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Multicomponent Access to Functionalized Mesoionic Structures Based on TFAA Activation of Isocyanides: Novel Domino Reactions

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The reactions of azines (isoquinolines, pyridine) with TFAA and isocyanides in a new domino process yield mesoionic acid fluorides with an imidazo[1,2-*a*]azine core. This multicomponent reaction has a general character, tolerating a wide range of substitution patterns on each component, and displays an unprecedented arrangement of reaction pathways. The protocol allows the incorporation of a fourth synthetic input by the reaction of a suitable nucleophile (alcohols, thiols, amines) with the acid fluoride moiety.

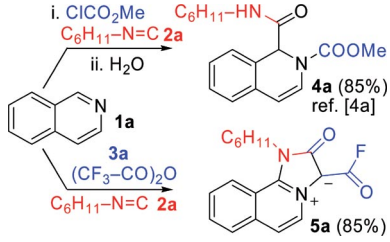
Introduction

Multicomponent reactions (MCRs, domino processes in which three or more starting materials interact to form an adduct) are specially attractive in organic synthesis because they maximize complexity and convergency while using structurally simple substrates in a single operation.[1] This approach is particularly beneficial for the preparation of libraries of compounds in which short synthetic sequences are mandatory. In this context, the participation of heterocyclic structures is critical as heterocycles are the most common motifs found in natural products and drugs, and are often considered privileged substructures.[2] The rich and intrinsic reactivity of heterocyclic systems brings fascinating possibilities to the design and implementation of domino reactions. However, the manifold evolutionary pathways of such complex systems make reliable predictions difficult and call for detailed mechanistic and synthetic experimentation. Therefore the development of new and efficient MCRs involving the participation of important heterocycles remains a challenging task in organic synthesis due to their wide-ranging applications in medicinal chemistry.[3]

Results and Discussion

Reactivity Studies

Continuing our interest in the development of MCRs based on heterocycles,[4] herein we report the direct functionalization of azines (pyridine, isoquinoline, etc.) with isocyanides and acylating agents to form new mesoionic structures.[5] We previously disclosed an efficient Ugi–Reissert reaction involving the interaction of isoquinolines, chloroformates and isocyanides in which the activated azine is carbamoylated at the α-position by the isocyanide to give dihydroazines such as **4a** (Scheme 1).[4a] Arndtsen and Mironov and their co-workers recently described related processes involving, respectively, acid chlorides and isothiocyanates in isocyanide MCRs.[6]



Scheme 1. Interaction of isoquinoline, acylating agents and isocyanides.

Several azines (pyridines for instance) are, however, inert under these conditions. In our search for more potent activation reagents to overcome this limitation and also to introduce a new point of diversity, we considered the use of triflic anhydride (Tf_2O), which was recently introduced by Corey and Tian to activate pyridines in the presence of C-nucleophiles.[7] However, its interaction with pyridine and isocyanides led to a mixture of α- and γ-carbamoylated *N*-triflyl-1,2- and 1,4-dihydropyridines and their oxidation products (the corresponding pyridines) in low overall yields, together with significant isocyanide polymerization. We then investigated the reactivity of trifluoroacetic anhydride (TFAA) in these systems. On mixing isoquinoline (**1a**) with

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cyclohexyl isocyanide (**2a**) and TFAA (**3a**) in dry THF, we isolated the mesoionic acid fluoride **5a** as a stable crystalline solid in 25% yield (Scheme 1).

Optimization of the process led us to perform the reaction in anhydrous CH_2Cl_2 with isoquinoline, TFAA and the isocyanide in a stoichiometric ratio of 1:2:3, which increased the yield of **5a** up to 85%. The structure of this compound was unambiguously established by spectroscopic methods and confirmed by X-ray diffraction (Figure 1).[8] A related dipole has been prepared by Moody et al. through a stepwise synthesis by the intramolecular reaction of a carbenoid with the nitrogen atom of a pyridine.[9]

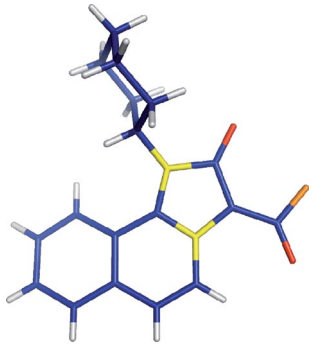
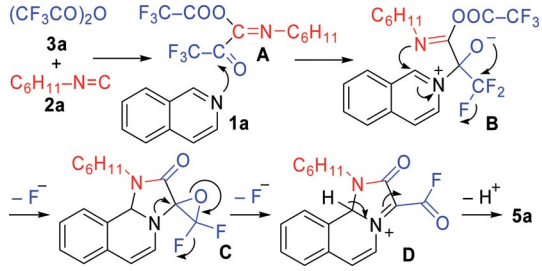


Figure 1. View of the X-ray crystal structure of **5a**.

Mechanistic Proposal

Regarding the constitution of acid fluoride **5a**, the connectivity between the three components indicates the occurrence of a completely different process, overriding the known pathway leading to the Ugi–Reissert products **4**. Note that the isocyanide moiety is linked to the isoquinoline ring through the N atom in the acid fluoride **5a**, whereas in the former process, which leads to **4a**, the bonding occurs through the C terminal atom. A plausible mechanistic explanation may involve the initial activation of the isocyanide by the TFAA, previously described by El Kaïm and co-workers,[10a,10b] to afford an adduct **A**. They have successfully developed this chemistry to promote a variety of useful transformations based on the reactivity of the trifluoropyruvamide intermediates.[10c,10d] In our system, this species undergoes nucleophilic attack by the isoquinoline to generate a reactive dipole **B**, which may evolve by intramolecular addition of the imine moiety to the α-position of the azinium ion and by fluoride elimination promoted by the oxyanion. The highly reactive amino epoxide intermediate **C** (or related species) would then undergo a ring-opening/rearrangement sequence, presumably triggered by the now nucleophilic heterocyclic nitrogen, to form the acyl fluoride **D**, which affords the dipole **5a** after proton loss (Scheme 2). Alternatively, TFAA activation of the isoquinoline ring followed by isocyanide attack upon the carbonyl may also lead to the epoxide intermediate **C**.[10e]

To the best of our knowledge, there are no precedents for the formation of an acid fluoride moiety from a trifluoroacetoxy group, although some elementary steps are reminiscent of known processes.[11] The overall anionic domino reaction consists of an orchestrated series of events in which electrophilic and nucleophilic species are precisely engaged to guarantee the formation of the C–C, C–N and C–O bonds. Several features of this mechanism remain hypothetical. However, the detection by MS of putative intermediates **B** and **C** (Scheme 2) together with species related to intermediates **A** in modified experiments (lower temperatures, short reaction times, exclusion of aqueous quenching) supports this proposal. Interestingly, the order of addition of the reactants does not substantially modify the synthetic outcome or the yield of the process. In this way, we have tested the addition of the isocyanide to a mixture of isoquinoline and TFAA (**5a**, 85%), the addition of TFAA to a solution of isoquinoline and the isocyanide (**5a**, 72%) and, finally, the addition of isoquinoline to a mixture of the isocyanide and TFAA (**5a**, 65%). These results may be consistent with a type II MCR[1c] in which a series of equilibria are affected by a final irreversible step.



Scheme 2. Mechanistic proposal for the formation of acid fluoride **5a**.

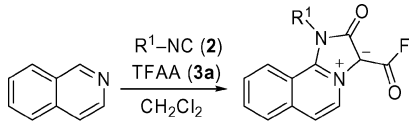
To test the scope of the reaction, a systematic screening of the three components was performed to fully exploit the synthetic possibilities of the transformation and to determine its practical limits.

Reaction Scope – Isocyanide Range

A representative set of isocyanides **2** were treated under the usual conditions with TFAA (**3a**) and isoquinoline (**1a**). The results show that the MCR is quite general with alkyl and benzyl isocyanides affording the expected dipoles **5** in reasonable yields (Table 1, entries 1–3). Note that even moderate yields are synthetically useful reactions taking into account the multicomponent nature of the process and the number of bonds formed. Notable exceptions are *tert*-butyl isocyanide (**2d**, entry 4, presumably because of the steric hindrance linked to the N atom) and the less nucleophilic isocyanide TOSMIC (**2e**, entry 5). In this experiment, the only new product was the hydrate of the *N*-tosylmethyltrifluoropyruvamide. This compound has previously been obtained by hydrolysis of the TFAA-activated isocyanide.[10b]

Interestingly, methyl isocyanoacetate (**2f**, entry 6) displays the expected reactivity although in a lower yield (**5d**, 21%). Remarkably, the formation of the Arndtsen-type dipole **6a** (14%; Figure 2)[6a] by TFAA activation of the iso-

Table 1. Reaction scope of the isocyanides **2** in the MCR.



Entry[a]	R^1	Adduct	Yield [%][b]
1	*c*-C_6H_{11} (**2a**)	**5a**	85
2	*n*Bu (**2b**)	**5b**	80
3	Bn (**2c**)	**5c**	65
4	*t*Bu (**2d**)	–	–
5	*p*TolSO_2CH_2 (**2e**)	–	–
6	MeO_2CCH_2 (**2f**)	**5d**	21[c,d]
7	4-ClC_6H_4 (**2g**)	**5e**	20
8	4-$MeOC_6H_4$ (**2h**)	**6b**	23
9	2,6-$Me_2C_6H_3$ (**2i**)	**5f**	26

[a] All reactions were performed following the standard procedure. [b] Isolated yield. [c] Dipole **6a** was also isolated. [d] Isoquinoline, TFAA and the isocyanide were allowed to react in a 1:1:1 stoichiometric ratio.

quinoline was also detected in this reaction, which suggests that competing pathways are operating (Scheme 3). This tendency is increased with 4-$MeOC_6H_4NC$ (**2h**, entry 8) in which the formation of **6b** (Figure 2) predominates. The diminished reactivity of the electron-rich intermediate **A** may divert the cascade towards the Arndtsen route. However, with less activated aromatic rings (**2g** and **2i**, entries 7 and 9) the expected mesoionic compounds are successfully obtained, albeit in lower yields. In these cases, the reduced nucleophilicity of the aniline-type nitrogen atoms in intermediates **B** (Scheme 2) may render the imidazole ring-closure less efficient than with aliphatic analogues and therefore account for the decrease in the overall yield. However, we still lack conclusive evidence to fully explain the behaviour of aromatic isocyanides.

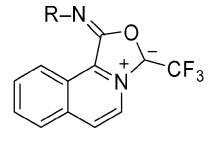
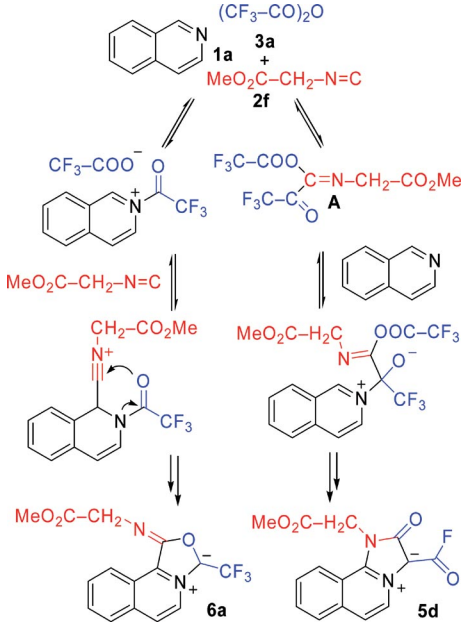


Figure 2. Additional mesoionic compounds isolated in the MCRs.

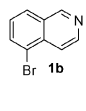
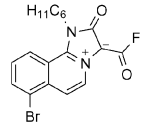
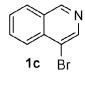
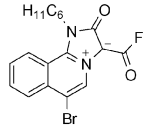
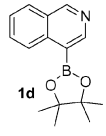
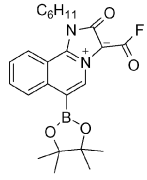
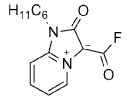
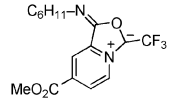
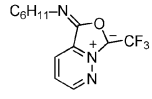
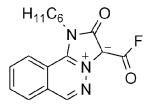


Scheme 3. Competitive reaction pathways leading to dipoles **5d** and **6a**.

Reaction Scope – Azine Range

Next, we examined the scope of reactive azines in the MCR (Table 2). Differently substituted isoquinolines (**1b**–**1d**, entries 1–3) gave the adduct **5** in good-to-moderate

Table 2. Reaction scope of the azines **1** in the MCR.

Entry[a]	Azine	Adduct	Yield (%)[b]
1	 **1b**	**5g** 	35
2	 **1c**	**5h** 	82
3	 **1d**	**5i** 	69
4	 **1e**	**5j** 	40
5	 **1f** COOMe	**6c** 	20
6	 **1g** OMe	–	–
7	 **1h**	–	–
8	 **1i**	**6d** 	54
9	 **1j**	**5k** 	traces

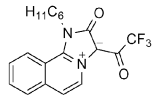
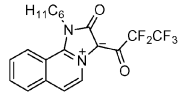
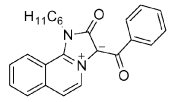
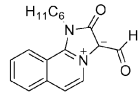
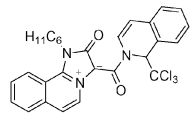
[a] All reactions were performed following the standard procedure. [b] Isolated yield.

yields, including the 4- and 5-bromo derivatives and the 4-boronate. Remarkably, pyridine (**1e**, entry 4), which is inert in Ugi–Reissert conditions,[4a] gave the adduct **5j**. Methyl isonicotinate (**1f**, entry 5) and 4-methoxypyridine (**1g**, entry 6) did not afford the corresponding acid fluorides **5**, the former yielding the corresponding Arndtsen dipole (**6c**, 20%). The rationale for these results may relate to the nucleophilic competition between the azine and the isocyanide in their reaction with TFAA and the relative reactivity of the resulting species: the intermediate azinium ion **B** and the corresponding *N*-acylazinium salt. In this respect, a somewhat restricted reaction window may appear as a consequence of the balance between the nucleophilicity of the azine and the electrophilicity of the azinium intermediate **B**. Thermodynamic aspects and the relative rates of the elementary steps involved in this manifold process may also determine the final outcome (Scheme 2 and Scheme 3). Quinoline (**1h**, entry 7) did not react under the standard conditions. Taking into account the similar reactivity of this heterocycle with isoquinoline, this suggests a steric requirement that does not allow substitution at the α-positions of the azine, presumably because of the structural and reactivity properties of the intermediate azinium ions **B** (Scheme 2). Pyridazine (**1i**, entry 8) showed different behaviour, forming the Arndtsen dipole **6d** (54%), whereas phthalazine (**1j**, entry 9) afforded a complex mixture in which **5k** was detected (MS evidence). In some cases, minor amounts of dipoles arising from the incorporation of two isocyanide units were generated.[12]

Reaction Scope – Anhydride Range

The third component in the reaction procedure was also examined (Table 3). Aside from TFAA, which leads to acid fluorides (Table 1 and Table 2), the results obtained show that for doubly α-fluorinated anhydrides (**3b**–**3e**, entries 1–4) the reaction is quite general and affords several different patterns of substitution, such as fluorinated ketones (**5l**, **5m**), aryl ketones (**5n**) or aldehydes (**5o**). Unfortunately the use of mixed anhydrides (to integrate the moiety deriving from the fluorinated acid precursor in a more efficient manner) was not successful.[13] Trichloroacetic anhydride (**3f**, entry 5)[10c] gives the amide **5p** in a yield of 30% in a remarkable process in which up to seven bonds are formed (Figure 3).[14] This MCR does not stop at the corresponding acid chloride (detected by MS), which, being more reactive than its fluoride counterpart, keeps the domino process alive, and by reacting with another equivalent of isoquinoline generates an *N*-acylisoquinolinium salt. This reactive intermediate then undergoes nucleophilic addition of a trichloromethyl anion (presumably generated in situ by decarboxylation of the trichloroacetate)[15] to finally yield **5p** (Scheme 4). The less electrophilic dichloroacetic anhydride (**3g**, entry 6) did not show any reactivity under the standard conditions tested and probably sets the activation threshold for the acylating component.

Table 3. Reaction scope of the anhydrides **3** in the MCR.

Entry[a]	Acid anhydride	Adduct		Yield (%)[b]
1	$(C_2F_5CO)_2O$ **3b**	**5l**		38
2	$(C_3F_7CO)_2O$ **3c**	**5m**		45
3	$(PhCF_2CO)_2O$ **3d**	**5n**		41
4	$(CHF_2CO)_2O$ **3e**	**5o**		32
5	$(CCl_3CO)_2O$ **3f**	**5p**		30
6	$(CHCl_2CO)_2O$ **3g**	–	–	–

[a] All reactions were performed following the standard procedure. [b] Isolated yield.

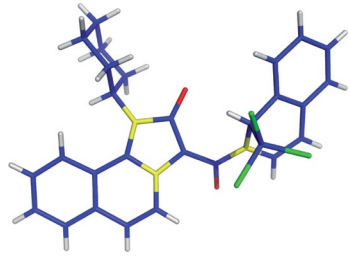
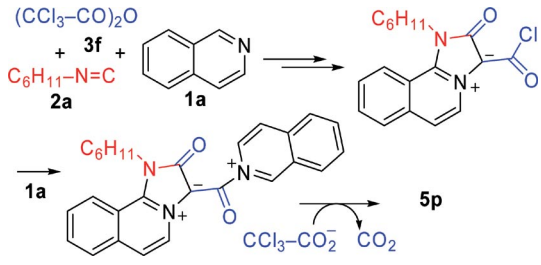


Figure 3. View of the X-ray crystal structure of **5p**.

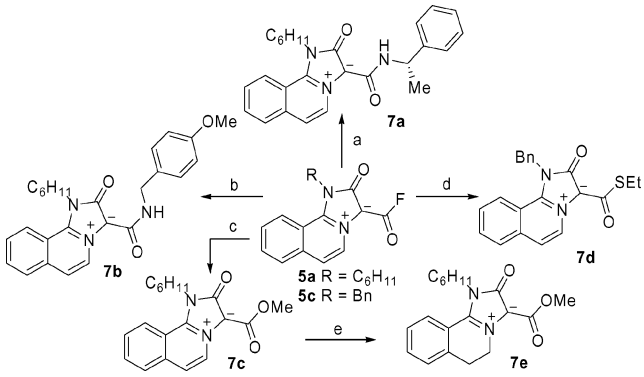


Scheme 4. MCR with trichloroacetic anhydride leading to **5p**.

Dipole Derivatization

Although remarkably stable (for instance, dipole **5a** does not react with acetylenedicarboxylate esters in [3+2] cycloaddition reactions),[9] the acid fluoride function present in dipoles **5** displays the expected reactivity and affords the corresponding mesoionic derivatives **7a**–**7d** on reaction with

nucleophiles (amines, alcohols and thiols). Interestingly, the isoquinolinium moiety can be selectively reduced, as shown by the formation of the dihydroisoquinoline derivative **7e** (Scheme 5).



Scheme 5. Reactivity of acid fluoride **5a**. Reagents and conditions: a) (*S*)-(–)-1-phenylethylamine, Et_3N, DCM (99%); b) *p*-methoxybenzylamine, Et_3N, DCM (75%); c) MeOH (excess), Et_3N, DCM (82%); d) EtSH (excess), DMAP, pyridine (62%); e) H_2, Pd/C, MeOH (85%).

Conclusions

We have described a new azine MCR based on the activation of isocyanides by anhydrides. This unique domino transformation, which features elements of the Ugi–Reissert, Chichibabin and organofluorine processes, yields mesoionic imidazo[1,2-*a*]azine (isoquinoline, pyridine) cores displaying a β-dicarbonyl moiety. These structures bear a close resemblance to neutral imidazoazines, a privileged scaffold of great importance in medicinal and combinatorial chemistry because of its broad spectrum of biological activities.[16] Our approach nicely complements the Bienaymé–Blackburn–Groebke reaction[17] and, although with some restrictions, allows the preparation of the heterocyclic scaffold directly from the azine, ready to be functionalized with a fourth component. Further studies are underway to fully understand the mechanistic implications of this unique transformation and to expand its synthetic outcome.

Experimental Section

General: Unless stated otherwise, all reactions were carried out under argon in dried glassware. Commercially available reactants were used without further purification. Reaction temperatures were controlled by an IKA temperature modulator. Thin-layer chromatography was conducted with Merck silica gel 60 F_{254} sheets and visualized by UV and $KMnO_4$ solution. Silica gel (particle size 35–70 μm) was used for flash column chromatography. ^1H, ^{13}C and ^{19}F NMR spectra were recorded with a Varian Mercury 400 spectrometer (at 400, 100 and 376 MHz, respectively). Unless otherwise stated, NMR spectra were recorded in $CDCl_3$ solution with TMS as an internal reference. Data for ^1H NMR spectra are reported as follows: chemical shift (δ/ppm), multiplicity, integration and coupling constant (Hz). Data for ^{13}C NMR spectra are reported in terms of chemical shift relative to the solvent peak of $CDCl_3$ set at δ = 77.0 ppm. ^{19}F NMR spectra are referenced to TFA as external reference (–78.5 ppm). IR spectra were recorded with a Thermo Nicolet Nexus spectrometer and are reported in frequency of absorption (cm^{-1}).

General Procedure for the Multicomponent Reaction: The acid anhydride (3 mmol, 3 equiv.) and isocyanide (2 mmol, 2 equiv.) were added to a solution of the corresponding azine (1 mmol, 1 equiv.) in anhydrous CH_2Cl_2 (5 mL) at –30 °C. Stirring was continued for 3 min at this temperature, then the cooling bath was removed and the reaction mixture was stirred for 14 h at room temperature. A saturated solution of Na_2CO_3 (10 mL) was added and the mixture extracted with dichloromethane (2 × 5 mL). The combined organic extracts were washed with brine (10 mL) and then dried (Na_2SO_4) and filtered. The solvent was removed under reduced pressure and the residue was purified by column chromatography (SiO_2, hexanes/ethyl acetate) to yield the pure mesoionic compound.

1-Cyclohexyl-3-(fluorocarbonyl)-2-oxo-2,3-dihydro-1*H*-imidazo[2,1-*a*]isoquinolin-4-ium-3-ide (5a): Obtained as a white solid (85%), m.p. 257 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.21 (d, *J* = 7.2 Hz, 1 H), 8.27 (d, *J* = 7.2 Hz, 1 H), 7.90 (d, *J* = 7.6 Hz, 1 H), 7.80–7.72 (m, 2 H), 7.43 (d, *J* = 7.2 Hz, 1 H), 4.78 (m, 1 H), 2.89 (m, 2 H), 2.02–1.42 (m, 8 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.0, 153.2 (d, *J* = 312 Hz), 135.2, 133.6, 131.1, 129.2, 128.9, 123.9, 123.6, 116.3, 115.8, 90.9 (d, *J* = 81 Hz), 59.2, 29.8, 26.5, 25.1 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = 14.9 ppm. IR (NaCl): $\tilde{\nu}$ = 2923, 1739, 1674, 1502, 1412, 1130 cm^{-1}. UV (MeOH): λ_{max} ($\log \varepsilon_0$) = 240 (4.44), 284 (4.47), 344 (4.13) nm. MS (EI): *m*/*z* (%) = 312 (9) $[M]^+$, 292 (8), 264 (4), 252 (34), 230 (29), 210 (100), 154 (36), 128 (13). HRMS: calcd. for $C_{18}H_{18}FN_2O_2^+$ 313.1352; found 313.1349.

1-Butyl-3-(fluorocarbonyl)-2-oxo-2,3-dihydro-1*H*-imidazo[2,1-*a*]isoquinolin-4-ium-3-ide (5b): Obtained as a yellow solid (80%, purified by crystallization from CH_2Cl_2/Et_2O), m.p. 205–206 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.23 (d, *J* = 7.2 Hz, 1 H), 8.37 (d, *J* = 7.6 Hz, 1 H), 7.92–7.97 (m, 1 H), 7.70–7.90 (m, 2 H), 7.50 (d, *J* = 7.2 Hz, 1 H), 4.52 (t, *J* = 7.6 Hz, 2 H), 1.89 (m, 2 H), 1.84–1.95 (m, 2 H), 1.03 (t, *J* = 7.6 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.9, 156.24 (d, *J* = 316 Hz), 134.8, 133.3, 131.4, 129.6, 128.8, 124.1, 123.2, 122.4, 115.8, 90.2 (d, *J* = 82 Hz), 41.7, 31.0, 20.2, 13.9 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = 11.8 ppm. IR (NaCl): $\tilde{\nu}$ = 1747, 1683, 1639, 1518, 1412, 1044, 747 cm^{-1}. UV (CH_2Cl_2): λ_{max} ($\log \varepsilon_0$) = 248 (4.24), 291 (4.38), 366 (3.82) nm. MS (EI): *m*/*z* (%) = 286 (26) $[M]^+$, 269 (38), 252 (16), 238 (17), 224 (26), 210 (100), 154 (51), 128 (27), 101 (14). HRMS: calcd. for $C_{16}H_{16}FN_2O_2^+$ 287.1190; found 287.1191.

1-Benzyl-3-(fluorocarbonyl)-2-oxo-2,3-dihydro-1*H*-imidazo[2,1-*a*]-isoquinolin-4-ium-3-ide (5c): Obtained as a white solid (65%), m.p. 257–258 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.30 (d, *J* = 7.2 Hz, 1 H), 8.24 (d, *J* = 8.8 Hz, 1 H), 7.89 (d, *J* = 8.0 Hz, 1 H), 7.73 (t, *J* = 7.6 Hz, 1 H), 7.57 (t, *J* = 8.0, 7.6 Hz, 1 H), 7.52 (d, *J* = 7.2 Hz, 1 H), 7.21–7.38 (m, 5 H), 5.74 (s, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.2, 153.1 (d, *J* = 312 Hz), 135.0, 133.2, 131.5, 129.5, 128.5, 128.3, 126.4, 126.3, 124.1, 123.9, 123.1, 116.3, 116.1, 90.2 (d, *J* = 83 Hz), 45.6 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = 12.2 ppm. IR (NaCl): $\tilde{\nu}$ = 3135, 2993, 1744, 1687, 1520, 1417, 1433, 1041, 1026, 937, 742, 649 cm^{-1}. UV (CH_2Cl_2): λ_{max} ($\log \varepsilon_0$) = 239 (3.99), 290 (4.05), 363 (3.50) nm. MS (EI): *m*/*z* (%) = 320 (27) $[M]^+$, 300 (7), 231 (10), 170 (5), 153 (6), 128 (6), 91 (100), 65 (11). HRMS: calcd. for $C_{19}H_{14}FN_2O_2^+$ 321.1033; found 321.1045.

3-(Fluorocarbonyl)-1-(2-methoxy-2-oxoethyl)-2-oxo-2,3-dihydro-1*H*-imidazo[2,1-*a*]isoquinolin-4-ium-3-ide (5d): In this experiment the stoichiometry of the reagents was modified: isoquinoline (360 mg,

2.78 mmol, 1 equiv.), TFAA (0.393 mL, 2.78 mmol, 1 equiv.) and isocyanide (0.253 mL, 2.78 mmol, 1 equiv.) were added in that order. After the extractions silica and Na_2SO_4 were added to the organic extracts and left to stir for 1 h and then were filtered through Celite. The precipitate was washed with AcOEt, and the collected filtrates were combined. The solvent was removed under reduced pressure and the residue was washed with Et_2O (10 mL) to yield the dipole as a brown solid (176.9 mg, 21%), m.p. 194–195 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.28 (d, J = 6.8 Hz, 1 H), 8.04 (d, J = 8.4 Hz, 1 H), 7.96 (d, J = 8.0 Hz, 1 H), 7.83 (m, J = 7.2, 8.0 Hz, 1 H), 7.76 (m, J = 8.4, 7.2 Hz, 1 H), 7.56 (d, J = 7.2 Hz, 1 H), 5.31 (s, 2 H), 3.80 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.8, 157.1, 152.9 (d, J = 310.5 Hz), 135.0, 133.3, 131.6, 129.8, 128.9, 124.1, 122.3, 116.6, 116.4, 90.7 (d, J = 81 Hz), 53.5, 43.4 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = 13.3 ppm. IR (NaCl): $\tilde{\nu}$ = 1746, 1699, 1522, 1441, 1419, 1364, 1224, 1042, 937, 748 cm^{-1}. UV (CH_2Cl_2): λ_{max} (log ε_0) = 246 (4.35), 277 (4.24), 363 (4.23) nm. MS (EI): m/z (%) = 302 (100) $[M]^+$, 215 (25), 195 (16), 168 (11), 156 (19), 140 (11), 128 (18), 115 (7), 101 (7). HRMS: calcd. for $C_{15}H_{12}FN_2O_4^+$ 303.0775; found 303.0776.

1-(4-Chlorophenyl)-3-(fluorocarbonyl)-2-oxo-2,3-dihydro-1*H*-imidazo[2,1-*a*]isoquinolin-4-ium-3-ide (5e): Obtained as a yellow solid (20%), m.p. 225–226 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.33 (d, J = 6.8 Hz, 1 H), 7.91 (d, J = 8.0 Hz, 1 H), 7.74 (m, J = 7.2, 7.6 Hz, 1 H), 7.65 (d, J = 8.8 Hz, 2 H), 7.59 (d, J = 7.2 Hz, 1 H), 7.39–7.50 (m, 3 H), 7.31 (d, J = 8.8 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.0, 153.1 (d, J = 314 Hz), 136.9, 134.3, 133.3, 132.5, 131.7, 131.0, 130.2, 129.3, 128.6, 124.1, 123.5, 116.7, 115.8, 90.1 (d, J = 83 Hz) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = 12.4 ppm. IR (NaCl): $\tilde{\nu}$ = 1740, 1670, 1415, 1001, 805, 739 cm^{-1}. UV (CH_2Cl_2): λ_{max} (log ε_0) = 251 (4.03), 291 (4.06), 363 (3.67) nm. MS (EI): m/z (%) = 340 (100) $[M]^+$, 319 (46), 265 (31), 230 (16), 203 (8), 175 (5), 111 (17), 75 (18). HRMS: calcd. for $C_{18}H_{11}ClFN_2O_2^+$ 341.0487; found 341.0496.

1-(2,6-Dimethylphenyl)-3-(fluorocarbonyl)-2-oxo-2,3-dihydro-1*H*-imidazo[2,1-*a*]isoquinolin-4-ium-3-ide (5f): Obtained as a yellow solid (26%), m.p. 214–216 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.35 (d, J = 7.2 Hz, 1 H), 7.91 (d, J = 8.0 Hz, 1 H), 7.68–7.75 (m, 1 H), 7.58 (d, J = 7.2 Hz, 1 H), 7.46 (t, J = 7.6 Hz, 1 H), 7.35–7.40 (m, 1 H), 7.30–7.39 (m, 2 H), 7.09 (d, J = 8.8 Hz, 1 H), 2.09 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.0, 153.16 (d, J = 311 Hz), 137.1, 133.1, 132.3, 131.7, 130.8, 129.8, 129.6, 128.4, 127.0, 124.2, 122.1, 116.3, 116.2, 90.6 (d, J = 83 Hz), 18.1 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = 12.0 ppm. IR (NaCl): $\tilde{\nu}$ = 2918, 2850, 1747, 1743, 1703, 1514, 1413, 997, 748, 665 cm^{-1}. UV (CH_2Cl_2): λ_{max} (log ε_0) = 263 (3.96), 292 (3.91), 363 (3.82) nm. MS (EI): m/z (%) = 334 (50) $[M]^+$, 314 (100), 299 (11), 285 (24), 271 (12), 258 (89), 245 (20), 232 (30), 217 (16), 103 (17), 77 (31). HRMS: calcd. for $C_{20}H_{16}FN_2O_2^+$ 335.1190; found 335.1198.

7-Bromo-1-cyclohexyl-3-(fluorocarbonyl)-2-oxo-2,3-dihydro-1*H*-imidazo[2,1-*a*]isoquinolin-4-ium-3-ide (5g): Obtained as a white waxy solid (35%), m.p. 275 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.30 (d, J = 7.6 Hz, 1 H), 8.24 (d, J = 8.4 Hz, 1 H), 8.08 (d, J = 7.6 Hz, 1 H), 7.93 (d, J = 7.2 Hz, 1 H), 7.61 (t, J = 7.6 Hz, 1 H), 4.74 (m, 1 H), 2.88 (m, 2 H), 2.02–1.42 (m, 8 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.5, 152.8 (d, J = 313 Hz), 134.7, 132.1, 129.1, 124.7, 123.6, 122.9, 120.9, 117.2, 114.6, 90.8 (d, J = 81 Hz), 59.3, 29.5, 26.2, 24.8 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = 15.9 ppm. IR (NaCl): $\tilde{\nu}$ = 2930, 1739, 1706, 1502, 1405, 1155 cm^{-1}. UV (MeOH): λ_{max} (log ε_0) = 247 (4.66), 294 (4.79), 348 (4.31) nm. MS (EI): m/z (%) = 390 (7) $[M]^+$, 370 (10), 344 (4), 308 (28), 288 (100), 234 (11), 209 (7), 153 (41), 127 (21). HRMS: calcd. for $C_{18}H_{17}BrFN_2O_2^+$ 391.0457; found 391.0453.

6-Bromo-1-cyclohexyl-3-(fluorocarbonyl)-2-oxo-2,3-dihydro-1*H*-imidazo[2,1*a*]isoquinolin-4-ium-3-ide (5h): Obtained as a purple solid (82%), m.p. 196–197 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.53 (s, 1 H), 8.34 (dd, J = 8.4, 0.8 Hz, 1 H), 8.30 (d, J = 8.3 Hz, 1 H), 7.92 (ddd, J = 8.3, 7.1, 1.0 Hz, 1 H), 7.84 (ddd, J = 8.4, 7.2, 1.3 Hz, 1 H), 4.77 (s, 1 H), 2.87 (m, 2 H), 2.09–1.91 (m, 4 H), 1.87–1.70 (m, 2 H), 1.52–1.36 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.6, 131.8, 129.8, 128.4, 124.5, 123.8, 120.2, 118.1, 116.3, 111.3, 59.3, 29.5, 26.2, 24.8 ppm (the signals of two quaternary carbon atoms were not detected). ^{19}F NMR (376 MHz, $CDCl_3$): δ = 11.5 ppm. IR (NaCl): $\tilde{\nu}$ = 2925, 1706, 1505, 1417 cm^{-1}. UV (MeOH): λ_{max} (log ε_0) = 245 (4.09), 294 (4.36), 353 (3.78) nm. MS (EI): m/z (%) = 392 (7) $[M]^+$, 390 (7) $[M]^+$, 372 (7), 370 (7), 310 (24), 308 (24), 290 (100), 288 (99), 234 (16), 232 (16). HRMS: calcd. for $C_{18}H_{17}BrFN_2O_2^+$ 391.0451; found 391.0452.

1-Cyclohexyl-3-(fluorocarbonyl)-2-oxo-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1*H*-imidazo[2,1-*a*]isoquinolin-4-ium-3-ide (5i): Obtained as an off-white solid (69%), m.p. 200–202 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.57 (s, 1 H), 8.87 (dd, J = 8.4, 0.8 Hz, 1 H), 8.24 (d, J = 8.2 Hz, 1 H), 7.82 (ddd, J = 8.3, 7.1, 1.0 Hz, 1 H), 7.73 (ddd, J = 8.4, 7.1, 1.2 Hz, 1 H), 4.79 (t, J = 11.6 Hz, 1 H), 2.90 (m, 2 H), 2.08–1.91 (m, 4 H), 1.50–1.36 (m, 2 H), 1.78 (m, 2 H), 1.42 (s, 12 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 159, 152 (d, J = 311 Hz), 137.8, 136.3, 131.6, 131.0, 129.6, 128.3, 123.6, 123.4, 115.7, 84.8, 59.3, 29.6, 26.2, 24.9 ppm (one signal overlapped, the signal of one quaternary carbon atom was not detected). ^{19}F NMR (376 MHz, $CDCl_3$): δ = 10.60 ppm. IR (NaCl): $\tilde{\nu}$ = 2977, 2931, 2851, 1738, 1692, 1389, 1365, 1317, 1142 cm^{-1}. UV (MeOH): λ_{max} (log ε_0) = 248 (4.01), 287 (4.13), 341 (3.74) nm. MS (EI): m/z (%) = 438 (7) $[M]^+$, 418 (7), 390 (8), 356 (17), 336 (100), 335 (24). HRMS: calcd. for $C_{24}H_{29}BFN_2O_4^+$ 439.2199; found 439.2204.

1-Cyclohexyl-3-(fluorocarbonyl)-2-oxo-2,3-dihydro-1*H*-imidazo[1,2-*a*]pyridin-4-ium-3-ide (5j): Obtained as a white solid (40%), m.p. 190 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.35 (d, J = 6.4 Hz, 1 H), 7.65 (d, J = 7.6 Hz, 1 H), 7.39 (d, J = 8.8 Hz, 1 H), 7.19 (d, J = 6.8 Hz, 1 H), 4.56 (m, 1 H), 1.97–1.48 (m, 10 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.4, 153.0 (d, J = 311 Hz), 137.6, 132.3, 129.6, 115.7, 107.8, 90.3 (d, J = 64 Hz), 52.2, 30.0, 26.1, 25.4 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = 9.5 ppm. IR (NaCl): $\tilde{\nu}$ = 2936, 1737, 1688, 1513, 1440, 1132 cm^{-1}. UV (MeOH): λ_{max} (log ε_0) = 255 (4.22), 304 (3.86), 333 (3.82) nm. MS (EI): m/z (%) = 262 (10) $[M]^+$, 242 (9), 214 (13), 180 (34), 160 (100), 104 (29), 78 (32). HRMS: calcd. for $C_{14}H_{16}FN_2O_2^+$ 263.1190; found 263.1197.

1-Cyclohexyl-2-oxo-3-(2,2,2-trifluoroacetyl)-2,3-dihydro-1*H*-imidazo[2,1-*a*]isoquinolin-4-ium-3-ide (5l): Obtained as a white solid (38%), m.p. 228 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.79 (d, J = 7.2 Hz, 1 H), 8.26 (d, J = 7.6 Hz, 1 H), 7.90 (d, J = 7.6 Hz, 1 H), 7.78 (t, J = 7.2 Hz, 1 H), 7.74 (m, J = 7.6, 1.6 Hz, 1 H), 7.42 (q, J = 7.2 Hz, 1 H), 4.76 (m, 1 H), 2.85 (m, 2 H), 2.02–1.38 (m, 8 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.3 (m), 158.6, 136.4, 134.2, 131.4, 128.9, 128.6, 124.9, 118.9, 116.0, 115.5, 58.9, 29.5, 26.2, 24.9 ppm (the signals of two quaternary carbon atoms were not detected). ^{19}F NMR (376 MHz, $CDCl_3$): δ = –79.1 ppm. IR (NaCl): $\tilde{\nu}$ = 2923, 1700, 1610, 1508, 1456, 1251, 1143 cm^{-1}. UV (MeOH): λ_{max} (log ε_0) = 262 (4.24), 279 (4.28), 294 (4.32), 359 (4.22) nm. MS (EI): m/z (%) = 362 (15) $[M]^+$, 280 (58), 211 (100), 155 (23), 128 (13). HRMS: calcd. for $C_{19}H_{18}F_3N_2O_2^+$ 363.1320; found 363.1313.

1-Cyclohexyl-2-oxo-3-(2,2,3,3,3-pentafluoropropanoyl)-2,3-dihydro-1*H*-imidazo[2,1-*a*]isoquinolin-4-ium-3-ide (5m): Obtained as a white solid (45%), m.p. 235 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.83

(d, J = 7.6 Hz, 1 H), 8.27 (d, J = 8.0 Hz, 1 H), 7.90 (d, J = 8.0 Hz, 1 H), 7.80 (t, J = 7.2 Hz, 1 H), 7.74 (t, J = 7.2 Hz, 1 H), 7.41 (d, J = 7.2 Hz, 1 H), 4.76 (m, 1 H), 2.86 (m, 2 H), 2.00–1.39 (m, 8 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.9 (m), 158.4, 136.7, 134.2, 131.5, 128.9, 128.6, 124.9, 118.9 (m), 115.6, 115.4, 108.8, 103.3, 59.0, 29.5, 26.2, 24.8 ppm (the signal of one quaternary carbon atom was not detected). ^{19}F NMR (376 MHz, $CDCl_3$): δ = –85.6, –124.4 ppm. IR (NaCl): $\tilde{\nu}$ = 2930, 1693, 1597, 1514, 1450, 1213, 1123 cm^{-1}. UV (MeOH): λ_{max} (log ε_0) = 280 (4.29), 361 (4.24), 371 (4.21) nm. MS (EI): m/z (%) = 412 (13) $[M]^+$, 330 (36), 211 (100), 155 (21), 128 (12). HRMS: calcd. for $C_{20}H_{18}F_5N_2O_2^+$ 413.1282; found 413.1280.

3-Benzoyl-1-cyclohexyl-2-oxo-2,3-dihydro-1*H*-imidazo[2,1-*a*]isoquinolin-4-ium-3-ide (5n): Oxalyl chloride (0.136 mL, 1.6 mmol, 3 equiv.) was slowly added to a suspension of potassium difluoro(phenyl)acetate (677.2 mg, 3.2 mmol, 6 equiv.)[18] in toluene (1.5 mL) at 0 °C. The reaction was left to stir under nitrogen at room temp. for 2 h and then heated at reflux for 2 h to yield difluoro(phenyl)acetic anhydride, which was used without purification. The mixture containing the anhydride was then cooled to –78 °C. At this temperature, CH_2Cl_2 (4 mL), cyclohexyl isocyanide (0.131 mL, 1.1 mmol, 2 equiv.) and isoquinoline (70.5 mg, 0.533 mmol, 1 equiv.) were added in that order. After 3 min, the dry ice bath was removed and the reaction mixture was left to stir for 24 h. An aqueous saturated solution of Na_2CO_3 (10 mL) was added and the mixture was extracted with dichloromethane (2 × 5 mL). The combined organic extracts were washed with brine (10 mL) and then dried (Na_2SO_4) and filtered. The solvent was removed under reduced pressure and the residue was washed with Et_2O (6 mL) to yield **5n** (81.1 mg, 41%) as a yellow solid, m.p. 128–129 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.99 (d, J = 7.6 Hz, 1 H), 8.28 (br., 1 H), 7.86–7.95 (m, 1 H), 7.82 (m, 2 H), 7.73 (m, 2 H), 7.39–7.49 (m, 4 H), 4.80 (br., 1 H), 2.85 (m, 2 H), 1.90–2.10 (m, 4 H), 1.70–1.80 (m, 1 H), 1.30–1.50 (m, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 183.9, 159.7, 140.0, 134.2, 131.0, 130.4, 128.9, 128.7, 128.6, 128.5, 127.8, 125.4, 123.8, 116.2, 115.1, 104.73, 59.0, 29.8, 26.5, 25.1 ppm. IR (NaCl): $\tilde{\nu}$ = 3128, 2926, 2854, 1675, 1587, 1557, 1509, 1447, 1410, 1366, 1345, 1321, 1227, 1140, 1026, 977, 809, 740, 650 cm^{-1}. UV (CH_2Cl_2): λ_{max}(log ε_0) = 241 (3.32), 292 (3.25), 392 (3.22) nm. MS (EI): m/z (%) = 370 (34) $[M]^+$, 288 (100), 211 (15), 155 (12), 128 (9), 105 (24), 77 (18). HRMS: calcd. for $C_{24}H_{23}N_2O_2^+$ 371.1754; found 371.1763.

1-Cyclohexyl-3-formyl-2-oxo-2,3-dihydro-1*H*-imidazo[2,1-*a*]isoquinolin-4-ium-3-ide (5o): Difluoroacetic anhydride (0.500 mL, 5 mmol, 5 equiv.) and cyclohexyl isocyanide (0.096 mL, 1 mmol, 1 equiv.) were added to a solution of the corresponding azine (100 mg, 0.78 mmol, 1 equiv.) in anhydrous CH_2Cl_2 (5 mL) at –30 °C. After stirring for 3 min at this temperature, the dry ice bath was removed and the reaction mixture was stirred for 14 h at room temperature. A saturated solution of Na_2CO_3 (10 mL) was added and the mixture was extracted with dichloromethane (2 × 5 mL). The combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4) and filtered. The solvent was removed under reduced pressure and the residue was purified by column chromatography [SiO_2, hexanes/ethyl acetate (1:5)] to yield **5o** (73.7 mg, 32%) as a white solid, m.p. 242 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.70 (s, 1 H), 9.64 (d, J = 7.2 Hz, 1 H), 8.28 (m, 1 H), 7.89 (d, J = 7.6 Hz, 1 H), 7.74 (m, 2 H), 7.40 (d, J = 7.2 Hz, 1 H), 4.79 (m, 1 H), 2.86 (m, 2 H), 2.00–1.42 (m, 8 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.3, 161.9, 133.3, 130.4, 128.8, 128.7, 124.2, 123.5, 122.3, 116.1, 115.5, 104.5, 58.6, 29.7, 26.2, 24.9 ppm. IR (NaCl): $\tilde{\nu}$ = 2923, 1668, 1617, 1514, 1450, 1354, 1149 cm^{-1}. UV (MeOH): λ_{max} (log ε_0) = 265 (4.44), 294 (4.42), 354 (4.36) nm. MS (EI): m/z (%) = 294 (27) $[M]^+$, 212 (100), 184 (46), 155 (23), 128 (16). HRMS: calcd. for $C_{18}H_{19}N_2O_2^+$ 295.1447; found 295.1446.

1-Cyclohexyl-2-oxo-3-[1-(trichloromethyl)-1,2-dihydroisoquinolin-2-ylcarbonyl]-2,3-dihydro-1*H*-imidazo[2,1-*a*]isoquinolin-4-ium-3-ide (5p): Obtained as a white solid (30%), m.p. 141.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.40 (d, J = 7.2 Hz, 1 H), 8.75 (m, 1 H), 8.39 (m, 1 H), 8.20–7.90 (m, 5 H), 7.82–7.60 (m, 4 H), 6.45 (br. d, J = 7.2 Hz, 1 H), 4.84 (br. s, 1 H), 2.84 (br. s, 2 H), 2.02–1.41 (m, 8 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, mixture of rotamers): δ = 171.3, 162.2, 158.6, 133.5, 132.4, 131.6, 129.9, 129.0, 128.8, 128.5, 128.3, 126.4, 124.9, 124.6, 124.2, 122.4, 122.3, 116.5, 114.9, 113.9, 96.3, 58.7, 41.8, 29.8, 26.2, 24.9 ppm. IR (NaCl): $\tilde{\nu}$ = 3430, 2923, 1643, 1617, 1508, 1454, 1245 cm^{-1}. UV (MeOH): λ_{max} (log ε_0) = 271 (4.67), 349 (4.99), 362 (4.95) nm. MS (EI): m/z (%) = 422, 328 (7), 293 (25), 246 (16), 211 (100), 176 (38), 155 (25), 128 (17). HRMS: calcd. for $C_{28}H_{25}Cl_3N_3O_2^+$ 540.1012; found 540.0987.

(2-Methoxy-2-oxoethylimino)-3-(trifluoromethyl)-1,3-dihydrooxazolo[4,3-*a*]isoquinolin-4-ium-3-ide (6a): In this experiment the order of addition was modified. The isocyanide (0.281 mL, 3.10 mmol, 2 equiv.), TFAA (0.658 mL, 4.64 mmol, 3 equiv.) and isoquinoline (200 mg, 1.55 mmol, 1 equiv.) were added in that order to yield under the standard conditions the dipole **6a** as a white solid (70.5 mg, 14%), m.p. 194–195 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07 (d, J = 7.2 Hz, 1 H), 7.95–8.05 (m, 1 H), 7.85–7.92 (m, 1 H), 7.68–7.76 (m, 2 H), 7.46 (d, J = 7.2 Hz, 1 H), 5.36 (s, 2 H), 3.79 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.0, 153.2, 131.1, 130.1, 129.8, 128.8, 121.9, 121.8, 121.7, 121.6, 119 (q, J = 264 Hz), 116.5, 53.4, 43.3 ppm (the signal of one quaternary carbon atom was not detected). ^{19}F NMR (376 MHz, $CDCl_3$): δ = –59.4 ppm. IR (NaCl): $\tilde{\nu}$ = 3138, 2955, 2926, 1751, 1676, 1639, 1523, 1477, 1449, 1220, 1126, 1064, 647 cm^{-1}. UV (CH_2Cl_2): λ_{max} (log ε_0) = 236 (4.17), 286 (4.25), 357 (4.17) nm. MS (EI): m/z (%) = 324 (100) $[M]^+$, 305 (10), 266 (12), 237 (20), 217 (18), 197 (10), 168 (11), 142 (9), 128 (13). HRMS: calcd. for $C_{15}H_{12}F_3N_2O_3^+$ 325.0794; found 325.0802. The acid fluoride product **5d** (23.5 mg, 5%) was also obtained in this experiment.

(4-Methoxyphenylimino)-3-(trifluoromethyl)-1,3-dihydrooxazolo-[4,3-*a*]isoquinolin-4-ium-3-ide (6b): In this experiment the typical stoichiometry was modified: isocyanide (1 equiv., TFAA 1 equiv.), isoquinoline (1 equiv.) The product **6b** was obtained as a white solid (23%), m.p. 196–197 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.09 (d, J = 7.2 Hz, 1 H), 7.81 (d, J = 8.4 Hz, 1 H), 7.59 (m, J = 7.6, 7.2 Hz, 1 H), 7.43 (d, J = 7.2 Hz, 1 H), 7.37 (m, J = 9.2 Hz, 2 H), 7.34 (m, J = 7.2 Hz, 1 H), 7.28 (m, J = 9.2 Hz, 1 H), 7.14 (m, J = 8.8 Hz, 2 H), 3.94 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.2, 154.7, 151.6, 133.3, 131.5, 130.0, 129.1, 128.4, 126.2, 124.0, 123.8, 116.4, 116.1, 116.0, 55.92 ppm (the signals of two quaternary carbon atoms were not detected). ^{19}F NMR (376 MHz, $CDCl_3$): δ = –76.9 ppm. IR (NaCl): $\tilde{\nu}$ = 2957, 2924, 1753, 1672, 1607, 1469, 1443, 1252, 1122, 666 cm^{-1}. UV (CH_2Cl_2): λ_{max} (log ε_0) = 265 (3.72), 295 (3.70), 334 (3.36), 371 (3.52) nm. MS (EI): m/z (%) = 358 (100) $[M]^+$, 337 (40), 261 (20), 218 (25), 191 (8), 128 (8), 92 (9), 77 (10). HRMS: calcd. for $C_{19}H_{14}F_3N_2O_2^+$ 359.1002, found 359.1008.

1-(Cyclohexylimino)-7-(methoxycarbonyl)-3-(trifluoromethyl)-1,3-dihydrooxazolo[3,4-*a*]pyridin-4-ium-3-ide (6c): Obtained as a white solid (20%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.08 (d, J = 4.0 Hz, 1 H), 7.87 (s, 1 H), 7.58 (dd, J = 6.8, 1.7 Hz, 1 H), 4.53 (m, 1 H), 3.96 (s, 3 H), 2.08–2.25 (m, 2 H), 1.65–2.00 (m, 5 H), 1.20–1.50 (m, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.3, 154.1, 131.7, 126.9, 123.6, 122.2 (q, J = 270 Hz), 114.8, 108.0, 53.04, 52.6, 30.2, 25.8, 25.0 ppm (the signal of one quaternary carbon atom was not

detected). ^{19}F NMR (376 MHz, $CDCl_3$): δ = –61.0 ppm. IR (NaCl): $\tilde{\nu}$ = 2956, 2867, 1718, 1510, 1301, 1198, 1112, 970, 760 cm^{-1}. MS (EI): *m*/*z* (%) = 342 (98) $[M]^+$, 301 (38), 260 (100), 240 (12), 81 (10). MS (ESI): *m*/*z* = 343 [M + H], 342 $[M]^+$.

5-(Cyclohexylimino)-7-(trifluoromethyl)-5,7-dihydrooxazolo[3,4-*b*]-pyridazin-8-ium-7-ide (6d): Obtained as a yellowish oil (54%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.41 (d, *J* = 5.2 Hz, 1 H), 7.59 (d, *J* = 8.8 Hz, 1 H), 7.15 (dd, *J* = 8.8, 5.2 Hz, 1 H), 4.63 (m, 1 H), 2.04–1.25 (m, 10 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.9, 142.5, 128.3, 121.5 (q, *J* = 264 Hz), 120.2, 115.2, 51.9, 30.7, 25.8, 25.2 ppm (the signal of one quaternary carbon atom was not detected). ^{19}F NMR (376 MHz, $CDCl_3$): δ = –65.8 ppm. MS (EI): *m*/*z* (%) = 285 (11) $[M]^+$, 203 (67), 177 (41), 120 (32), 95 (100), 69 (49), 55 (58).

(*S*)-1-Cyclohexyl-2-oxo-3-(1-phenylethylcarbamoyl)-2,3-dihydro-1*H*-imidazo[2,1-*a*]isoquinolin-4-ium-3-ide (7a): Triethylamine (0.053 mL, 0.38 mmol, 2 equiv.) was added to a solution of **5a** (50 mg, 0.19 mmol, 1 equiv.) in anhydrous CH_2Cl_2 (2 mL) under nitrogen. After stirring for 2 min (*S*)-(–)-α-methylbenzylamine (0.029 mL, 0.23 mmol, 1.2 equiv.) was added dropwise and the reaction mixture was stirred at room temperature overnight. A saturated solution of brine (7 mL) was added and the mixture was extracted with dichloromethane (2 × 5 mL). The combined organic extracts were dried (Na_2SO_4) and filtered. The solvent was removed under reduced pressure and the residue was purified by column chromatography [SiO_2, hexanes/ethyl acetate (1:3)] to yield **7a** (77.9 mg, 99%) as a gum. $[\alpha]_D^{20}$ = +56.35 (*c* = 2.7, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.88 (d, *J* = 7.2 Hz, 1 H), 8.94 (d, *J* = 7.6 Hz, 1 H), 8.22 (br. s, 1 H), 7.85 (m, 1 H), 7.60–7.80 (m, 2 H), 7.47 (m, 2 H), 7.35 (m, 3 H), 7.20 (m, 1 H), 5.30 (m, 1 H), 4.9 (br. s, 1 H), 2.95 (br. s, 2 H) 2.00–2.1 (m, 4 H), 1.75–1.85 (br., 1 H), 1.59 (d, *J* = 7.2 Hz, 3 H) 1.45–1.55 (m, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.8, 158.9, 145.2, 131.9, 129.1, 129.0, 128.9, 128.7, 128.6, 128.5, 127.0, 126.3, 124.5, 122.7, 116.7, 115.1, 59.14, 48.4, 30.1, 26.5, 25.3, 23.5 ppm. IR (NaCl): $\tilde{\nu}$ = 2929, 2854, 1653, 1624, 1534, 1506, 1452, 1415, 1369, 1214, 742, 699 cm^{-1}. UV (CH_2Cl_2): λ_{max} ($\log\varepsilon_0$) = 249 (3.96), 270 (3.99), 2.96 (4.00), 371 (3.88) nm. MS (EI): *m*/*z* (%) = 413 (49) $[M]^+$, 396 (23), 294 (41), 266 (38), 227 (82), 211 (100), 184 (92), 155 (55), 120 (62), 105 (70). HRMS: calcd. for $C_{26}H_{28}N_3O_2^+$ 414.2176; found 414.2180.

1-Cyclohexyl-3-(4-methoxybenzylcarbamoyl)-2-oxo-2,3-dihydro-1*H*-imidazo[2,1-*a*]isoquinolin-4-ium-3-ide (7b): By using the same procedure as above with *p*-methoxybenzylamine, **7b** (75%) was obtained as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.90 (d, *J* = 7.2 Hz, 1 H), 8.85 (m, 1 H), 8.19 (m, 1 H), 7.82 (d, *J* = 8.0 Hz, 1 H), 7.64 (m, 2 H), 7.31 (m, 3 H), 6.83 (m, 2 H), 4.84 (m, 1 H), 4.55 (d, *J* = 6.0 Hz, 2 H), 3.76 (s, 3 H), 2.84 (m, 2 H), 2.02–1.39 (m, 8 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.2, 158.6, 131.6, 129.0, 128.8, 128.5, 128.3, 124.2, 122.4, 122.3, 122.2, 116.5, 114.9, 113.9, 96.3, 58.7, 55.2, 41.8, 29.8, 26.2, 24.9 ppm (the signal of one quaternary carbon atom was not detected). IR (NaCl): $\tilde{\nu}$ = 3429, 2923, 1645, 11617, 1508, 1412, 1245, 1028 cm^{-1}. UV (MeOH): λ_{max} ($\log\varepsilon_0$) = 262 (4.45), 288 (4.33), 348 (4.24) nm. MS (EI): *m*/*z* (%) = 429 (56) $[M]^+$, 294 (17), 266 (23), 211 (40), 184 (43), 155 (22), 121 (100). HRMS: calcd. for $C_{26}H_{28}N_3O_3^+$ 430.2131; found 430.2124.

1-Cyclohexyl-3-(methoxycarbonyl)-2-oxo-2,3-dihydro-1*H*-imidazo-[2,1-*a*]isoquinoline-4-ium-3-ide (7c): Triethylamine (0.4 mL, 3.2 mmol, 10 equiv.) was added to a solution of **5a** (100 mg, 0.3 mmol, 1 equiv.) in MeOH (5 mL) under nitrogen and the reaction mixture was heated at reflux overnight. Then the solvent was removed under reduced pressure and the residue was dissolved in CH_2Cl_2 (5 mL). The mixture was extracted with brine (4 × 5 mL) and the combined organic extracts were dried (Na_2SO_4) and filtered. The solvent was removed under reduced pressure and the residue was purified by column chromatography [SiO_2, hexanes/ethyl acetate (1:1)] to yield **7c** (88.0 mg, 82%) as a white glassy solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.58 (d, *J* = 7.6 Hz, 1 H), 8.24 (m, 1 H), 7.86 (d, *J* = 8.6 Hz, 1 H), 7.70 (m, 2 H), 7.37 (d, *J* = 7.6 Hz, 1 H), 4.80 (m, 1 H), 3.93 (m, 3 H), 2.96 (m, 2 H), 2.02–1.41 (m, 8 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.6, 158.0, 132.3, 129.8, 128.6, 128.5, 123.9, 123.0, 122.9, 116.2, 115.1, 95.0, 59.0, 51.1, 29.6, 26.3, 24.9 ppm. IR (NaCl): $\tilde{\nu}$ = 2930, 1783, 1655, 1597, 1463, 1200, 1072 cm^{-1}. UV (MeOH): λ_{max} ($\log\varepsilon_0$) = 262 (4.42), 287 (4.52), 344 (4.18) nm. MS (EI): *m*/*z* (%) = 324 (21) $[M]^+$, 242 (78), 210 (100), 184 (22), 154 (33), 128 (16). HRMS: calcd. for $C_{19}H_{21}N_2O_3^+$ 325.1552; found 325.1547.

1-Benzyl-3-(ethylthiocarbonyl)-2-oxo-2,3-dihydro-1*H*-imidazo[2,1-*a*]-isoquinolin-4-ium-3-ide (7d): DMAP (10 mg, 81.8 μmol, 0.5 equiv.) and ethanethiol (0.5 mL, 9.6 mmol, 61.4 equiv.) were added to a solution of **5c** (50.0 mg, 0.156 mmol, 1 equiv.) in pyridine (2 mL). The reaction mixture was left to stir for 40 h under an inert atmosphere at room temp. A saturated solution of Na_2CO_3 (6 mL) was added and the mixture was extracted with dichloromethane (2 × 3 mL). The combined organic extracts were washed with brine (6 mL) and then dried (Na_2SO_4) and filtered. The solvent was removed under reduced pressure and the residue was washed with Et_2O (6 mL) to yield **7d** (35.1 mg, 62%) as a yellow solid M.p. 224–225 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.83 (d, *J* = 7.3 Hz, 1 H), 8.21 (d, *J* = 8.6 Hz, 1 H), 7.83 (d, *J* = 8.0 Hz, 1 H), 7.65 (t, *J* = 7.5 Hz, 1 H), 7.51 (t, *J* = 7.6 Hz, 1 H), 7.42 (d, *J* = 7.3 Hz, 1 H), 7.23–7.37 (m, 5 H), 5.75 (s, 2 H), 3.08 (m, *J* = 7.4 Hz, 2 H), 1.39 (t, *J* = 7.4 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 179.5, 158.2, 153.3, 132.6, 132.2, 130.5, 129.4, 129.0, 128.3, 128.1, 126.4, 124.7, 123.7, 116.2, 115.7, 102.2, 45.52, 21.96, 15.31 ppm. IR (NaCl): $\tilde{\nu}$ = 2923, 1747, 1673, 1593, 1520, 1455, 1406, 1347, 917 cm^{-1}. UV (CH_2Cl_2): λ_{max} ($\log\varepsilon_0$) = 241 (3.88), 271 (3.92), 298 (3.96), 380 (3.86) nm. MS (EI): *m*/*z* (%) = 362 (29) $[M]^+$, 301 (92), 273 (18), 91 (100). HRMS: calcd. for $C_{21}H_{19}N_2O_2S^+$ 363.1161, found 363.1169.

1-Cyclohexyl-3-(methoxycarbonyl)-2-oxo-2,3,5,6-tetrahydro-1*H*-imidazo[2,1-*a*]isoquinolin-4-ium-3-ide (7e): Pd/C (10%, 15 mg) was added to a stirring suspension of **7c** (35.8 mg, 0.110 mmol) in MeOH (3 mL) under hydrogen at atmospheric pressure. After 48 h the hydrogen atmosphere was removed, CH_2Cl_2 (1 mL) was added and the solution was filtered through Celite. A saturated solution of Na_2CO_3 (6 mL) was added and the mixture was extracted with dichloromethane (2 × 3 mL). The combined organic extracts were washed with brine (6 mL) and then dried (Na_2SO_4) and filtered. The solvent was removed under reduced pressure and the residue was purified by column chromatography (SiO_2, hexanes/ethyl acetate) to yield the pure reduced mesoionic ester as a white solid (30.6 mg, 85%), m.p. 123–124 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44–7.49 (m, 3 H), 7.35–7.40 (m, 1 H), 4.60 (m, *J* = 6.8, 6.6 Hz, 2 H), 4.26 (m, 1 H), 3.84 (s, 3 H), 3.07 (m, *J* = 6.9, 6.6 Hz, 2 H), 2.80–3.00 (m, 1 H), 1.90–2.00 (m, 2 H), 1.80–1.88 (m, 2 H), 1.60–1.70 (m, 1 H), 1.20–1.40 (m, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.54, 158.25, 153.86, 133.08, 130.60, 128.77, 127.84, 124.76, 120.89, 97.49, 57.76, 50.79, 42.07, 29.37, 28.34, 26.09, 24.89 ppm. IR (NaCl): $\tilde{\nu}$ = 2932, 2855, 1743, 1646, 1456, 1384, 1339, 1201, 1166 cm^{-1}. UV (CH_2Cl_2): λ_{max} ($\log\varepsilon_0$) = 251 (3.70), 297 (4.00), 384 (3.90) nm. MS (EI): *m*/*z* (%) = 326 (23) $[M]^+$, 244 (100), 212 (53), 186 (15), 156 (23), 130 (22), 116 (15), 103 (9). HRMS: calcd. for $C_{19}H_{23}N_2O_3^+$ 327.1703; found 327.1705.

Supporting Information (see also the footnote on the first page of this article): ^{1}H and ^{13}C NMR spectra of all new compounds.

Acknowledgments

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[1] For overviews, see: a) J. Zhu, H. Bienaymé (Eds.), *Multicomponent reactions*, Wiley-VCH, Weinheim, **2005**; b) L. F. Tietze, G. Brasche, K. M. Gericke (Eds.), *Domino reactions in Organic Synthesis*, Wiley-VCH, Weinheim, **2006**; for recent reviews, see: c) A. Dömling, I. Ugi, *Angew. Chem. Int. Ed.* **2000**, *39*, 3168–3210; *Angew. Chem.* **2000**, *112*, 3300–3344; d) H. Bienaymé, C. Hulme, G. Oddon, P. Schmitt, *Chem. Eur. J.* **2000**, *6*, 3321–3329; e) R. V. A. Orru, M. de Greef, *Synthesis* **2003**, 1471–1499; f) C. Hulme, V. Gore, *Curr. Med. Chem.* **2003**, *10*, 51–80; g) D. J. Ramón, M. Yus, *Angew. Chem. Int. Ed.* **2005** *44*, 1602–1634; *Angew. Chem.* **2005**, *117*, 1628–1661; h) A. Dömling, *Chem. Rev.* **2006**, *106*, 17–89; i) K. C. Nicolaou, D. J. Edmonds, P. G. Bulger, *Angew. Chem. Int. Ed.* **2006**, *45*, 7134–7186; *Angew. Chem.* **2006**, *118*, 7292–7344.

[2] a) C. Merlot, D. Domine, C. Cleva, D. J. Church, *Drug Discov. Today* **2003**, *8*, 594–602; b) L. Constantino, D. Barlocco, *Curr. Med. Chem.* **2006**, *13*, 65–85; c) D. A. Horton, G. T. Bourne, M. L. Symthe, *Chem. Rev.* **2003**, *103*, 893–930.

[3] For a heterocyclic domino process, including MCRs, see: a) A. Padwa, S. K. Bur, *Tetrahedron* **2007**, *63*, 5341–5378; b) for a review on MCRs involving heterocycles, see: N. Isambert, R. Lavilla, *Chem. Eur. J.* **2008**, 8444–8454.

[4] a) J. L. Díaz, M. Miguel, R. Lavilla, *J. Org. Chem.* **2004**, *69*, 3550–3553; b) I. Carranco, J. L. Díaz, O. Jiménez, M. Vendrell, F. Albericio, M. Royo, R. Lavilla, *J. Comb. Chem.* **2005**, *7*, 33–41; c) O. Jiménez, G. de la Rosa, R. Lavilla, *Angew. Chem. Int. Ed.* **2005**, *44*, 6521–6525; *Angew. Chem.* **2005**, *117*, 6679–6683; d) N. Isambert, M. Cruz, M. J. Arévalo, E. Gómez, R. Lavilla, *Org. Lett.* **2007**, *9*, 4199–4202; e) C. Masdeu, E. Gómez, N. A. O. Williams, R. Lavilla, *Angew. Chem. Int. Ed.* **2007**, *46*, 3043–3046; *Angew. Chem.* **2007**, *119*, 3103–3106.

[5] a) C. G. Newton, C. A. Ramsden, *Tetrahedron* **1982**, *38*, 2965–3011, and references cited therein; b) L. S. Beall, A. Padwa in *Advances in Nitrogen Heterocycles* (Ed.: C. J. Moody), JAI Press, Greenwich, CT, **1998**, vol. 3, pp. 117–158.

[6] a) D. J. St. Cyr, N. Martin, B. A. Arndtsen, *Org. Lett.* **2007**, *9*, 449–452; b) M. A. Mironov, S. S. Maltsev, V. S. Morushin, V. A. Bakulev, *Mol. Diversity* **2005**, *9*, 221–227. In this latter case, the process presumably involves the electrophilic activation of the isocyanide component by the isothiocyanate.

[7] E. J. Corey, Y. Tian, *Org. Lett.* **2005**, *7*, 5535–5537.

[8] Crystallographic data for **5a**: $C_{18}H_{17}FN_2O_2$, M_r = 312.34, monoclinic, space group $P2_1/n$, a = 5.08900(10), b = 17.8638(3), c = 15.6258(3) Å, V = 1411.56(5) Å^3, T = 100(2) K, d = 1.470 Mg m^{-3}, 0.106 mm^{-1}, 33721 reflections measured, 3512 unique reflections (R_{int} = 0.0413), R_1 = 0.0394, wR_2 = 0.0906. CCDC-684676 contains the supplementary crystallographic data for **5a**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[9] C. J. Moody, S. Miah, A. M. Z. Slawin, D. J. Mansfield, I. C. Richards, *Tetrahedron* **1998**, *54*, 9689–9700.

[10] a) L. El Kaïm, *Tetrahedron Lett.* **1994**, *35*, 6669–6670; b) L. El Kaïm, E. Pinot-Périgord, *Tetrahedron* **1998**, *54*, 3799–3806; c) L. El Kaïm, L. Gaultier, L. Grimaud, E. Vieu, *Tetrahedron Lett.* **2004**, *45*, 8047–8048; d) see also: T. Colin, L. El Kaïm, L. Gaultier, L. Grimaud, L. Gatay, V. Michaut, *Tetrahedron Lett.* **2004**, *45*, 5611–5613; e) this interesting possibility was kindly suggested by a referee.

[11] a) R. Loska, M. Makosza, *Chem. Eur. J.* **2008**, *14*, 2577–2589; b) S. M. Igumnov, G. I. Lekontseva, A. A. Shipigusev, V. F. Mukhametshin, *Russ. J. Appl. Chem.* **2005**, *78*, 435–437; c) B. B. Randolph, D. D. DesMarteau, *J. Fluorine Chem.* **1993**, *64*, 129–149; d) O. Sieck, M. Ehwald, J. Liebscher, *Eur. J. Org. Chem.* **2005**, 663–672; e) H. Ueki, T. Kitazume, *J. Org. Chem.* **2005**, *70*, 9354–9363.

[12] For some examples of the double insertion of isocyanides at electrophilic centers, see: a) H. J. Kabbe, *Chem. Ber.* **1969**, *102*, 1404–1409; b) G. Bez, C.-G. Zao, *Org. Lett.* **2003**, *5*, 4991–4993; c) M. Oshita, K. Yamashita, M. Tobisu, N. Chatani, *J. Am. Chem. Soc.* **2005**, *127*, 761–766; d) V. S. Korotkov, O. V. Larionov, A. de Meijere, *Synthesis* **2006**, 3542–3546; e) Also see refs.[3a,3e].

[13] See, for instance: S. Montiel-Smith, S. Meza-Reyes, O. Viñas-Bravo, M. A. Fernández-Herrera, R. Martínez-Pascual, J. Sandoval-Ramírez, A. Fuente, M. Reyes, J. A. Ruiz, *ARKIVOC* **2005**, 127–135, and references cited therein.

[14] Crystallographic data for **5p**: $C_{28}H_{24}Cl_3N_3O_2$, M_r = 540.85, monoclinic, space group $P2_1/n$, a = 9.8728(2), b = 24.8023(5), c = 10.1993(2) Å, V = 2420.67(8) Å^3, T = 100(2) K, d = 1.484 Mg m^{-3}, 0.412 mm^{-1}, 58646 reflections measured, 7086 unique reflections (R_{int} = 0.064), R_1 = 0.0405, wR_2 = 0.0866. CCDC-684677 contains the supplementary crystallographic data for **5p**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[15] The addition of trichloromethyl anions (by decarboxylation of sodium trichloroacetate) to *N*-alkylazinium salts has been reported: M. Grignon-Dubois, F. Diaba, M.-C. Grellier-Marly, *Synthesis* **1994**, 800–804.

[16] a) A. M. Palmer, B. Grobbel, C. Jecke, C. Brehm, P. J. Zimmermann, W. Burh, M. P. Feth, W.-A. Simon, W. Kroemer, *J. Med. Chem.* **2007**, *50*, 6240–6264; b) L. Cai, J.-S. Liow, S. S. Zoghbi, J. Cuevas, C. Baetas, J. Hong, H. U. Shetty, N. M. Seneca, A. K. Brown, R. Gladding, S. S. Temme, M. H. Herman, R. B. Innis, V. W. Pike, *J. Med. Chem.* **2008**, *51*, 148–158; c) R. Szabo, M. D. Crozet, P. Vanelle, *Synthesis* **2008**, 127–135, and references cited therein.

[17] a) H. Bienaymé, K. Bouzid, *Angew. Chem. Int. Ed.* **1998**, *37*, 2234–2237; *Angew. Chem.* **1998**, *110*, 2349–2352; b) C. Blackburn, B. Guan, P. Fleming, K. Shiosaki, S. Tsai, *Tetrahedron Lett.* **1998**, *39*, 3635–3638; c) K. Groebcke, L. Weber, F. Mehlin, *Synlett* **1998**, 661–663.

[18] W. J. Middleton, E. M. Bingham, *J. Org. Chem.* **1980**, *45*, 2883–2887.

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