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Synthesis of 3,3-Diarylazetidines by Calcium(II)-Catalyzed Friedel−Crafts Reaction of Azetidinols with Unexpected Cbz Enhanced Reactivity

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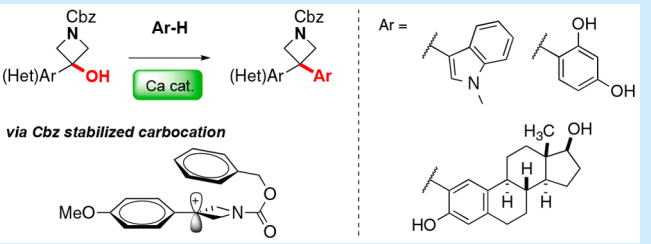
Supporting Information

ABSTRACT: Azetidines are valuable motifs that readily access under explored chemical space for drug discovery. 3,3-Diarylazetidines are prepared in high yield from *N*-Cbz azetidinols in a calcium(II)-catalyzed Friedel−Crafts alkylation of (hetero)aromatics and phenols, including complex phenols such as *β*-estradiol. Electron poor phenols undergo *O*-alkylation. The product azetidines can be derivatized to drug-like compounds through the azetidine nitrogen and the aromatic groups. The *N*-Cbz group is crucial to reactivity by providing stabilization of an intermediate carbocation on the four-membered ring.



Saturated nitrogen heterocycles are among the most abundant pharmacophores in pharmaceutical products, dominated by five- and six-membered rings.[1] In marked contrast, 4-membered azetidines are much less explored, despite offering attractive physicochemical properties for drug discovery being low molecular weight and polar structures with defined 3D vectors for substituents.[2] The development of new synthetic methods for azetidine synthesis[3] can readily access new biologically relevant chemical space for exploitation by medicinal chemists.[4] Recent years have seen high profile examples of azetidines in biologically active compounds, including antimalarial BRD9185,[5] and azelnidipine, an anti-hypertensive containing an azetidine ether (Figure 1a).[6] New azetidine motifs have recently been targeted as screening compounds and bioisosteres, including fused and spirocyclic derivatives.[7,8]

Diarylmethanes and related derivatives display a wide range of important biological activity.[9] We are recently interested in small ring derivatives as alternative linking groups for diarylmethane and diarylketone motifs, to mask potentially metabolically vulnerable sites (Figure 1b).[10] We reported the first examples of 3,3-diaryloxetanes, formed through a mild lithium-catalyzed Friedel−Crafts reaction of oxetan-3-ols with phenols.

We envisaged the application of 3,3-diarylazetidines to maintain the polar functional group, and to provide an additional vector for functionalization through the nitrogen atom. 3,3-Diarylazetidines are relatively little studied but can be found in biologically active compounds in the patent literature,[11] and a prolylcarboxypeptidase (PrCP) inhibitor (Figure 1c).[12]

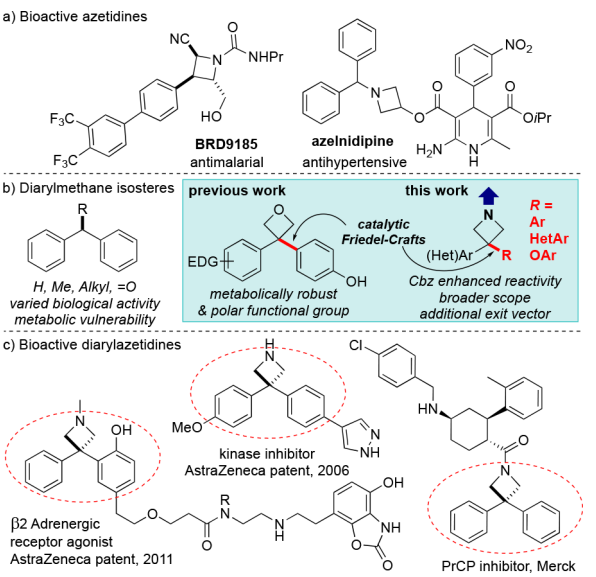


Figure 1. Bioactive azetidine structures and targeted 3,3-diarylazetidines.

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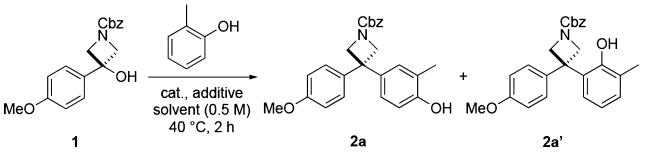
These 3,3-diarylazetidines also provide interesting scaffold structures, enable increased F(sp^3), and reduce planarity without the introduction of a chiral center. Limited prior methods to access these motifs are lengthy and low yielding. These include a cyclization strategy,[13] and previous Friedel–Crafts approaches employing excess $AlCl_3$ or TfOH, limiting the functional group compatibility.[11a,b] Here we describe a rapid and divergent synthesis of 3,3-diarylazetidines. A calcium catalyst generates azetidine carbocations from 3-arylazetidin-3-ols under mild conditions. The reaction is compatible with functionalized substrates and a wide range of electron-rich aromatic and heteroaromatic nucleophiles. The choice of the *N*-Cbz group was shown to be crucial, being uniquely effective in enhancing the reactivity.

Catalytic functionalization of π-activated alcohols has undergone considerable development in recent years.[14,15] However, carbocation formation on small four-membered rings is challenging due to the existing ring strain and increased barrier to planarization. In targeting 3,3-diarylazetidines, we also required selective coordination of a catalyst to an azetidinol hydroxyl group over the Lewis basic *N*-functionality. Initially, we examined *N*-Boc azetidinols bearing a 4-methoxyphenyl group using catalytic amounts of various Lewis acids and phenols such as *o*-cresol as nucleophiles. The system was unreactive using lithium triflimide, which was previously successful for oxetanols,[10] calcium triflimide,[15a] and iron chloride,[16] indicating significantly reduced reactivity of this substrate compared to the oxetane derivatives. Remarkably, effective catalysis was enabled by changing to the *N*-Cbz azetidinol. With this substrate, lithium, calcium, and iron catalysts were all successful using azetidinol **1** (Table 1, entries 1–3), with a dramatic increase in reactivity.

Table 1. Selected Optimization Studies for Friedel–Crafts Arylation of Azetidinol 1 with *o*-Cresol

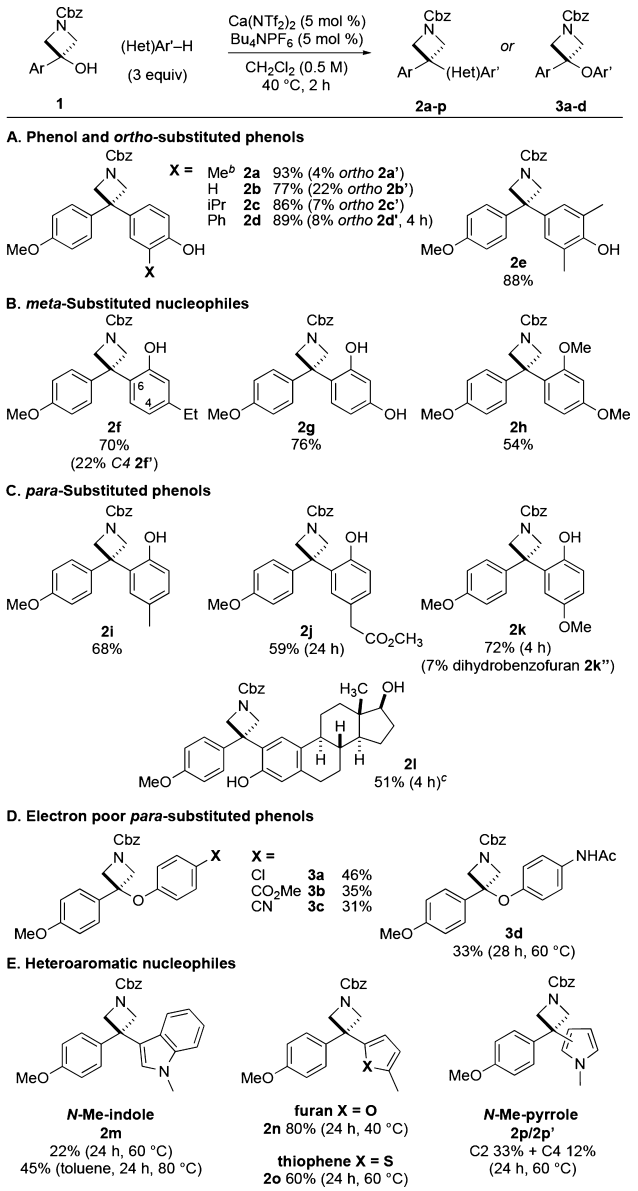


entry[a]	cat. (mol %)	equiv of *o*-cresol	solvent	yield[b] **2a**/**2a′** (%)
1	$Li(NTf_2)/Bu_4NPF_6$ (11/5.5)	5	CH_2Cl_2	45/1
2	$FeCl_3$ (5/–)	5	CH_2Cl_2	75/4
3	$Ca(NTf_2)_2/Bu_4NPF_6$ (5/5)	5	CH_2Cl_2	92/6
4	$Ca(NTf_2)_2$ (5)	5	CH_2Cl_2	0
5	$Ca(NTf_2)_2/Bu_4NPF_6$ (5/5)	3	CH_2Cl_2	94/5
6	$Ca(NTf_2)_2/Bu_4NPF_6$ (5/5)	3	PhMe	96/3
7	$Ca(NTf_2)_2/Bu_4NPF_6$ (5/5)	3	heptane	91/4

[a]Using 0.25 mmol of **1**. [b]Yield determined by ^1H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard.

Using $Ca(NTf_2)_2$ with a Bu_4NPF_6 additive afforded *para*- and *ortho*-substituted products **2a** and **2a′** in 92% and 6% yield respectively, which could be separated by column chromatography (entry 3). The Bu_4NPF_6 additive was crucial, with no reaction in its absence (entry 4), likely due to anion metathesis providing a more Lewis acidic catalyst.[14d,15a] Decreasing the equivalents of phenol from five to three maintained the excellent yield and provided the optimal conditions (entry 5). Toluene and heptane were shown to also be very suitable solvents (entries 6 and 7), but dichloromethane was chosen for reasons of improved substrate solubility. The reaction using *o*-cresol as a nucleophile could be scaled to 4.0 mmol preserving a high yield of **2a** (1.5 g, 93% yield, Scheme 1).

Scheme 1. Scope of Phenol Derivatives and Heteroaromatics as Nucleophiles



[a]Reaction conditions: **1** (0.50 mmol), $Ca(NTf_2)_2$ (5 mol %), Bu_4NPF_6 (5 mol %), CH_2Cl_2 (0.5 M), 40 °C, 2 h. Different temperatures or times indicated in parentheses where appropriate. [b]4.0 mmol scale. [c]0.25 mmol scale.

A wide range of aromatic and heteroaromatic nucleophiles were then investigated (Scheme 1). Phenol itself gave *para*/*ortho* products **2b** and **2b′** in 77% and 22% yields respectively, which were readily separable by flash chromatography. *ortho*-Substituted (*i*Pr and Ph) and disubstituted (Me) phenols afforded 3,3-diarylazetidines **2c**, **2d**, and **2e** selectively in 86% to

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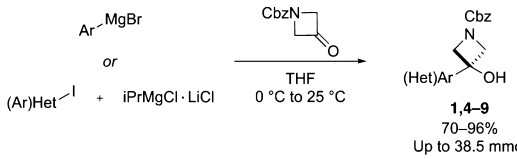
89% yields. 3-Ethylphenol gave the 6-substituted product **2f** in 70% yield as a major regioisomer, due to minimization of the steric clash from the ethyl group (Scheme 1B). Resorcinol underwent reaction at the 4-position, forming **2g** in 76% yield. Dimethoxybenzene reacted similarly, without phenol functionality (**2h**), demonstrating enhanced reactivity in the Cbz-azetidines versus the oxetane system. 4-Substituted phenols gave the Friedel–Crafts products, substituting at the 2-position (Scheme 1C). The reaction occurred in good yield (68% and 59%) for 4-methyl and 4-(methyl acetate) substrates (**2i** and **2j**), the latter providing a substructure related to compounds contained in a published patent application as a β2 adrenergic receptor agonist, and muscarinic receptor antagonist.[11b] *para*-Methoxy phenol gave the 2-substituted phenol product **2k**, as well as a small quantity of a dihydrobenzofuran (7% **2k′′**, not shown), formed via ring opening of azetidine **2k** by the phenolic OH. This contrasts with the oxetanes where the dihydrobenzofuran was the major product and the intermediate *ortho*-phenol could not be detected. Pleasingly, complex phenols such as β-estradiol were successful in the reaction, furnishing the desired product **2l** in 51% yield, and opening the possibility to apply this reaction for late stage functionalization. In contrast, *para*-substituted phenols bearing electron-withdrawing groups gave azetidine-ether products **3a** to **3c** in 31–46% yield (Scheme 1D). Using acetaminophen (paracetamol) as a nucleophile also afforded ether product **3d**. These represent relatively rare examples of phenol *O*-alkylation in Friedel–Crafts reactions.[10c] 3-Ether azetidines have been reported as potential ligands for monoamine transporters and modulators of melanocortin receptors involved in obesity and skin disorders.[17,18]

Importantly for medicinal chemistry programs, heteroaromatic nucleophiles were successful (Scheme 1E). *N*-Methylindole, 2-methylfuran, and 2-methylthiophene all successfully gave 3,3-diarylazetidines **2m–2o** in good yield by using increased reaction temperatures and times.[19] *N*-Methylpyrrole was also suitable in this reaction, giving a separable mixture of the 2- and 3-substituted pyrrole derivatives **2p** and **2p′**.

Alternative 3-aryl-3-azetidinol substrates were readily prepared using Grignard reagents formed by exchange from the aryl halide (**4–9**, Scheme 2). It is worth noting that azetidinol **1** was

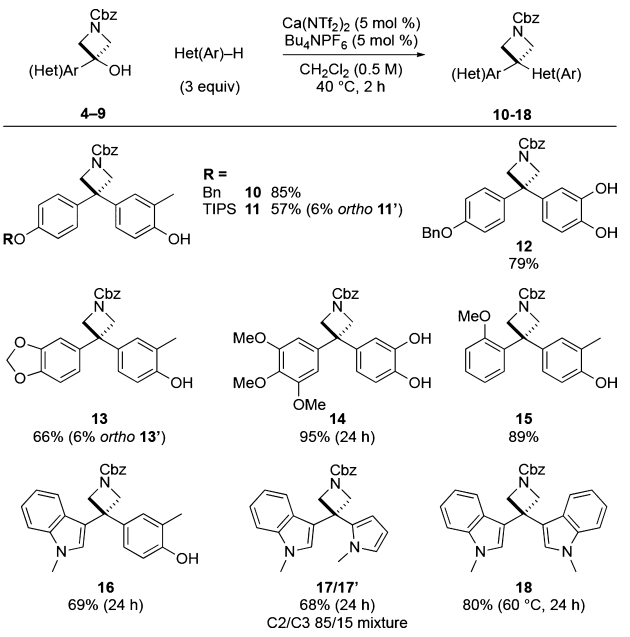
Scheme 2. Synthesis of Azetidinols



formed on scales of up to 38.5 mmol using a commercial Grignard solution. The use of the organolithium reagents led to deprotonation at the benzylic position of the Cbz group.

The azetidinol derivatives were then tested with various nucleophiles (Scheme 3). Aromatics bearing OBn and OTIPS groups were successful substrates and gave azetidines **10** and **11** in 85% and 57% yield respectively with *o*-cresol, with the potential for deprotection and further elaboration. Catechol was also shown to be a suitable nucleophile to give OBn derivative **12**. Benzodioxole and trimethoxybenzene derivatives were also successful (**13** and **14**). Furthermore, the *ortho*-methoxy phenyl group was suitable in promoting the reaction (**15**). Importantly, indole containing azetidine **16** was formed in high yield as well as azetidines containing two nitrogen heteroaryls **17** and **18**. As

Scheme 3. Scope of Azetidinols

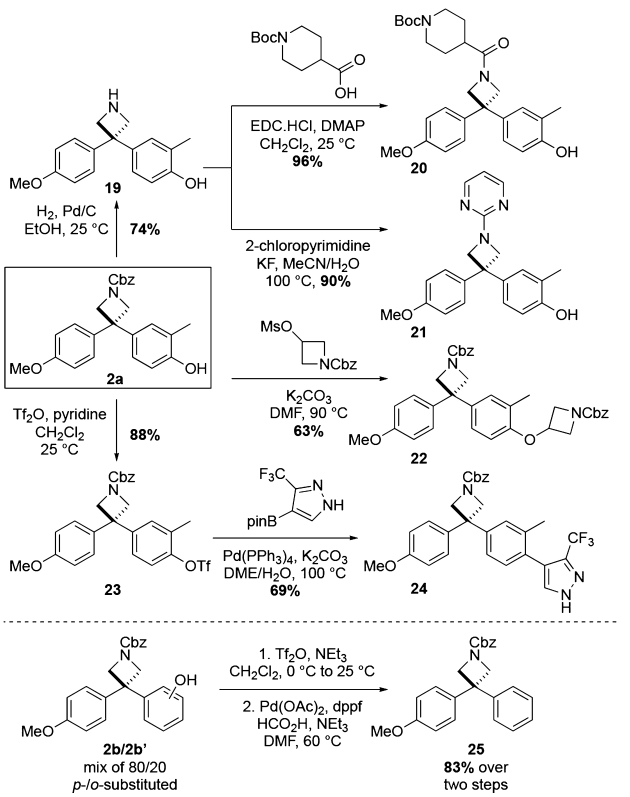


such, a variety of 3,3-diarylazetidines can be easily prepared using different nucleophiles and preinstalled aryl groups with appealing functionalities of interest for medicinal chemistry.

To show the applicability of this method to access drug-like compounds, the potential to further functionalize azetidine **2a** was explored (Scheme 4).

Removal of the Cbz group by using H_2 and Pd/C revealed the NH-azetidine **19** in 74% yield, important for further functionalization. This was derivatized through amide formation

Scheme 4. Derivatization of 3,3-Diarylazetidines



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using EDC coupling to introduce a pyrrolidine amide **20** in 96% yield. Pyrimidine **21** could be installed in high efficiency through an SNAr reaction, both occurring selectively in the presence of the unprotected phenol. The phenol itself provides a valuable synthetic handle for functionalization. A second azetidine could be readily installed by alkylation giving **22** in 63% yield. Phenol **2a** was also converted to triflate **23** and used in a Suzuki–Miyaura cross-coupling to afford **24**, which is related to a compound reported by AstraZeneca in a patent application (Figure 1c).[11a] Finally, the phenol functionality was removed from a mixture of azetidine **2b** and **2b′** (80/20 ratio), and a single phenyl-azetidine product **25** was obtained in 83% overall yield by triflation followed by palladium catalyzed deoxygenation.

To probe the role of the Cbz group in enabling reactivity, we applied the final conditions to azetidine derivatives with different N-groups (Figure 2). Alternative carbamates with

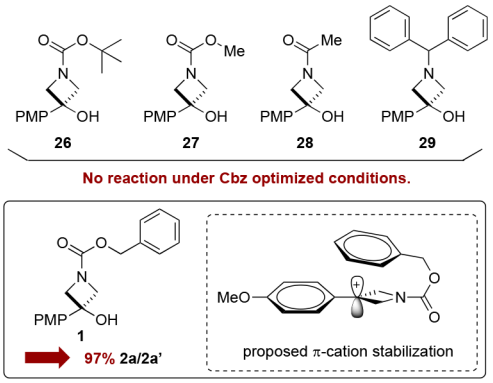

Figure 2. Alternative *N*-protecting groups, and proposed π–cation stabilization

varied steric requirements (*t*Bu or Me) were unsuccessful, giving no reaction. Similarly, acetyl and benzhydryl group also resulted in no conversion. The reactivity of the Ac or Bh groups may be explained by a change in the electronics of the carbocation or complexation of the Lewis basic sites with the catalyst. On the other hand, the similarity of the carbamates suggest a positive enhancing role of the Cbz group. The reason for this effect is unclear, but we propose that the aryl ring provides a stabilizing interaction with the carbocation to lower the barrier to carbocation formation. This may occur through a cation–π interaction as illustrated in Figure 2,[20] or alternatively through a directing effect on the catalyst.

In summary, we have developed a Friedel–Crafts alkylation with readily available azetidinols using calcium(II) catalysis to form diarylazetidines. This is compatible with a variety of phenols and heteroaromatic nucleophiles to afford a wide range of 3,3-diarylazetidines. These provide attractive functionality for inclusion as screening compounds or incorporation into medicinal chemistry programs. The Cbz group is shown to be crucial to a successful reaction. Further efforts to exploit and develop the Cbz-enhanced reactivity are underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03745.

Experimental procedures, characterization data, and copies of ^{1}H and ^{13}C NMR spectra (PDF)

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Author Contributions

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Vitaku, E.; Smith, D. T.; Njardarson, J. T. *J. Med. Chem.* **2014**, *57*, 10257. (b) Taylor, R. D.; MacCoss, M.; Lawson, A. D. G. *J. Med. Chem.* **2014**, *57*, 5845.

(2) (a) Lovering, F.; Bikker, J.; Humblet, C. *J. Med. Chem.* **2009**, *52*, 6752. (b) Nadin, A.; Hattotuwagama, C.; Churcher, I. *Angew. Chem., Int. Ed.* **2012**, *51*, 1114. (c) Murray, C. W.; Rees, D. C. *Angew. Chem., Int. Ed.* **2016**, *55*, 488.

(3) For recent synthetic developments, see: (a) For C–H functionalization: Maetani, M.; Zoller, J.; Melillo, B.; Verho, O.; Kato, N.; Pu, J.; Comer, E.; Schreiber, S. L. *J. Am. Chem. Soc.* **2017**, *139*, 11300. (b) For 2 + 2: Sakamoto, R.; Inada, T.; Sakurai, S.; Maruoka, K. *Org. Lett.* **2016**, *18*, 6252. (c) For metalation approaches: Antermite, D.; Degennaro, L.; Luisi, R. *Org. Biomol. Chem.* **2017**, *15*, 34. (d) Hodgson, D. M.; Kloesges, J. *Angew. Chem., Int. Ed.* **2010**, *49*, 2900. (e) Pancholi, A. K.; Geden, J. V.; Clarkson, G. J.; Shipman, M. *J. Org. Chem.* **2016**, *81*, 7984. (f) Parisi, G.; Capitanelli, E.; Pierro, A.; Romanazzi, G.; Clarkson, G. J.; Degennaro, L.; Luisi, R. *Chem. Commun.* **2015**, *51*, 15588. (g) Cyclisation; Wright, K.; Drouillat, B.; Menguy, L.; Marrot, J.; Couty, F. *Eur. J. Org. Chem.* **2017**, *2017*, 7195. (h) Couty, F.; Drouillat, B.; Evano, G.; David, O. *Eur. J. Org. Chem.* **2013**, *2013*, 2045.

(4) Blakemore, D. C.; Castro, L.; Churcher, I.; Rees, D. C.; Thomas, A. W.; Wilson, D. M.; Wood, A. *Nat. Chem.* **2018**, *10*, 383.

(5) Maetani, M.; Kato, N.; Jabor, V. A. P.; Calil, F. A.; Nonato, M. C.; Scherer, C. A.; Schreiber, S. L. *ACS Med. Chem. Lett.* **2017**, *8*, 438.

(6) Yagil, Y.; Miyamoto, M.; Frasier, L.; Oizumi, K.; Koike, H. *Am. J. Hypertens.* **1994**, *7*, 637.

(7) For recent examples: (a) Kirichok, A. A.; Shton, I.; Kliachyna, M.; Pishel, I.; Mykhailiuk, P. K. *Angew. Chem., Int. Ed.* **2017**, *56*, 8865. (b) Kirichok, A. A.; Shton, I. O.; Pishel, I. M.; Zozulya, S. A.; Borysko, P. O.; Kubyshkin, V.; Zaporozhets, O. A.; Tolmachev, A. A.; Mykhailiuk, P. K. *Chem. - Eur. J.* **2018**, *24*, 5444. (c) Guérot, C.; Tchitchanov, B. H.; Knust, H.; Carreira, E. M. *Org. Lett.* **2011**, *13*, 780. (d) Burkhard, J. A.; Wagner, B.; Fischer, H.; Schuler, F.; Müller, K.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2010**, *49*, 3524.

(8) Lowe, J. T.; Lee IV, M. D.; Akella, L. B.; Davoine, E.; Donckele, E. J.; Durak, L.; Duvall, J. R.; Gerard, B.; Holson, E. B.; Joliton, A.; Kesavan, S.; Lemercier, B. C.; Liu, H.; Marié, J.-C.; Mulrooney, C. A.; Muncipinto, G.; Welzel-O'Shea, M.; Panko, L. M.; Rowley, A.; Suh, B.-

DOI: 10.1021/acs.orglett.8b03745
Org. Lett. XXXX, XXX, XXX–XXX

C.; Thomas, M.; Wagner, F. F.; Wei, J.; Foley, M. A.; Marcaurelle, L. A. *J. Org. Chem.* **2012**, *77*, 7187.
(9) (a) For review: Mondal, S.; Panda, G. *RSC Adv.* **2014**, *4*, 28317. (b) For examples, see: Tolterodine; Rovner, E. S. *Expert Opin. Pharmacother.* **2005**, *6*, 653. (c) Peperomin, B.; Tsutsui, C.; Yamada, Y.; Ando, M.; Toyama, D.; Wu, J.-L.; Wang, L.; Taketani, S.; Kataoka, T. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4084. (d) Walter, F. R.; Veszelka, S.; Pásztói, M.; Péterfi, Z. A.; Tóth, A.; Rákhely, G.; Cervenak, L.; Ábrahám, C. S.; Deli, M. A. *J. Neurochem.* **2015**, *134*, 1040.
(10) (a) Croft, R. A.; Mousseau, J. J.; Choi, C.; Bull, J. A. *Chem. - Eur. J.* **2016**, *22*, 16271. (b) Croft, R. A.; Mousseau, J. J.; Choi, C.; Bull, J. A. *Tetrahedron* **2018**, *74*, 5427. (c) Croft, R. A.; Mousseau, J. J.; Choi, C.; Bull, J. A. *Chem. - Eur. J.* **2018**, *24*, 818.
(11) (a) Woodhead, S. J.; Downham, R.; Hamlett, C.; Howard, S.; Sore, H. F.; Verdonk, M. L.; Walker, D. W.; Luke, R. W. A. Aryl-alkylamines and heteroaryl-alkylamines as protein kinase inhibitors. PCT Int. Appl. WO2006136830A1, Dec 26, 2006. (b) Donald, D. K.; Jennings, A. S. R.; Ray, N. C.; Roussel, F.; Sutton, J. M.; Tisselli, P.; Wilson, M. Cyclic amine derivatives having beta2 adrenergic receptor agonist and muscarinic receptor antagonist activity. PCT Int. Appl. WO2011048409A1, Apr 28, 2011.
(12) Graham, T. H.; Shu, M.; Verras, A.; Chen, Q.; Garcia-Calvo, M.; Li, X.; Lisnock, J.; Tong, X.; Tung, E. C.; Wiltsie, J.; Hale, J. J.; Pinto, S.; Shen, D. M. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 1657.
(13) Fröhlich, J.; Sauter, F.; Blasl, K. *Heterocycles* **1994**, *37*, 1879.
(14) For recent reviews on catalytic C−O activation, see: (a) Dryzhakov, M.; Richmond, E.; Moran, J. *Synthesis* **2016**, *48*, 935. (b) Rueping, M.; Nachtsheim, B. J. *Beilstein J. Org. Chem.*, **2010**, *6*, DOI: 10.3762/bjoc.6.6. (c) Chen, L.; Yin, X.-P.; Wang, C.-H.; Zhou, J. *Org. Biomol. Chem.* **2014**, *12*, 6033. (d) Lebœuf, D.; Gandon, V. *Synthesis* **2017**, *49*, 1500.
(15) For selected leading references, see: (a) Niggemann, M.; Meel, M. J. *Angew. Chem., Int. Ed.* **2010**, *49*, 3684. (b) Dryzhakov, M.; Hellal, M.; Wolf, E.; Falk, F. C.; Moran, J. *J. Am. Chem. Soc.* **2015**, *137*, 9555. (c) Haubenreisser, S.; Niggemann, M. *Adv. Synth. Catal.* **2011**, *353*, 469.
(16) Attempts to force the reaction using 20 mol% calcium triflimide catalyst gave a 21% yield, and using 1 equiv of $FeCl_3$ catalyst gave a 36% yield.
(17) Thaxton, A.; Izenwasser, S.; Wade, D.; Stevens, E. D.; Mobley, D. L.; Jaber, V.; Lomenzo, S. A.; Trudell, M. L. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 4404.
(18) Bouix-Peter, C.; Suzuki, I.; Rodeville, N.; Mauvais, P.; Pascal, J.-C. Oxoazetidine derivatives, process for the preparation thereof and use thereof in human medicine and in cosmetics. PCT Int. Appl. WO 2010/136830 A1.
(19) For indole **2m** using toluene as solvent allowed an increase in the reaction temperature to 80 °C, which indicates the four-membered carbocation species can tolerate the increased temperatures required for nucleophilic attack.
(20) For examples of stabilizing cation−π interactions, see: (a) Yamada, S.; Inoue, M. *Org. Lett.* **2007**, *9*, 1477. (b) Yamada, S.; Morita, C. *J. Am. Chem. Soc.* **2002**, *124*, 8184.

DOI: 10.1021/acs.orglett.8b03745
Org. Lett. XXXX, XXX, XXX−XXX