Visible-Light-Assisted Synthesis of Allylic Triflamides via Dual Acridinium/Co Catalysis

Visible light assisted synthesis of allylic-triflamides via dual acridinium/Co catalysis

Simone Battaglioli,[a] Giulio Bertuzzi,[a] Riccardo Pedrazzani,[a] Jessica Benetti,[a] Giovanni Valenti,[a] Marco Montalti,[a] Magda Monari,[a] Marco Bandini*[a,b]

[a] Dipartimento di Chimica "Giacomo Ciamician", Alma Mater Studiorum – Università di Bologna, via Selmi 2, 40126 – Bologna, Italy
[b] Consorzio C.I.N.M.P.I.S., via Selmi 2, 40126 – Bologna, Italy.

Received: ((will be filled in by the editorial staff))

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201######.((Please delete if not appropriate))

Abstract. An efficient dehydrogenative functionalization of styryl carbon-carbon double bonds with triflamide is described via dual visible-light photoredox/cobaloxime catalysis. A range of allylic triflamides (20 examples) were isolated in good to excellent yields (up to 88%) under stoichiometric acceptorless conditions. Dedicated labelling, as well as spectroscopic experiments, enabled to shed light on the concatenated photo- and chemo-catalytic cycles.

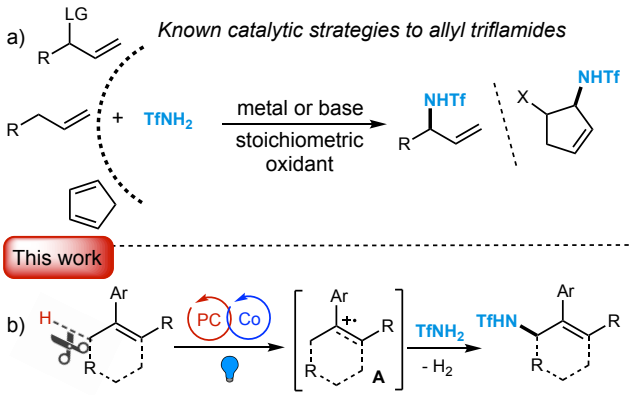
Keywords: Allyl amines; Triflamide; C-H activation; Photocatalysis; Cobaloxime.

Unsaturated triflamides and more specifically allylic triflamides[1] have rapidly reached the status of key building blocks in organic synthesis for the creation of chemical diversity and complexity.[2] The marked Brønsted acidity of the "NHTf" motif (pKa ca. 6.3, for $TfNH_2$),[3a-c] the ready access to unprotected amino groups[3d-g] and the chemical flexibility of the allyl unit[2a,c] account for the prominent role played by this class of nitrogen-based compounds in the organic chemistry scenario.

Common synthetic strategies for the preparation of allylic triflamides require the use of pre-functionalized allylic scaffolds and dienes[4a] or the direct metal-catalysed activation/amination of allylic Csp^3 C-H bonds in the presence of stoichiometric organic as well as inorganic oxidants (Figure 1a).[4b-d]

In this context, major progresses were recently achieved by combining chemo-catalysis and visible-light assisted protocols for the construction of new C-N bond connectivity under stoichiometric acceptorless conditions.[5] Despite this flourishing scenario, the use of trifluoromethansulfonamide (*i.e.* triflimide, $TfNH_2$) has never been systematically investigated under a visible-light photoredox aminative regime, so far.[6]

Herein, we tackle this intriguing scientific "vacancy", exploiting the well-consolidated dual cobaloxime/acridinium-based photoredox formal β-hydrogen elimination coupling[7] as a direct synthetic route to allylic triflamides under mild and stoichiometric acceptorless conditions. The present working plan stems from our recent findings, directed to the synthesis of allylic carboxylates via photoredox dual-catalyzed condensations of carboxylic acids and styrenes.[8,9] The pKa of the nucleophilic partner was found as a reliable parameter for predicting the effectiveness of the process, with the optimal values ranging from 5 to 6. Therefore, the similarity in pKa values between common carboxylic acids and $TfNH_2$ elected the titled nitrogen-based compound for the trapping of the *in situ* formed radical cation intermediate **A** (Figure 1b).



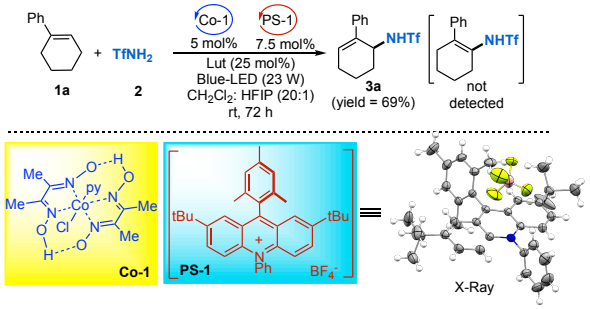
Scheme 1. (a) Common synthetic protocols to allyl triflamides and (b) present dual catalyzed dehydrogenative coupling with styryl compounds.

The successful realization of the postulated working plan would represent a significant synthetic advancement toward the obtainment of allylic triflamides in a simple, selective and sustainable manner.

In this study, a large portfolio of reaction parameters, such as the nature of the photosensitizer and cobalt complex, solvent, light source, concentration and additives,[10] were assessed (see Table 1) in the dehydrogenative coupling of 1-phenyl-1-cyclohexene **1a** with $TfNH_2$ **2**. Optimal conditions were found to employ [Co(III)(dmgH)$_2$pyCl] **Co-1** (dmgH = dimethylglyoximate, py = pyridine)[11] (5 mol%), *N*-phenyl acridinium **PS-1** (7.5 mol%)[8] and 2,6-lutidine (lut, 0,25 eq.) in a DCM:HFIP (20:1) solvent mixture, under blue-LED (23 W, 461 nm) irradiation at room

temperature for 72 h. These conditions delivered the desired allylic triflamide **3a** (*anti*-Markovnikov regioselectivity) in 69% yield as a single regioisomer.[12]

Table 1. Optimization of the reaction conditions.

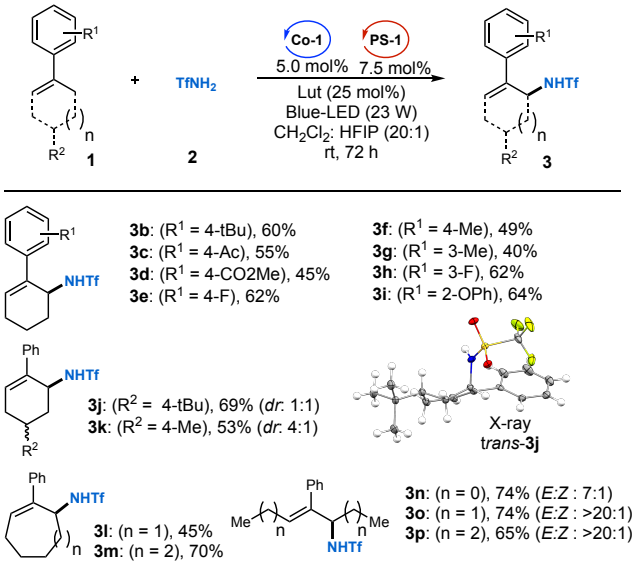


Run[a]	Deviation from optimal	Yield of **3a** (%)[b]
1	-	72 (69)
2	No cobaloxime (**Co-1**)	NR
3	No photosensitizer (**PS-1**)	NR
4	dark	NR
5	No HFIP	48
6	No base	NR
7	Cs_2CO_3 as base (0.25 eq.)	62
8	Pyridine as base (0.25 eq.)	64
9	2,6-$(tBu)_2$-py as base (0.25 eq.)	44
10	Lut (1 eq.)	59
11	$PhCF_3$ as solvent	5
12	$(CH_2)_2Cl_2$ as solvent	61
13	Blue-LED (1 W)	29
14[c]	Blue-LED (40 W)	28
15	**2** (2 eq.)	59
16	**2** (2 eq.)	69
17	With TEMPO (5 mol%)	NR
18	With TEMPO (1 eq.), no **Co-1**	60

[a] Reaction conditions: **1a** (0.1 mmol, 0.1 M), **2** (5 eq), **Co-1** (5 mol%), **PS-1** (7.5 mol%), lutidine (25 mol%), Blue-LED (461 nm) under nitrogen and degassed solvent, unless otherwise specified. [b] Determined by ^{1}H-NMR analysis on the reaction crude with ethylene carbonate as an internal standard. Isolated yields upon flash chromatography are reported in parenthesis. [c] Reaction time 24 h. NR: no reaction and **1a** was recovered untouched.

The synergistic role of both cobaloxime **Co-1** and acridium salt **PS-1**[13] was verified by running the model transformation in their absence (entries 2 and 3). Additionally, the genuine photocatalysis was proved by the failure of the protocol carried out in the dark (entry 4). Moreover, and the presence of a base was proved to be analogously important (specifically 2,6-lutidine: lut, entries 6-10). Concerning the reaction media, halogenated solvents (*i.e.* CH_2Cl_2, $(CH_2)_2Cl_2$) proved to be far superior, and a remarkable improvement in the chemical outcome was obtained by using HFIP (hexafluoroisopropanol) as a cosolvent (entry 5).[14] Finally, variations on the light source intensity (entries 13 and 14) and **1a**/**2** stoichiometric ratios (entries 15 and 16) did not enable higher yields to be accomplished.

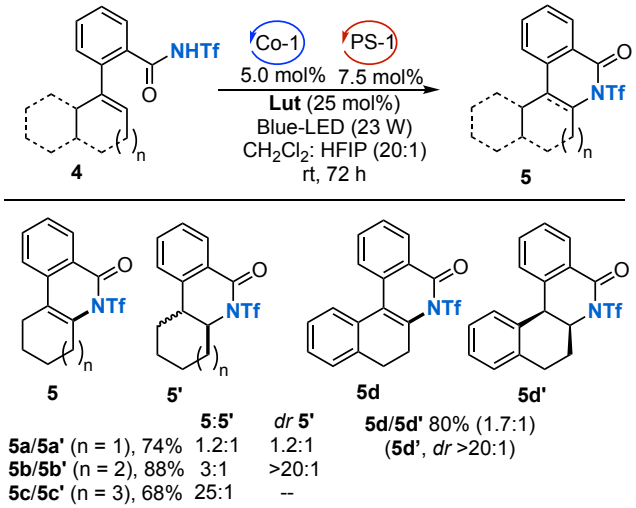
With the optimal reaction conditions in hand, we evaluated the generality of the process (Scheme 1). Substituents of different electronic nature such as mild electron-rich *tert*-butyl or electron-withdrawing ketone, ester or fluorine were well tolerated at the *para* position of the aryl moiety of aryl-cyclohexenes **1**, delivering the corresponding products **3b-e** in 45-62% yield. Methyl-substituted **3f** and **3g** were however isolated in slightly lower yields, probably due to concomitant side-oxidation of the tolyl group. On the other hand, substitution at the *meta* (**3h**) or sterically encumbering *ortho*-positions (**3i**) was also well-tolerated, as well as substituents on the cyclohexene moieties (**3j** and **3k**). Products **3l** and **3m**, featuring a 7- and an 8-membered ring, could be productively isolated by subjecting 1-phenylcycloheptene **1l** and 1-phenylcyclooctene **1m** to the optimized reaction conditions (yields up to 70%), showing that the size of the ring of aryl-cycloakenes **1** is not a substantial limitation of the disclosed protocol. Furthermore, by productively employing styrenes **1n-1p**, the process is shown to be applicable to acyclic alkenes as well, delivering products **3n-3p** in good (65-74%) yield.



Scheme 1. Generality of the methodology towards intermolecular condensations.

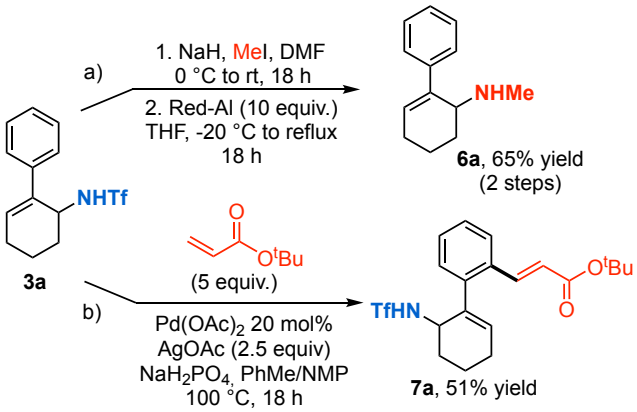
An intramolecular variant of the disclosed process could be implemented by subjecting styryl-triflimido compounds **4** to the optimized reaction conditions (Scheme 2).[15] This provided access to intriguing nitrogen-containing tri- or tetracyclic scaffolds **5**. Compounds **4** performed differently in comparison with simple styrenes **1**. Indeed, fully hydrogenated compounds **5'** (mixtures of diastereoisomers) were sometimes isolated in substantial amounts, along with expected products **5**. Compounds **5a-d** were found to have an endocyclic conjugated double bond, thus resulting in vinyl-triflimide moieties, as opposed to

non-conjugated allyl-triflamides **3**. On the other hand, the intramolecular process was found to be generally more efficient and high yielding. Tetrahydrophenantridone **5a** and hexahydrophenantridone **5a'** were thus obtained in 74% combined yield from cyclohexene **4a**. Cycloheptene **4b** rendered the respected cyclized products **5b**/**5b'** in high yield (88%). Interestingly, in the case of cyclooctenyl derivative **5c**, no evidence of further reductions was detected (yield = 80%). Furthermore, by productively engaging tetralone-derivative **5d** in the desired process, we demonstrated the possibility to obtain benzo-fused scaffolds as well, without appreciable levels of full re-aromatization.



Scheme 2. Generality of the methodology towards intramolecular condensations.

The introduction of the triflamide group onto styrenes **1** is a general platform for the preparation of a variety of substituted allylamines. This was verified by subjecting **3a** to a facile alkylation (MeI/NaH/DMF)-deprotection (Red-Al) sequence (Scheme 3a), delivering the desired product **6a** in useful synthetic overall yield (65%, 2 steps). Additionally, the photochemically introduced triflamide group was demonstrated to effectively serve as a directing group for site-selective *ortho*-Csp^2-H activation reactions. In particular, the treatment of **3a** with excess *tert*-butyl acrylate ($Pd(OAc)_2$ 20 mol%, AgOAc 2.5 eq and NaH_2PO_4), resulted in the C-H functionalization product **7a** in moderate yield (51% unoptimized, Scheme 3b).



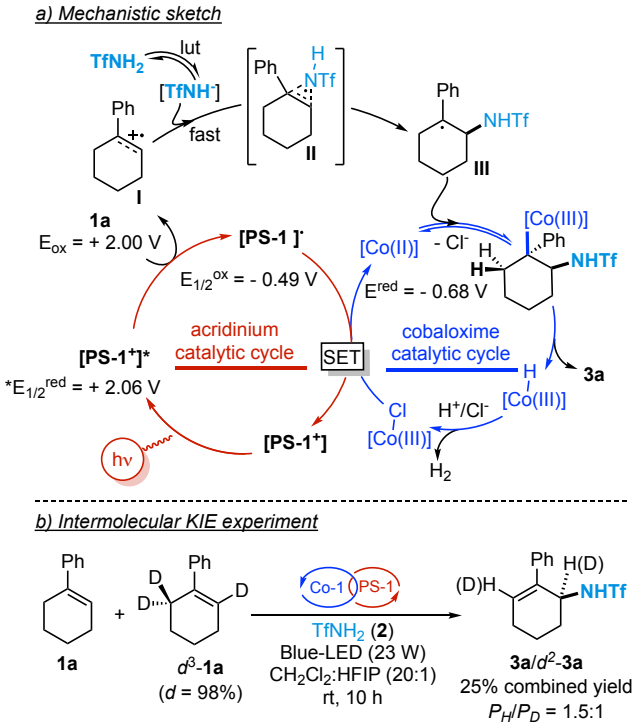
Scheme 3. Examples of chemical manipulation of compound **3a**.

In order to shed light on the reaction pathway, dedicate mechanistic control experiments were targeted. First, the on/off irradiation study (Scheme S1) proved the authentic light-promoted reaction profile of the present methodology (**1a**/**2**), with negligible advancements in absence of irradiation. Radical trap experiments with TEMPO (5 mol%), led to the complete inhibition of the mechanistic cycle (Table 1, entry 17). In addition, the replacement of **Co-1** with TEMPO (1 eq.) resulted in the formation of **3a** in 60% yield (Table 1, entry 18),[16] underlying the role of the cobaloxime as the "catalytic" oxidant of the present dehydrogenative amination process.[17] In Scheme 4a our tentative mechanistic hypothesis is depicted. Under blue-led irradiation (23 W, 461 nm), [**PS-1**$^+$/BF_4^-] is excited to [**PS-1**$^+$/BF_4^-]* (**PS-1***) (E^{red}[**PS-1**$^+$/**PS-1**•] = +2.06 V *vs* SCE)[8] with consequent oxidation of **1a** (E^{ox} **1a**/**1a**•+ = +2.00 V vs SCE)[18a] delivering the aryl cation **I**. Then, the oxidation of **PS-1**• by **Co-1** (Co(III)-Cl) ($E^{1/2red}$ Co(III)/Co(II) = −0.67 V vs SCE)[18b] would re-generate the [**PS-1**$^+$/BF_4^-] and the [Co(II)] intermediate.

Subsequently, the radical cation **I** is believed to undergo *anti*-Markovnikov addition with the triflimide anion formed upon deprotonation of **2** by lutidine. The resulting benzyl radical **III** could be reversibly intercepted by the [Co(II)] species delivering the key [Co(III)]−alkyl intermediate[19] that, upon irradiation would rapidly evolve into the final product **3a** through β-H elimination.[20] Finally, protonation of [Co(III)−H] equivalent by [lut-H$^+$][21] or $TfNH_2$ would restore the active [Co(III)] complex via hydrogen evolution reaction (HER).[22,23]

To corroborate the initial stages of the catalytic cycle, we carried out some Stern-Volmer quenching experiments between **PS-1** and substrates **1a** and **2**/lut mixture. Interestingly, time correlated single photon counting (TCSPC) measurements demonstrated that the excited state lifetime of acridinium **PS-1*** (17.6 ns) did not change in the presence of **2** up to 10 mM concentrations, either in the presence or in the absence of lut (10% with respect to **2**).[24] TCSPC and electrochemical results clearly proved that no direct interaction of the **PS-1** excited state with either **2** or **2**/lut mixtures occurred. In agreement with the

proposed mechanism, the oxidation potential of **2** was measured to be > 2.5 V (vs SCE).[25] In the presence of lut, this was found to be is shifted at 2.2 V, which is still higher than the one of **1a** or **PS-1*** (see Figure S2).[26] On the other hand, the quenching of **PS-1** excited state by substrate **1a** was previously reported, supporting the mechanism described in Scheme 4.



Scheme 4. a) Proposed mechanistic sketch. b) Labelling experiment.

Finally, a dedicated kinetic competition isotope effect (KIE) experiment was carried out by subjecting equimolar amounts of deuterated phenyl-cyclohexene d^3-**1a** and **1a** to the best conditions for the dehydrogenative C-N bond forming coupling reaction (Scheme 4b).[27] By stopping the reaction at 25% conversion (12 h), a 1.5:1 mixture of **3a**/d^2-**3a** was detected by ^{1}H-NMR, revealing a moderate but not negligible isotopic effect. This evidence is in contrast to our previous findings related to the synthesis of allylic carboxylates (no isotopic effect was detected).[8] Although a conclusive picture of the overall kinetics of the protocol is not available yet, the presence of an anionic nucleophile (*i.e.* $TfNH^-$) likely renders the initial C-N bond forming event with intermediate **I** faster than that of a conclusive β-elimination step.

In conclusion, we have presented a new synthetic methodology to cyclic and acyclic allylic triflamides (yield up to 88%) via dual visible-light/cobalt catalyzed redox protocol. The present formal β-hydrogen elimination tool exploits a direct Csp^3–H oxidation of styryl compounds under stoichiometric acceptorless conditions. The development of an intramolecular variant, ascertainment of the chemical flexibility of C-N coupled compounds, and mechanistic control experiments (photo, voltametric, kinetics) completed the present unprecedented methodology.

Experimental Section

Optimized general procedure for the intermolecular process.

A 5 mL dry vial equipped with a stirring bar was charged with: acridinium **PS-1** (4.2 mg, 7.5 mol%), [Co(dmgH)$_2$(Py)(Cl)] **Co-1** (2.0 mg, 5 mol%), dry DCM (1 mL), HFIP (50 µL), styryl derivative **1** (0.1 mmol), 2,6-lutidine (2.7 mg, 3.0 µL, 25 mol%) and triflamide **2** (72.0 mg, 0.5 mmol). The solution was gently degassed with N_2 then stirred under 23 W blue LED irradiation (465 nm) for 72 h. Then, the solvent was removed under vacuum and the residue purified via flash chromatography.

3a. Viscous oil. *n*Hex:EtOAc: from 40:1 to 20:1. Yield = 69% (21.0 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41 – 7.26 (m, 5H), 6.21 (t, *J* = 4.0 Hz, 1H), 4.78 – 4.68 (m, 1H), 4.64 (d, *J* = 7.7 Hz, 1H), 2.38 – 2.09 (m, 3H), 1.94 (dddd, *J* = 13.9, 12.6, 4.2, 3.1 Hz, 1H), 1.86 – 1.75 (m, 1H), 1.73 – 1.59 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 138.7, 135.8, 132.2, 128.6 (2C), 127.9, 126.4 (2C), 119.3 (q, *J* = 321.2 Hz), 51.9, 30.6, 25.5, 16.7; **^{19}F NMR** (376 MHz, $CDCl_3$) δ -77.5 (s, 3F); **GC-MS**: 305 (11), 172 (13), 156 (100); **Anal. Calc.** for ($C_{13}H_{14}F_3NO_2S$: 305.07): C, 51.14; H, 4.62; found: C, 51.10; H, 4.63.

Optimized general procedure for the intramolecular process.

A 5 mL dry vial equipped with a stirring bar was charged with: acridinium **PS-1** (4.2 mg, 7.5 mol%), [Co(dmgH)$_2$(Py)(Cl)] **Co-1** (2.0 mg, 5 mol%), dry DCM (1 mL), HFIP (50 µL), triflimide **3** (0.1 mmol) and 2,6-lutidine (2.7 mg, 3.0 µL, 25 mol%). The solution was gently degassed with N_2 then stirred under 23 W blue LED irradiation (465 nm) for 72 h. Then, the solvent was removed under vacuum and the residue purified via flash chromatography.

5a. White solid (m.p. = 175 – 177 °C). *n*Hex:EtOAc: from 60:1 to 40:1 (third eluting fraction from the column). Yield = 40% (22.7 mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.38 (dd, *J* = 8.7, 1.5 Hz, 1H), 7.86 (td, *J* = 7.6, 1.4 Hz, 1H), 7.63 – 7.51 (m, 2H), 2.79 – 2.66 (m, 4H), 1.99 – 1.81 (m, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 163.4, 153.0, 136.9, 136.7, 129.6, 128.5, 121.8, 119.3, 119.2 (q, *J* = 319.7 Hz), 113.0, 26.9, 22.7, 21.7, 21.6 ; **^{19}F NMR** (376 MHz, $CDCl_3$) δ -79.0 (s, 3F); **GC-MS**: 331 (5), 198 (94), 180 (100); **Anal. Calc.** for ($C_{14}H_{12}F_3NO_3S$: 331.05): C, 50.75; H, 3.75; found: C, 50.61; H, 3.98.

5a'. Viscous oil. *n*Hex:EtOAc: from 60:1 to 40:1 (first and second eluting fraction from the column). Yield = 34% (11.6 mg), *dr : 1.2:1*. **^{1}H NMR** *of the major diastereoisomer* (400 MHz, $CDCl_3$) δ 8.22 – 8.14 (m, 1H), 7.65 (td, *J* = 7.5, 1.5 Hz, 1H), 7.45 – 7.37 (m, 2H), 4.58 (dt, *J* = 12.2, 4.6 Hz, 1H), 3.63 (s, 1H), 2.61 (dt, *J* = 14.6, 3.0 Hz, 1H), 1.94 – 1.80 (m, 2H), 1.72 – 1.61 (m, 1H), 1.58 – 1.35 (m, 4H); . **^{1}H NMR** *of the minor diastereoisomer* (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 7.9 Hz, 1H), 7.66 (t, *J* = 7.7 Hz, 1H), 7.40 (t, *J* = 7.7 Hz, 1H), 7.34 (d, *J* = 7.8 Hz, 1H), 4.22 (td, *J* = 11.7, 4.4 Hz, 1H), 2.90 (td, *J* = 11.6, 4.0 Hz, 1H), 2.62 – 2.50 (m, 1H), 2.43 – 2.33 (m, 1H), 2.05 – 1.75 (m, 4H), 1.49 – 1.28 (m, 2H); **^{13}C NMR** *of the major diastereoisomer* (100 MHz, $CDCl_3$) δ 162.7, 139.6, 135.0, 130.2, 127.4, 127.2, 126.0, 119.4 (q, *J* = 324.2 Hz), 60.4, 37.4, 28.3, 26.7, 24.9, 19.0; **^{13}C NMR** *of the minor diastereoisomer* (100 MHz, $CDCl_3$) δ 167.6, 142.4, 135.7, 130.6, 127.8, 123.9, 119.0 (q, *J* = 319.1 Hz), 113.0, 84.6, 39.5, 31.0, 26.8, 24.6, 23.7; **^{19}F NMR** *of the*

major diastereoisomer (376 MHz, $CDCl_3$) δ -72.1 (s, 3F); **^{19}F NMR** *of the minor diastereoisomer* (376 MHz, $CDCl_3$) δ -79.5 (s, 3F); **GC-MS** *of the major diastereoisomer*: 333 (5), 200 (87), 182 (100); **GC-MS** *of the minor diastereoisomer*: 333 (11), 200 (96), 182 (100); **Anal. Calc.** for ($C_{14}H_{12}F_3NO_3S$: 333.06): C, 50.45; H, 4.23; found: C, 50.59; H, 4.03 (*major diastereoisomer*); C, 50.51; H, 4.11 (*minor diastereoisomer*).

Acknowledgements

MB and SB are grateful to the University of Bologna for financial support and PRIN-2017 project 2017W8KNZW. MM is grateful to the MIUR, project PRIN 2017 n. 2017E44A9P (BacHound).

References

[1] For general reviews see: a) B. A. Shainyan, L. L. Tolstikova, *Chem. Rev.* **2013**, *113*, 699-733; b) B. A. Shainyan, *Eur. J. Org. Chem.* **2018**, 3594-3608.

[2] For representative studies stressing the importance of triflamides in diversified synthetic organic chemistry areas see: a) B. A. Shainyan, V. V. Astakhova, A. S. Ganin, M. Y. Moskalik, I. V. Sterkova, *RSC Adv.* **2017**, *7*, 38951-38955; b) S. Shi, R. Lalancette, R. Szostak, M. Szostak, *Org Lett.* **2019**, *21*, 1253-1257; c) A. S. Ganin, M. Y. Moskalik, V. V. Astakhova, I. V. Sterkhova, B. A. Shainyan, *Tetrahedron* **2020**, *76*, 131374.

[3] a) Sumit, D. Chandra, U. Sharma, *Org. Biomol. Chem.* **2021**, *19*, 4014-4026; b) A. Sarbajna, P. Pandey, S. M. Wahidur Rahaman, K. Singh, A. Tyagi, P. H. Dixneuf, J. K. Bera, *ChemCatChem* **2017**, *9*, 1397-1401; c) Z. Zhang, J. Wang, J. Li, F. Yang, G. Liu, W. Tang, W. He, J.-J. Fu, Y.-H. Shen, A. Li, W.-D. Zhang, *J. Am. Chem. Soc.* **2017**, *139*, 5558-5567; d) K. Miyamoto, M. M. Hoque, S. Ogasa, *J. Org. Chem.* **2012**, *77*, 8317-8320; e) P.I. Jolly, N. Fleary-Roberts, S. O'Sullivan, E. Doni, S. Zhou, J. A. Murphy, *Org. Biomol. Chem.* **2012**, *10*, 5807-5810; f) K. Yanai, H. Togo, *Tetrahedron*, **2020**, *76*, 131503.

[4] a) M. Y. Moskalik, B. A. Shainyan, V. V. Astakhova, U. Schilde, *Tetrahedron*, **2013**, *69*, 705-711; b) R. Manoharan, M. Jeganmohan, *Eur. J. Org. Chem.* **2020**, 7304-7319; c) M. Ochiai, K. Miyamoto, T. Kaneaki, S. Hayashi, W. Nakanichi, *Science*, **2011**, *332*, 448-451 d) A. E. Bosnidou, K. Muniz, *Angew. Chem. Int. Ed.* **2019**, *58*, 7485-7489.

[5] a) J.-R. Chen, X.-Q. Hu, L.-Q. Lu, W.-J. Xiao, *Chem. Soc. Rev.* **2016**, *45*, 2044-2056; b) Q.-Q. Kang, W. Wu, Q. Li, W.-T. Wei, *Green Chem.* **2020**, *22*, 3060-3068; c) C.-M. Chan, Y.-C. Chow, W.-Y. Yu, *Synthesis* **2020**, *52*, 1719-1737; d) S. Singh, V. J. Roy, N. Dagar, P. P. Sen, S. R. Roy, *Adv. Synth. Catal.* **2021**, *363*, 937-979, and reference therein.

[6] For an example of photocatalyzed addition of $TfNH_2$ to cyclic olefins see: T. M. Nguyen, D. A. Nicewicz, *J. Am. Chem. Soc.* **2013**, *135*, 9588-9591.

[7] a) G. Zhang, C. Bian, A. Lei, *Chin. J. Catal.* **2015**, *36*, 1428-1439; b) G. Zhang, X. Hu, C.-W. Chiang, H. Yi, P. Pei, A. K. Singh, A. Lei, *J. Am. Chem. Soc.* **2016**, *138*, 12037-12040; c) H. Yi, L. Niu, L.; C. Song, Y. Li, B. Dou, A. K. Singh, A. Lei, *Angew. Chem. Int. Ed.* **2017**, *56*, 1120;-1124 d) X. Hu, G. Zhang, F. Bu, A. Lei, *Angew. Chem. Int. Ed.* **2018**, *57*, 1286-1290; e) W.-Q.; Liu, T. Lei, S. Zhou, X.-L. Yang, J. Li, J.; B. Chen, J. Sivaguru, C.-H. Tung, L. Z. Wu, *J. Am. Chem. Soc.* **2019**, *141*, 13941-13947; f) J.-L. Tu, W. Tang, W. Xu, F. Liu, *J. Org. Chem*. **2021**, *86*, 2929-2940; g) D. Dolui, S. Khandelwal, P. Majumder, A. Dutta, *Chem. Commun.* **2020**, *56*, 8166-8181; h) K. C. Cartwright, A. M. Davies, J. A. Tunge, *Eur. J. Org. Chem.* **2020**, 1245-1258; i) M. Kojima, S. Matsunaga, *Trends Chem.* **2020**, *2*, 410-426.

[8] Y. Liu, S. Battaglioli, L. Lombardi, A. Menichetti, G. Valenti, M. Montalti, M. Bandini, *Org. Lett* **2021**, *23*, 4441-4446.

[9] a) Q.-Q. Yang, M. Marchini, W.-J. Xiao, P. Ceroni, M. Bandini, *Chem. Eur. J.* **2015**, *21*, 18052-18056; b) C. Sauer, Y. Liu, A. De Nisi, S. Protti, M. Fagnoni, M. Bandini. *ChemCatChem* **2017**, *9*, 4456-4459; c) Y. Liu, A. Parodi, S. Battaglioli, M. Monari, S. Protti, M. Bandini, *Org. Lett*. **2019**, *21*, 7782-7786.

[10] See supporting information for a complete list of attempts during the optimization of reaction.

[11] a) D. Dolui, A. Q. Mir, A. Dutta, *Chem. Commun.* **2020**, *56*, 14841-14844; b) K. C. Cartwright, E. Joseph, C. G. Comadoll, J. A. Tunge, *Chem. Eur. J.* **2020**, *26*, 12454-12471.

[12] a) N. A. Romero, D. A. Nicewicz, *J. Am. Chem. Soc*. **2014**, *136*, 17024-17035; b) P. Bayer, J. Schachtner, M. Májek, A. J. von Wangeling, *Org. Chem. Front*. **2019**, *6*, 2877-2883; c) J. B. McManus, J. D. Griffin, A. R. White, D. A. Nicewicz, *J. Am. Chem. Soc*. **2020**, *142*, 10325-10330.

[13] For general and recent review articles on the use of acridinium salts in photocatalysis, see: a) N. A. Romero, D. A. Nicewicz, *Chem. Rev.* **2016**, *116*, 10075-10166; b) B. Zilate, C. Pischer and C. Sparr, *Chem. Commun.* **2020**, *56*, 1767-1775; c) M. V. Bobo, J. J. Kuchta III, A. K. Vannucci, *Org. Biomol. Chem.* **2021**, *19*, 4816-4834; d) A. Tlili, S. Lakhdar, *Angew. Chem. Int. Ed.* **2021**, *60*, 19526-19549; e) V. Hutskalova, C. Sparr, *Synlett* **2021**, *32*, A-D; see also: f) K. Ohkubo, S. Fukuzumi, *Org. Lett.* **2000**, *2*, 3647-3650; g) K. Ohkubo, K. Suga, K. Morikawaand, S. Fukuzumi, *J. Am. Chem. Soc.* **2003**, *125*, 12850-12859.

[14] Although a conclusive answer to the role of HFIP in still not available yet, we could speculate that its high ionization power could contribute in stabilizing radical as well as charged intermediates during the mechanism. Additionally, the strong hydrogen donor donation attitude might accelerate the final dehydrogenative event. a) I. A. Shuklov, N. V. Dubrovina, A. Borner, *Synlett*, **2007**, 2925-2943; b) S. Khaksar, *J. Fluorine Chem.* **2015**, *172*, 51-61; c) E. Kim, C. Y. Lee, S.-G. Kim, *Adv. Synth. Catal.* **2020**, *362*, 3594-3603.

[15] a) Q. Yang, Z. Jia, L. Li, L. Zhang, S. Luo, *Org. Chem. Front.* **2018**, *8*, 237-241; b) M. Zhang, R. Ruzi, N. Li, J. Xie, C. Zhu, *Org. Chem. Front.* **2018**, *5*, 769-752; c) M.-

M. Qiao, Y.-Y. Liu, S. Yao, T.-C. Ma, Z.-L. Tang, D.-Q. Shi, W.-J. Xiao, *J. Org. Chem.* **2019**, *84*, 6798-6806.

[16] No detectable covalent intermediates were isolated from the reaction mixture.

[17] a) P. Schroll, B. König, *Eur. J. Org. Chem*. **2015**, 309-313; b) X.-Q. Hu, X. Qi, J.-R. Chen, Q.-Q. Zhao, Q. Wei, Y. Lan, W.-J. Xiao, *Nat. Commun.* **2016**, *7*, 11188; c) W. Chen, Z. Huang, N. E. S. Tay, B. Giglio, M. Wang, H. Wang, Z. Wu, D. A. Nicewicz, Z. Li, *Science*, **2019**, *364*, 1170-1174.

[18] D. Mangion, J. Kendall, D. R. Arnold, *Org. Lett.* **2001**, *3*, 45.

[19] a) G.N. Schrauzer, L.-P. Lee, J. W. Sibert, *J. Am. Chem. Soc.* **1970**, *92*, 2997-3005; b) Ph. Maillard, C. Giannotti, *J. Organomet. Chem.* **1979**, *182*, 225-237; c) H. Bhandal, G. Patterden, *J. Chem. Soc., Chem. Commun.* **1988**, 1110-1112; d) B. P. Branchaud, Y. L. Choi, *Tetrahedron Lett.* **1988**, *29*, 6037-6038; e) C. D. Garr, R. G. Finke*, J. Am. Chem. Soc*. **1992**, *114*, 10440-10445.

[20] a) A.A. Gridnev, S.D. Ittel, *Chem. Rev.* **2001**, *101*, 3611-3660; b) P.V. Kattamuri, J.G. West, *Synlett* **2021**, *32*, 1179-1186; c) J.G. West, D. Huang, E.J. Sorensen, *Nat. Commun.*, **2015**, *6*, 10093; d) H. Zhao, A. J. McMillan, T. Constantin, R. C. Mykura, F. Juliá, and D. Leonori, *J. Am. Chem. Soc*., **2021**, *143*, 14806-14813.

[21] a) G. Li, A. Han, M. E. Pulling, D. P. Estes, J.R. Norton, *J. Am. Chem. Soc*. **2012**, *134*, 14662-14665; b) D.P. Estes, D.C. Grills, J.R. Norton, *J. Am. Chem. Soc*. **2014**, *136*, 1736217365; c) C. Lacy, G. M. Roberts, J. C. Peters, *J. Am. Chem. Soc*. **2015**, *137*, 4860-4864.

[22] a) T. Lazarides, T. McCormick, P. Du, G. Luo, B. Lindley, R. Eisenberg, *J. Am. Chem. Soc.* **2009**, *131*, 9192-9194; b) V. Artero, M. Chavarot-Kerlidou, M. Fontecave, *Angew. Chem. Int. Ed.* **2011**, *50*, 7238-7266.

[23] For a comprehensive article dealing with hydrogen evolution processes mediated by cobaloximes see: J.L. Dempsey, B.S. Brunschwig, J.R. Winkler, H.B. Gray, *Acc. Chem. Res.* **2009**, *42*, 1995-2004.

[24] A. Mavridi-Printezi, A. Menichetti, M. Guernelli, M. Montalti, *Nanoscale*, **2021**, *13*, 9147-9159.

[25] T. Shono, Y. Matsumura, K. Tsubata, K. Uchida, T. Kanazewa, K. Tsuda, *J. Org. Chem.* **1984**, *49*, 3711-3716.

[26] I. Bosque, G. Magallanes, M. Rigoulet, M. D. Karkas, C. R. J. Stephenson, *ACS Cent. Sci.* **2017**, *3*, 621-628.

[27] E. M. Simmons, J. F. Hartwig, *Angew. Chem. Int. Ed.* **2012**, *51*, 3066-3072.