃ bond formation reactions have emerged as powerful synthetic tools in this area in the past decade.^[3b–d] For these methods, the aromatic rings have to be pre-functionalized, such as

aryl halides, boronic acids, sulfonates or as arenes bearing a directing group.^[4] Direct C–H trifluoromethylation protocols, which obviate the need for pre-functionalization of the substrates, become the focus of many researchers.^[5] These methods provide straightforward and efficient routes to aromatic and heterocyclic trifluoromethylated products. However, the regioselectivity of these transformations is often questionable.^[6]

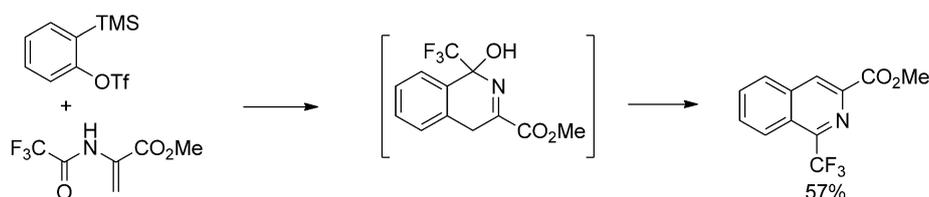
In particular, trifluoromethylated isoquinoline derivatives are frequently encountered in pharmaceuticals and natural products.^[7] Methods to access these valuable structures are very limited.^[8] Trifluoromethylations of isoquinolines at C-3 (the poorest electron density) or C-4 (the highest electron density) position can be achieved regioselectively,^[8c–g] while 1-CF₃-isoquinolines have seldom been accessed. As observed by Akiyama and co-workers,^[8a] direct trifluoromethylation of isoquinoline under irradiation of a high-pressure mercury lamp with gaseous CF₃Br led to a mixture of four regioisomers in 13.4% overall yield. 4-CF₃-isoquinoline was isolated as a major product in 8.2% yield while the 1-CF₃-isomer was only produced in 1.5% yield as a minor product (Figure 1, A). The Stoltz group reported an elegant synthesis of a 1-CF₃-isoquinoline derivative *via* aryne annulation.^[8b] Only one example was mentioned in this work (Figure 1, B). So it remains an unsolved challenge to diversely access 1-CF₃-isoquinoline derivatives regiospecifically.

Recently, our group became interested in visible light-promoted somophilic triple bond insertions to provide functionalized (hetero)arenes.^[9] Comparing to biphenyl isocyanides, which have frequently been used to construct phenanthridine derivatives,^[9b,c,10] the chemistry of vinyl isocyanides remains mainly unexplored.^[11] Very recently, we reported the synthesis of

A: Direct trifluoromethylation of isoquinolines (ref.^[8a])



B: Synthesis of 1-CF₃-isoquinoline via aryne annulation (ref.^[8b])



C: Regiospecific synthesis of 1-CF₃-isoquinolines via vinyl isocyanide insertion (**this work**)

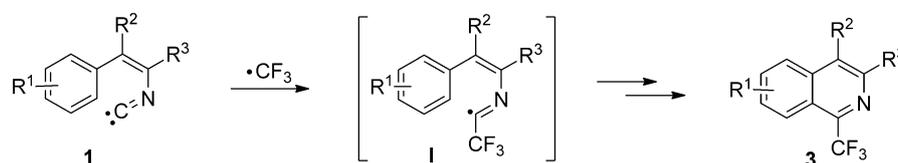


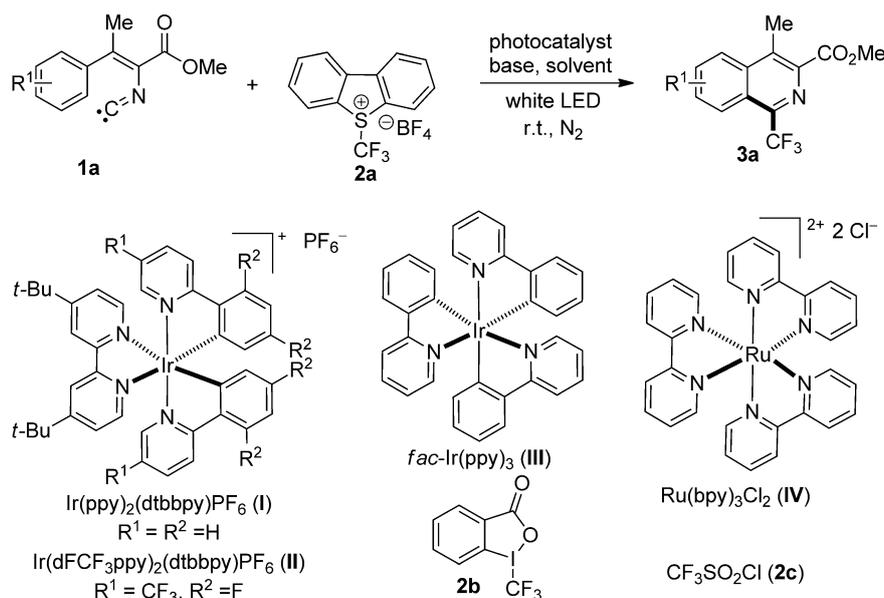
Figure 1. Strategies for the synthesis of 1-CF₃-isoquinolines.

1-arylisquinoline derivatives using the somophilic insertion of vinyl isocyanides.^[9d] Based on this work, we speculated that 1-CF₃-isoquinoline derivatives could be accessed with the help of this strategy. When vinyl isocyanide **1** is employed as a somophile to react with the CF₃[•] radical, an imidoyl radical **I** can be generated. After intramolecular homolytic aromatic substitution (HAS)^[12] and an oxidation and deprotonation sequence, 1-CF₃-isoquinoline derivatives **3** can be formed ultimately (Figure 1, C). This *de novo* strategy to access 1-CF₃-isoquinolines assisted by somophilic vinyl isocyanide insertion can address the regioselectivity issue and can also be realized under mild conditions. Herein, we would like to report a visible light-promoted trifluoromethylation of vinyl isocyanides as a modular approach to 1-trifluoromethylated isoquinolines.^[13,14]

Initially, we examined this hypothesis using methyl (*Z*)-2-isocyano-3-phenylbut-2-enoate (**1a**) and Umemoto's reagent (**2a**)^[15] as model substrates (Table 1). When a solution of **1a** and **2a** in DMF was irradiated by 13 W white LED in the presence of the photocatalyst Ir(ppy)₂(dtbbpy)PF₆ (**I**) and Na₂HPO₄ for 3 h, the desired isoquinoline **3a** was isolated in 62% yield (entry 1). Several common polar solvents were screened, such as DMSO, CH₃CN, THF, but they could not give any improved results (entries 2–4). The non-polar solvents, such as toluene, were not effective at all (entry 5). To our delight, an 88% yield was

achieved when MeOH was used as a solvent (entry 6). EtOH could not improve the result (entry 7). The bases, such as Na₂CO₃, NaHCO₃, and K₂HPO₄, were also tested, but none of them gave better results (entries 8–10). Other photocatalysts, such as **II**, **III** and **IV**, also gave good yields of the isolated products, which showed that the photocatalyst did not affect this transformation significantly (entries 11–13). Other CF₃[•] radical precursors, such as Togni's reagent (**2b**) and CF₃SO₂Cl (**2c**), were also investigated, but none of them gave better yields (entries 14 and 15). Control experiments verified the necessity of the base, irradiation and photocatalyst (entries 16–18). Without light and photocatalyst, no desired product was isolated even if the reaction mixture was heated up to 60 °C.

Having identified the optimal conditions, we proceeded to explore the scope of this reaction (Table 2). Firstly, aliphatic aryl ketone-derived vinyl isocyanides were examined. Generally, the reactions proceeded quite well and 1-CF₃-isoquinolines **3a–h** were generated in 28–89% yields. It was found that the electronic property of phenyl groups had a significant effect on this transformation. The isocyanide with an electron-rich phenyl group is more reactive than the one with an electron-deficient phenyl group (**3b** vs. **3c**). The low yield of the isocyanide with an electron-deficient phenyl group was due to the decomposition of the isocyanide. The reactions with diaryl ketone-derived

Table 1. Optimization of the reaction conditions.^[a]


Entry	Catalyst	Solvent	Base	Yield [%] ^[b]
1	I	DMF	Na_2HPO_4	62
2	I	DMSO	Na_2HPO_4	53
3	I	CH_3CN	Na_2HPO_4	56
4	I	THF	Na_2HPO_4	57
5	I	toluene	Na_2HPO_4	trace
6	I	MeOH	Na_2HPO_4	88
7	I	EtOH	Na_2HPO_4	84
8	I	MeOH	Na_2CO_3	78
9	I	MeOH	NaHCO_3	80
10	I	MeOH	K_2HPO_4	68
11	II	MeOH	Na_2HPO_4	73
12	III	MeOH	Na_2HPO_4	83
13	IV	MeOH	Na_2HPO_4	84
14 ^[c]	I	MeOH	Na_2HPO_4	49
15 ^[d]	I	MeOH	Na_2HPO_4	62
16	I	MeOH	none	47
17	none	MeOH	Na_2HPO_4	trace
18 ^[e]	I	MeOH	Na_2HPO_4	NR

^[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), base (0.3 mmol) and catalyst (0.002 mmol, 1.0 mol%) in the indicated solvent (2.0 mL) were irradiated by 13 W white LED for 3 h at room temperature. DMF = *N,N*-dimethylformamide, DMSO = dimethyl sulfoxide, THF = tetrahydrofuran.

^[b] Isolated yield.

^[c] **2b** instead of **2a**.

^[d] **2c** instead of **2a**.

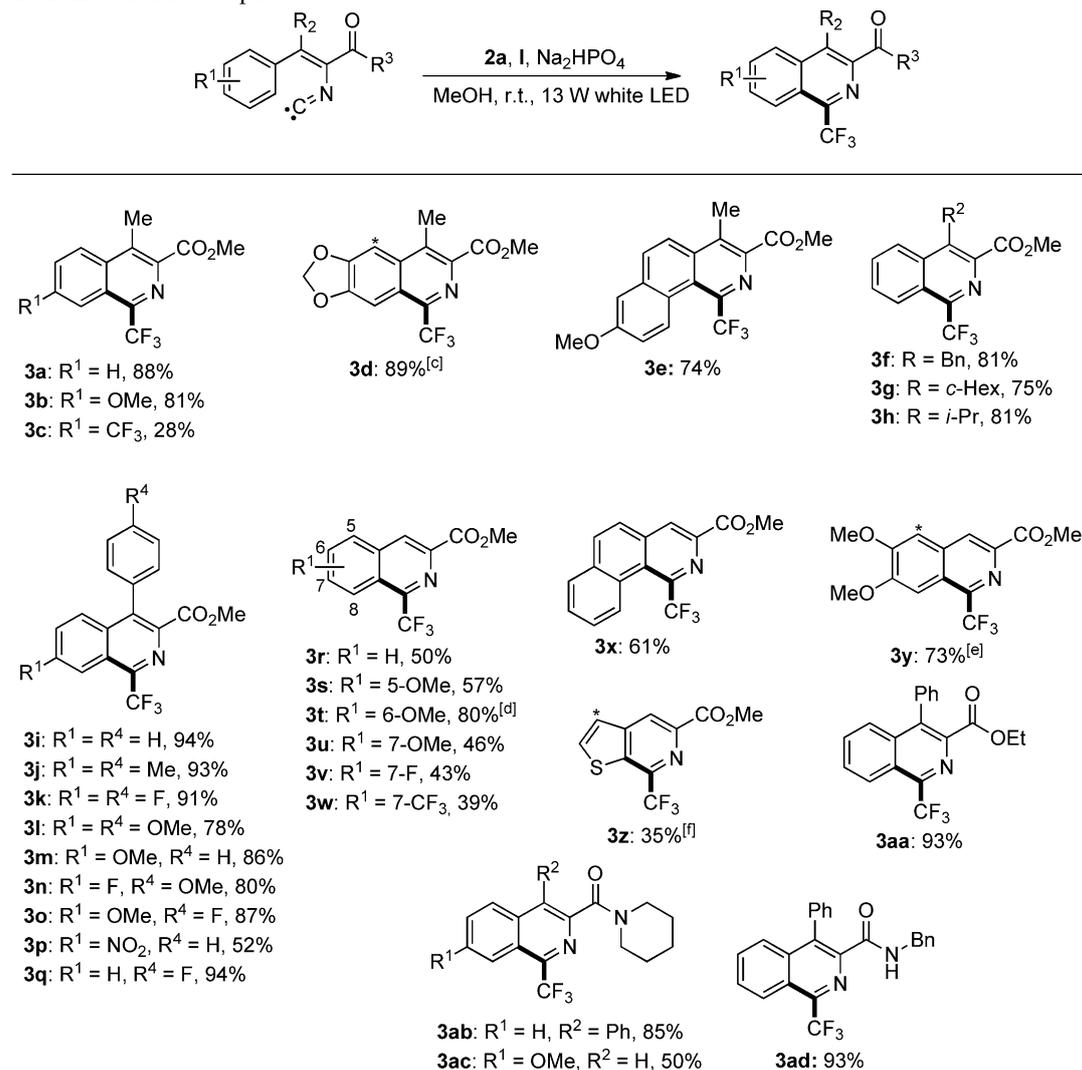
^[e] No irradiation.

vinyl isocyanides worked also quite well. The corresponding isoquinolines **3i–q** could be provided in satisfactory yields (52–94%). Then aryl aldehyde-derived vinyl isocyanides were employed. Generally, the reactivity of this type of vinyl isocyanide was lower than that of the ketone-derived counterparts. The desired isoquinolines **3r–z** could be obtained in acceptable yields (35–80%). Ethyl ester- or amide-based vinyl isocyanides also underwent this transformation

smoothly, the corresponding isoquinolines **3aa–ad** were generated in good yields (50–93%). The vinyl isocyanides without electron-withdrawing groups are quite unstable, and have thus not prepared successfully by us at this stage.

In order to obtain further insights into the reaction mechanism, a series of TEMPO trapping experiments was employed. As shown in Scheme 1, when Umemoto's reagent **2a** was treated with the radical scavenger

Table 2. Substrate scope.^[a,b]



^[a] Reaction conditions: **1** (0.2 mmol), **2** (0.3 mmol), NaHPO₄ (0.3 mmol) and **I** (0.002 mmol, 1.0 mol%) in MeOH (2.0 mL) was irradiated by 13 W white LED for 1–4 h at room temperature.

^[b] Isolated yield.

^[c] Regioisomer ratio: 3.5:1, determined by ¹⁹F NMR.

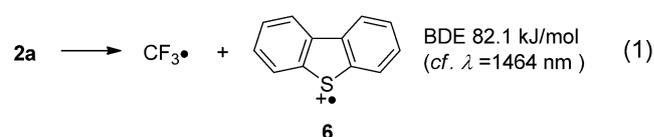
^[d] Regioisomer ratio: 1:1, determined by ¹⁹F NMR.

^[e] Regioisomer ratio: 7.6:1, determined by ¹⁹F NMR.

^[f] Regioisomer ratio: 1:1, determined by ¹H NMR.

TEMPO in the dark, only a trace of trapping product **4** was detected based on ¹⁹F NMR analysis. Instead, the adduct **4** was observed in comparable yields when the trapping reactions were carried out under visible light irradiation irrespective of whether the photocatalyst **I** was present. When isocyanide **1i** was introduced into the trapping experiments, no obvious changes were observed. These observations strongly suggest that generation of the CF₃• radical from Umemoto's reagent can be achieved only under visible light irradiation and is independent of the photocatalyst and isocyanide.

These experimental observations can be supported by theoretical calculations. Density functional theory [B3LYP/6-311++G(d,p)] calculation indicates that the C–S bond in **2a** is rather weak with a low bond dissociation energy (BDE) ($\Delta G_{298} = 82.1 \text{ kJ mol}^{-1}$) [Eq. (1)], which is located in the infrared area. Visible light is strong enough to induce the homolytic cleavage of the C–S bond in **2a**.



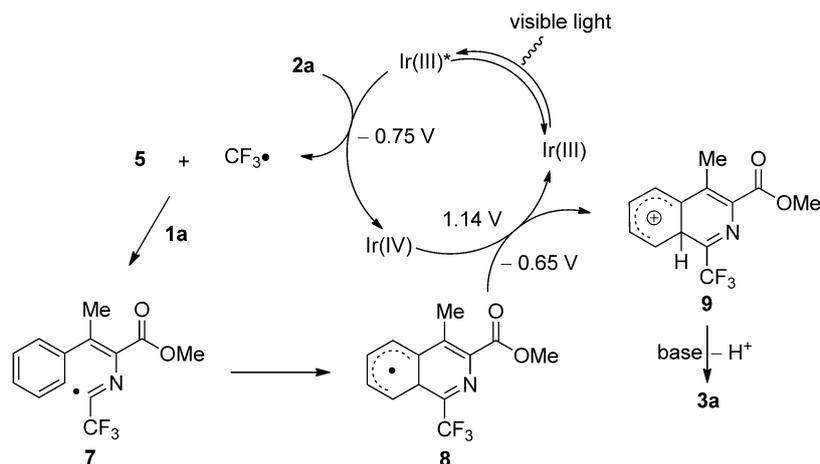


Figure 3. Alternative reaction mechanism.

ature in good-to-excellent chemical yields. The mechanism of this reaction was investigated experimentally and theoretically. A novel and reasonable mechanism was proposed. Further explorations on the chemistry of vinyl isocyanides and the biological evaluation of 1-CF₃-isoquinolines, as well as more detailed mechanism investigations are underway in our laboratory.

Experimental Section

General Procedure

A 10-mL round-bottom flask was equipped with a rubber septum and magnetic stir bar and was charged with vinyl isocyanide **1** (0.2 mmol, 1.0 equiv.), Umemoto's reagent **2a** (0.3 mmol, 1.5 equiv.), Ir(ppy)₂(dtbbpy)PF₆ (0.002 mmol, 0.01 equiv.), Na₂HPO₄ (0.3 mmol, 1.5 equiv.). The flask was evacuated and backfilled with argon for 3 times. MeOH (2.0 mL, 0.1 M) were added with syringe under argon. The mixture was then irradiated by a 13 W white LED strip. After the reaction was complete (as judged by TLC analysis), the solvent was removed under reduced pressure directly. The crude product was purified by flash chromatography on silica gel to afford the desired product **3**.

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