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Organocatalytic Aziridine Synthesis Using F^+ Salts

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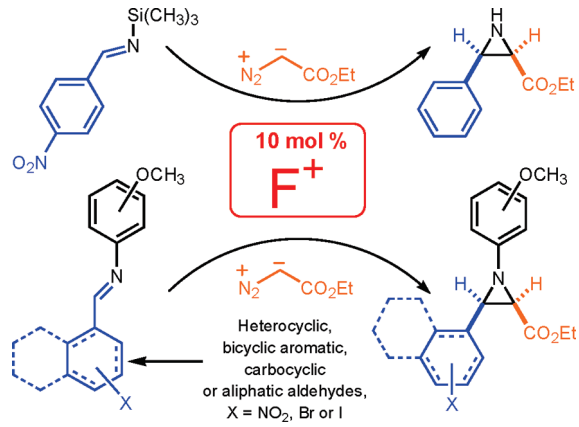
ABSTRACT



This paper describes a unique application of the fluoronium cation (F^+) as an organocatalyst for mediating the reaction between N-substituted imines and ethyl diazoacetate affording excellent yields of N-substituted aziridines.

We report the first application of the fluoronium cation, i.e., F^+ derived from an N-fluoroheterocyclic salt,[1] as a convenient, highly effective organocatalyst for aziridine synthesis. As part of our ongoing investigation toward new synthetic routes to aziridines,[2] we wanted to develop a single organocatalytic entity capable of generating both *N*-aryl- and NH-$C_{2,3}$-disubstituted aziridines. We demonstrate that N-fluoroheterocyclic salts are powerful, versatile organocatalysts that mediate the reaction between ethyl diazoacetate and *N*-arylimines or *N*-trimethysilylimines such that a diverse range of *N*-aryl-$C_{2,3}$-disubstituted aziridines or NH-$C_{2,3}$-disubstituted aziridines are generated in good yields and often with good stereoselectivities.

Aziridines are relatively reactive, synthetically useful, three-membered heterocycles that are commonly employed in the synthesis of other heterocyclic entities.[3] Although there are numerous protocols for the synthesis of N-activated aziridines,[4] there are in comparison fewer protocols that detail

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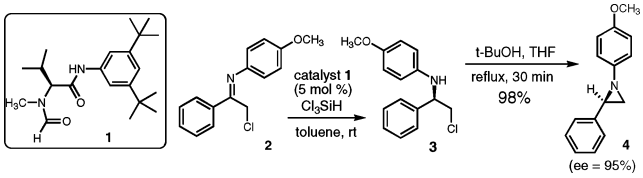
generally applicable methods for *N*-trimethylsilyl or *N*-arylaziridine synthesis from imines.[5]

Furthermore, few innovative organocatalytic methods that generate NH[6] and *N*-arylaziridines[7] have been reported, despite the acknowledged potent biological activity of *N*-arylaziridines.[8] Thus, Kocovsky et al. detailed a two-step procedure for the asymmetric synthesis of 2-substituted *N*-arylaziridines, i.e., **4**, via the asymmetric reduction of imine **2** (performed with 5 mol % of organocatalyst **1** and trichlorosilane) affording **3**, followed by its cyclization generating **4** (Scheme 1).

Scheme 1. Organocatalytic Synthesis of *N*-Arylaziridines



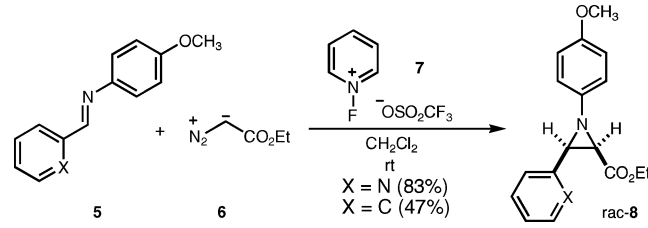
An alternative methodology for *N*-arylaziridine synthesis has focused, in the main, on employing strong Lewis acid or transition-metal complexes. Thus, Templeton et al.[9] reacted EDA with a Lewis acid, i.e., BF_3OEt_2, $AlCl_3$, or $TiCl_4$ (10 mol %) activated *N*-arylimine and generated racemic mixtures of *cis*- and *trans*-$C_{2,3}$-disubstituted *N*-arylaziridines in variable yields (2−76%).

Furthermore, for the purposes of our research, we discounted the use of triflic acid (cf. Johnston work)[10] or the application of protic salts because of their incompatibility[11] with our desire to utilize *N*-TMS imines as precursors to $C_{2,3}$-disubstituted *N*-TMS-aziridines.

Searching for an alternative to metal-based Lewis acids or the highly electrophilic H^+ species, we considered the fluoronium cation, i.e., F^+, as a possible alternative. The highly electrophilic nature of F^+ should allow, presumably in a process similar to H^+, imine activation and subsequent nucleophilic attack by EDA. Importantly, the nonacidic nature of either the N-fluoroheterocyclic salt or the fluoronium cation may allow the use of acid-sensitive functional and/or protecting groups. We also considered the fluoronium salts to have properties and benefits that many currently employed Lewis and Brønsted acids do not always have, i.e., easily handled, stable, crystalline, nonhygroscopic, organic soluble salts which produce a relatively benign and easily removed byproduct.

Our preliminary studies focused on the reaction between *N*-arylimine **5** (X = N), EDA **6**, and *N*-fluoropyridinium triflate **7** (10 mol %, Scheme 2). Gratifyingly, after 5 h at ambient temperature, TLC analysis indicated complete consumption of **5**.

Scheme 2. Efficient Synthesis of *N*-Arylaziridines from **5**



Workup (filter through alumina) and ^1H NMR analysis indicated that rac-**8** (83% yield) was afforded cleanly and with a coupling constant of $J_{2,3}$ = 6.8 Hz to have $C_{2,3}$-cis-stereochemistry. There was no indication that any of the trans-isomer of rac-**8** was present. Subsequent X-ray analysis confirmed our cis-stereochemical assignment (Figure 1).

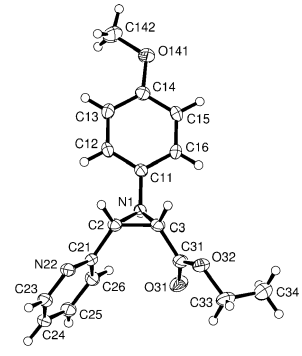


Figure 1. X-ray crystal structure of rac-*cis*-**8** (X = N).

Repeating the reaction in Scheme 2 but employing **5** (X = C), the corresponding *cis*-aziridine rac-**8** (X = C) was afforded in a 47% yield.

Confident that **7** was a viable catalyst, we elected using **5** (X = N) and **6** to screen solvents with disparate polarities

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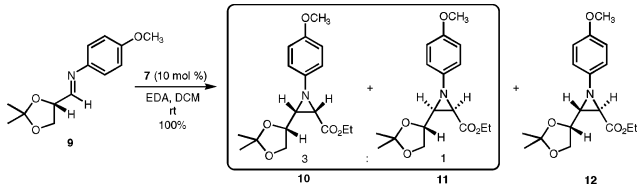
for their effect, if any, on the yield and cis/trans-stereochemistry of the resulting rac-**8**. The reaction was consistently high yielding, i.e., 63−83%, and no deterioration of the cis-stereoselectivity was observed (Table 1).

Table 1. Solvent Effect on the Yield and Stereochemistry of rac-**8**

solvent	yield	cis/trans	solvent	yield	cis/trans
THF	77%	100:0	DMF	63%	100:0
DCM	83%	100:0	DMA	77%	100:0
Et_2O	76%	100:0	toluene	71%	100:0
CH_3CN	74%	100:0	anisole	72%	100:0
EtOAc	82%	100:0	dioxane	71%	100:0
$CHCl_3$	82%	100:0	IPA	67%	100:0

Ilustrating the nonacidic nature of **7**, it was reacted with **6** and **9**. The reaction afforded a quantitative yield of the *N*-arylaziridine product as an inseperable mixture of stereoisomers **10**−**12** (Scheme 3). The excellent yield is testament

Scheme 3. Synthesis of *N*-Arylaziridines **10**−**12** from Imine **9**



to the fact that *N*-fluoroorganocatalysts are tolerant of acid-sensitive groups such as acetals.

We wanted to probe if **7** was actually performing a critical role within the reaction. Accordingly, ^{1}H NMR analysis of a solution of **5** (X = N, $CDCl_3$) and **6** was shaken (NMR tube, 180 min), and no reaction occurred. Adding **7** (10 mol %) to the sample lead to the immediate appearance of two new doublets ($J_{2,3}$ = 6.8 Hz) at δ3.2 and δ3.7 ppm, clearly indicating that the formation of *cis*-**8** only occurs when **7** is present. Probing the scope of the reaction with different N-fluorinated salts, the reaction in Scheme 2 (X = N) was repeated using (individually) Selectfluor and 1-fluoropyridinium pyridine heptafluorodiborate. Both induced the stereoselective formation of rac-*cis*-**8** in 63% and 15% yields, respectively, thus emphasizing the superiority of **7** among the fluoropyridinium catalysts tested.

In an effort to expand the structural diversity of the *N*-arylaziridines created and explore the scope of the reaction, a series of alternative *N*-arylimines were synthesized. When these were reacted with **6** and **7**, we were delighted to observe the formation of rac-**13**−**21** (Figure 2). These preliminary

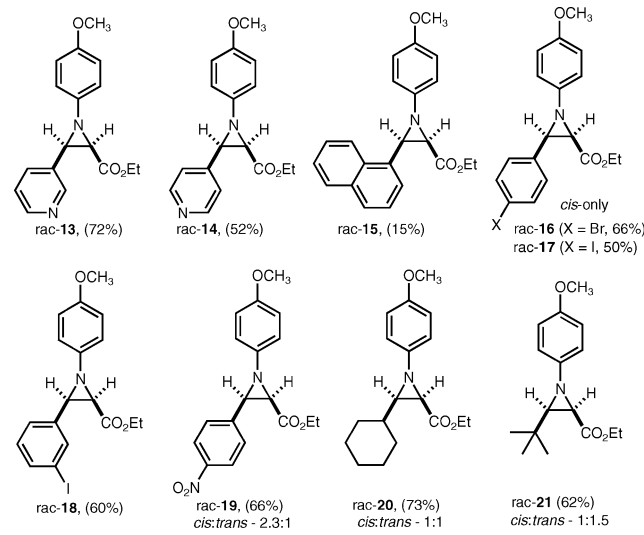


Figure 2. Racemic *N*-(*p*-methoxyphenyl) derived aziridines **13**−**21**.

results indicate our F^+-mediated reaction to be broadly applicable to the synthesis of a wide variety of *N*-arylaziridines. Thus, the reaction is amenable to the incorporation of heterocyclic motifs, i.e., **13** and **14**, but electron-rich, i.e., 2-furyl and 2-pyrrole-containing, imines were unreactive (not shown). Similarly, the imines derived from 4-methoxyaniline and cinnamaldehyde or 3,4,5-trimethoxybenzaldehyde failed to react with **6** in the presence of **7**. Gratifyingly, the protocol was capable of generating bicyclic aromatic species, i.e., **15**. Utilizing *p*- or *m*-halogenated or *p*-nitro aryl starting materials afforded rac-**16**−**19**, with rac-**19** returned in a 2.3:1 cis/trans ratio.

Similarly, incorporating bulky C_3-*tert*-butyl and C_3-cyclohexyl groups afforded good yields of rac-**20** and rac-**21**, respectively, and in nearly equal cis/trans ratios.

A key step in our design strategy was the ability to generate NH aziridines either via a one-pot organocatalytic protocol (vida infra) or the expeditious cleave of a suitable electron-rich group off an aziridine.[12] Synthesizing rac-*cis*-**23** (via addition of **6** to **22** mediated by 10 mol % of **7**) on a multigram scale allowed the efficient oxidative cleavage of the N-substituent off rac-*cis*-**23** using CAN, affording rac-*cis*-**24** in a pleasing 72% yield (Scheme 4).

We investigated the feasibility of using **7** to generate a protolytically labile *N*-TMS aziridine. Reacting **6**, **7**, and **25**[13]

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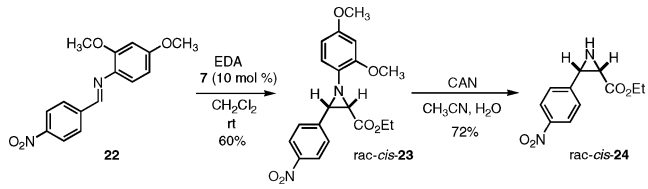
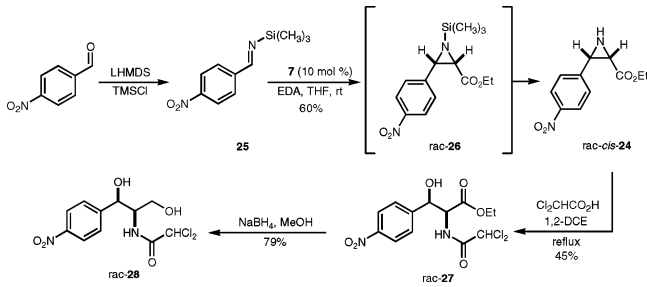
(15) Shibata, N.; Suzuki, E.; Aashi, T.; Shiro, M. *J. Am. Chem. Soc.* **2001**, *123*, 7001.

Scheme 4. Cleavage of an Electron-Rich Aryl Group off rac-**23**



(Scheme 5) afforded, presumably, (not isolated) rac-**26**. Gratifyingly, when rac-**26** was purified (column chromatography using silica gel), the TMS group cleaved affording rac-*cis*-**24** ($J_{2,3} = 6.4$ Hz, 60% yield from **25**). Exemplifying our methodology, we synthesized chloramphenicol.[14] Racemic *cis*-**24** was ring-opened with dichloroacetic acid affording rac-**27**, and subsequent reduction of the ethyl ester on **27** afforded the corresponding primary alcohol and completed the synthesis of rac-**28** in four steps.

Scheme 5. Synthesis of rac-Chloramphenicol from **28**



We considered utilizing *N*-fluorochinchona salts[15] as a source of electrophilic "optically active F^+" that may be capable of generating optically active aziridines. Reacting **5** and **6** with in situ synthesized N-fluorinated $(DHQD)_2$-PHAL (10 mol %) afforded *cis*-**8** (X = N, 78% yield), and disappointingly, chiral HPLC indicated this to be racemic.

We presume a critical aspect of our reaction to be the F^+ activation of the imines.[16] We were concerned however that small amounts of extraneous water may hydrolyze **7** forming catalytically active PyTf.[6] Mitigating this possibility, vigorous exclusion of water was achieved via use of dry solvent, flame-dried glassware, Schlenk techniques, dried inert gas, and recrystallized **7**. Given our rigorous efforts to exclude water, the relatively fast rate of the aziridination reaction (6 h) and, critically, the stability of **7** to hydrolysis at ambient temperature, cf. $t_{1/2}$ 312 h, in neat D_2O, it seems improbable that enough in situ PyTf be generated to catalyze the process such that the reaction proceeds, to completion, in the observed reaction time.

Using mass spectroscopy as a sensitive investigative tool, we analyzed recrystallized **7**[17] for contaminating pyridinium triflate. A "control" mass spectrum of pyridinium triflate afforded three peaks, i.e., 309.1 (5%, $[2PyH{\bullet}OTf]^+$), 158.9 (5%, $[Py{\bullet}PyH]^+$), and 80.1 (100%, $[PyH]^+$). For **7**, five peaks were observed: two were unidentifiable at 173 (2%) and 124 (3%, importantly neither are in the pyridinium triflate spectrum) and three were at 109.9 (100%, [*ortho*-methoxy-$PyH]^+$ via reaction of **7** with methanol (solvent) for running the spectra), 97.9 (30%, $[N$-FluoroPy$]^+$), and a very small peak at 80 (<0.5%, $[PyH]^+$). Given the very strong, i.e., 100%, stable molecular ion peak for $[PyH]^+$ in the control pyridinium triflate spectrum and the correspondingly very small molecular ion peak, i.e., <0.5%, for $[PyH]^+$ located in the spectrum of **7**, it seems reasonable to conclude that **7** does not contain enough, if any, contaminating pyridinium triflate capable of catalyzing the reactions at a rate fast enough for them to be complete within the observed reaction time. Testing this theory, we performed two reactions side-by-side using **5** (X = C) and **6** (Scheme 2). One contained 10 mol % of **7**, and the other contained 0.5 mol % of pyridinium triflate (0.5 mol % equates to a potential "contaminating" 5 mol % present within 10 mol % of **7** used in the first control reaction). The former/control reaction using 10 mol % of **7** was, as expected, complete within 6 h. The latter reaction using 0.5 mol % of pyridinium triflate contained 95% starting material after 6 h. Thus if(?) small amounts of contaminating pyridinium triflate were present in **7** and given our rigorous exclusion of water this seems unlikely, the observed fast reaction rate for the formation of rac-**8** cannot be accounted for by the presence of contaminating pyridinium triflate potentially generated by the hydrolysis of **7**.

In summary, we report the first application of an F^+ organocatalyst as an efficient, mild, and straightforward protocol that affords structurally diverse racemic *N*-aryl and NH aziridines in good yields and stereoselectivity. The minutiae of the reaction, i.e., mechanistic features and asymmetric processes, are currently being investigated.

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Supporting Information Available: Experimental and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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