Access to functionalized Mannich scaffolds via a calcium-catalyzed dehydrative aza-Friedel-Crafts reaction

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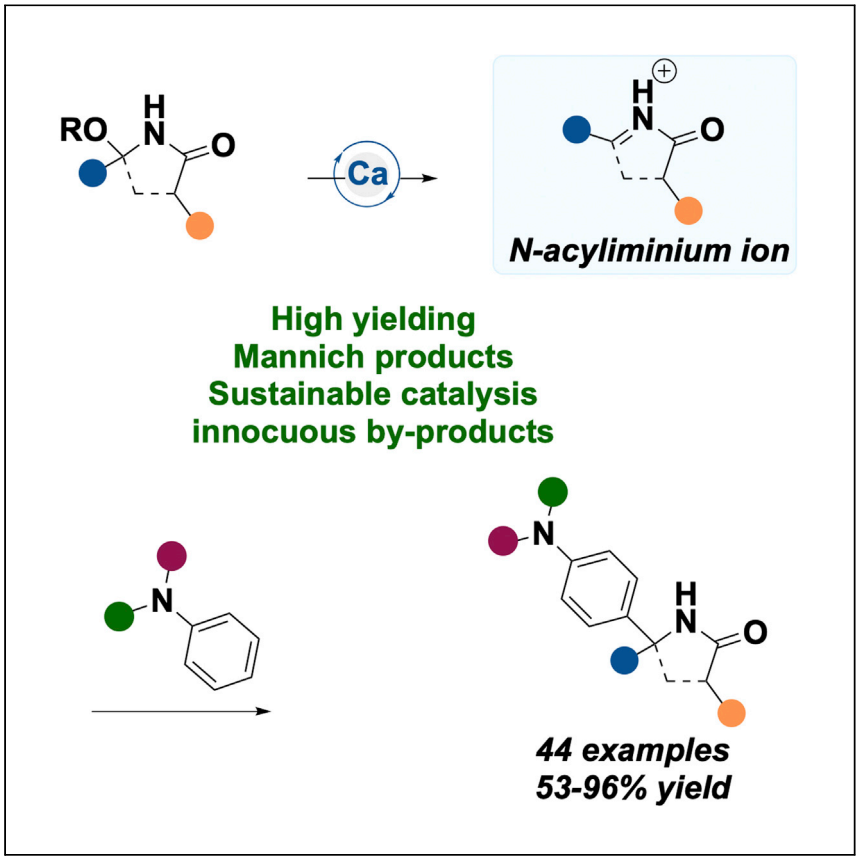

Basson et al. report their investigation into a facile and operationally simple dehydrative-Friedel-Crafts reaction of N-acyliminium ions to produce high-value molecule scaffolds. Employing readily available starting materials and a sustainable catalyst, the authors synthesize a range of functionally diverse amides in good yield while producing innocuous byproducts.

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Highlights

N,O-acetals readily undergo catalytic dehydration to furnish N-acyliminium ions

A facile Friedel-Crafts reaction is employed to access a range of Mannich products

Both cyclic and acyclic scaffolds are employed in this α-functionalization

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Access to functionalized Mannich scaffolds via a calcium-catalyzed dehydrative aza-Friedel-Crafts reaction

Ashley J. Basson[1] and Mark G. McLaughlin[1,2,3,*]

SUMMARY

The α-functionalization of amines and related scaffolds plays a key role in both target synthesis and medicinal chemistry. As such, elegant solutions employing transition metal catalysis, photoredox catalysis, and electrosynthetic methods have been described. The methods often rely on harsh activation conditions or difficult-to-access catalysts and experimental setups. Here, we report a calcium-catalyzed addition of aniline derivatives into *N*-acyliminium ions under mild conditions to access a diverse range of Mannich-type products. The reaction is unified and can be applied to N,O-acetal derivatives to access di-substituted amides and also isoindolinones as a method to functionalize medicinally relevant scaffolds. The reaction displays a high level of functional group tolerance and provides access to a diverse range of scaffolds.

INTRODUCTION

Amines remain at the forefront of reactions in drug discovery programs, and their use in the assembly of fragment libraries is continually increasing.[1] Given this wide use, however, few reactions still dominate the field.[2] This is in part due to the slow increase in availability of unique amines coupled with the lack of development of innovative and robust methods to access them. Often, breakthroughs in chemical synthesis initially begin with high amounts of method complexity, with further developments then focusing on the same disconnections being tailored toward methods termed "robust," which are viewed more favorably by drug discovery groups.[3] Methods defined as robust for medicinal chemistry must include the following: (1) provide structures for medicinal chemistry; (2) be technically straightforward with no special equipment; (3) be moderately sensitive to reaction parameters; (4) have broad applicability with polar substrates; (5) have broad functional group tolerance, (6) have a simple operational procedure, and (6) have low-risk reagents.[3]

In spite of this, the use of amines in Lewis-acid-catalyzed transformations is a long-standing impediment to their use in synthetic chemistry, which therefore limits their inclusion in fragment-based drug discovery. This is due to their low compatibility with many of the Lewis acid catalysts employed in these reactions along with chemo- and regioselectivity issues, thus limiting reaction robustness. It is therefore unsurprising that the use of N-substituted anilines as C4-nucleophilic coupling partners in aza-Friedel-Crafts-type reactions is reported sparingly within the literature (Scheme 1). MacMillan reported the first organocatalytic aza-Friedel-Crafts reaction of di-substituted anilines into α,β-unsaturated carbonyls.[4] In 2014, Bertrand reported a gold-catalyzed hydroarylation reaction of alkenes with di-substituted alkenes to afford a range of functionalized amines.[5] In the same year, Halimehjani

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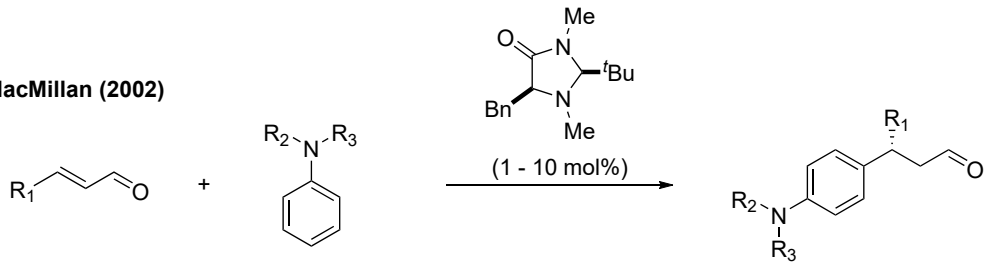
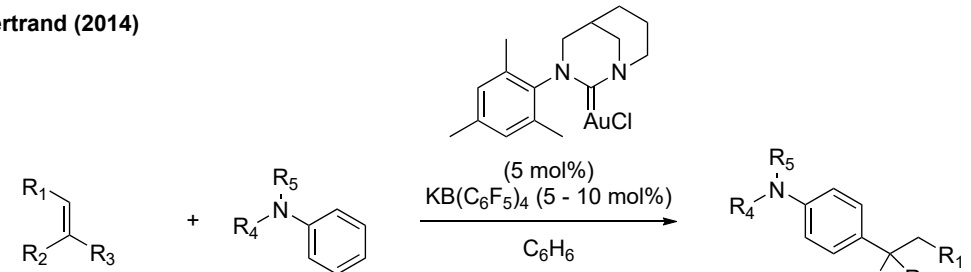
Previous successes using di-substituted anilines in alkyations

MacMillan (2002)



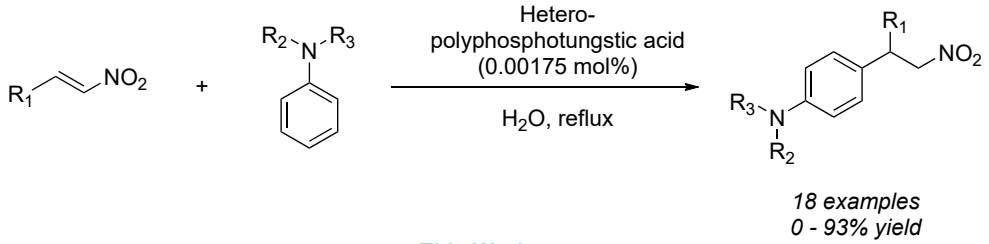
25 examples
70 - 95% yield

Bertrand (2014)



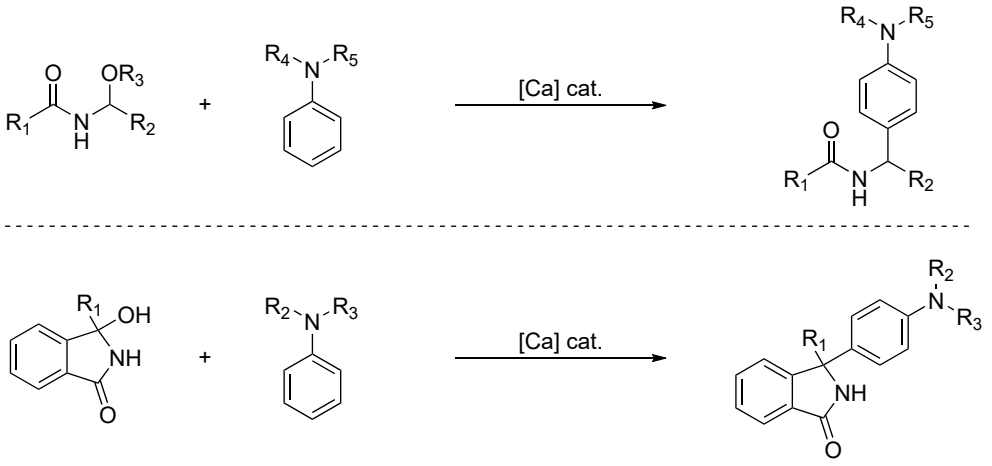
16 examples
56 - 98% yield

Halimehjani (2014)



18 examples
0 - 93% yield

This Work:
Development of a calcium catalysed Aza-Friedel crafts reaction



Scheme 1. Successes in using di-substituted anilines in alkylations

reported a Friedel-Crafts reaction using nitroalkenes as the electrophilic coupling partner.[6] While these examples all provide access to versatile scaffolds with a varying electrophilic component, we wanted to explore this same reactivity with *N*-acyliminium ions to assemble functionalized amides. Various non-catalytic[7,8] gold-catalyzed[9] and zinc-catalyzed[10] examples have been reported in this context; however, we reasoned we could use calcium catalysis to develop a general Lewis-acid-catalyzed approach.

Calcium catalysis has seen extensive growth over the last decade.[11–13] Harder, Niggemann,[14–18] Lebœuf,[19–21] and others[22,23] have shown calcium complexes to be highly effective in catalyzing a range of transformations. Owing to this, our group has a burgeoning interest in a developing robust, mild, and sustainable methodology using calcium complexes as Earth-abundant Lewis acid catalysts.[24–28] In particular we have focused on developing methods to incorporate amines into medicinally relevant scaffolds, and we,[25,26] and others[14,19,20] have shown $Ca(NTf_2)_2/nBu_4NPF_6$ to be an effective catalyst in reactions employing Lewis basic amines (Scheme 2).

Owing to these recent successes, we sought to develop a catalytic and modular approach for the addition of N-substituted anilines into both cyclic and acyclic *N*-acyliminium ions (Figure 1). *N*-acyliminium ions are highly reactive electrophilic intermediates allowing functionalization alpha to an amide.[29–38] This will provide access to useful small building blocks derived from acyclic *N*-acyliminium ions, which are useful small building blocks and can be used for further functionalization, notwithstanding their anti-malarial[39] and CB2 inverse agonistic[40] properties. Extending this chemistry to the functionalization of isoindolinone-derived, cyclic *N*-acyliminium ions shows how our methodology is unified and can also be applied to the direct functionalization of medicinal scaffolds, which have been shown to display activity against various targets.[41] We describe an operationally simple method to afford Mannich-type products from readily available starting materials.

RESULTS AND DISCUSSION

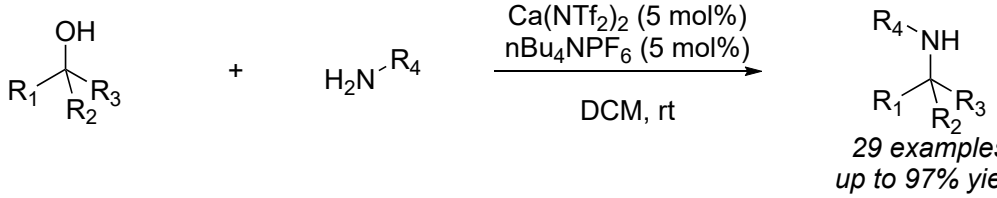
Reaction development

We began our investigation by subjecting N,O-acetal **1a** and N,N-dimethylaniline **2a** to our previously reported conditions reaction calcium catalyzed reactions in the presence of amines[26] (Table 1). To our delight, the desired product was formed in high yield (entry 1). Lowering the catalyst loading had little effect on yield (entry 2). Lowering the catalyst loading further saw a significant increase in reaction time and a decrease in yield (entry 3). Screening a range of solvents typically also used in calcium-catalyzed transformations proved unsuccessful (entries 4–6). Lowering the temperature resulted in no reaction taking place with unreacted starting material re-isolated (entry 7), and both $Ca(NTf_2)_2$ and nBu_4NPF_6 were required for the reaction to proceed (entries 8 and 9).

With the optimized conditions in hand, we began probing the substrate scope. We first explored the reactivity of various aniline derivates toward our optimized conditions (Figure 2). In addition to N,N-dimethyl aniline **3a**, the reaction was tolerant to benzyl-substituted anilines **3b**. N-benzyl-substituted anilines of varying electronics, **3c**–**3f**, were also well tolerated in good yields. Alkyl substituents in the form of *iso*-butyl **3g** and cyclohexyl **3h** also worked well along with heterocyclic-substituted aniline derivative **3i**. We also studied the effect secondary substituted aniline derivatives had on the reaction outcome. N-benzyl-substituted aniline worked well (**3j**), allowing the incorporation of a useful protecting group, while electron-rich **3k** derivatives were also tolerated, albeit in lower yields.

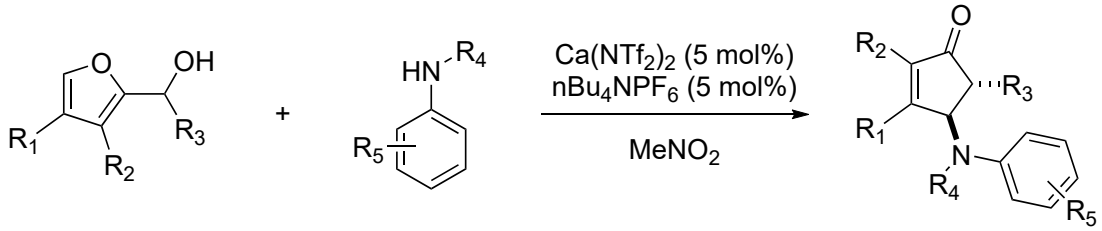
Calcium catalyzed transformations involving amines

Niggemann (2011)



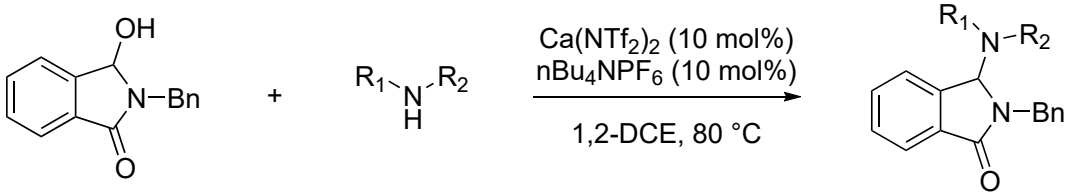
29 examples
up to 97% yield

Lebeouf (2018)



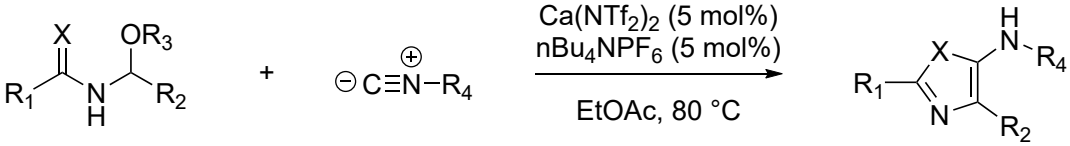
22 examples
up to 97% yield

McLaughlin (2020)



5 examples
up to 93% yield

McLaughlin (2021)



34 examples
up to 97% yield

Scheme 2. Calcium catalyzed transformations involving amine derivatives

To complete our study of modular assembly of unsymmetrical amide derivatives, we then studied the reactivity by varying the N-acyl-N,O-acetal at both the amide and aldehyde components (Figure 3). We began by studying the derivatization of the amide component, which proved successful. The reaction was tolerant to halo-substituted **4a**,**4b** and electron-withdrawing **4c** acetal precursors. Electron-donating groups were also well-tolerated (**4d**), and reactivity was unaffected by *meta*-substituted aromatic **4e**. Heterocyclic motifs in the form of furan also worked well

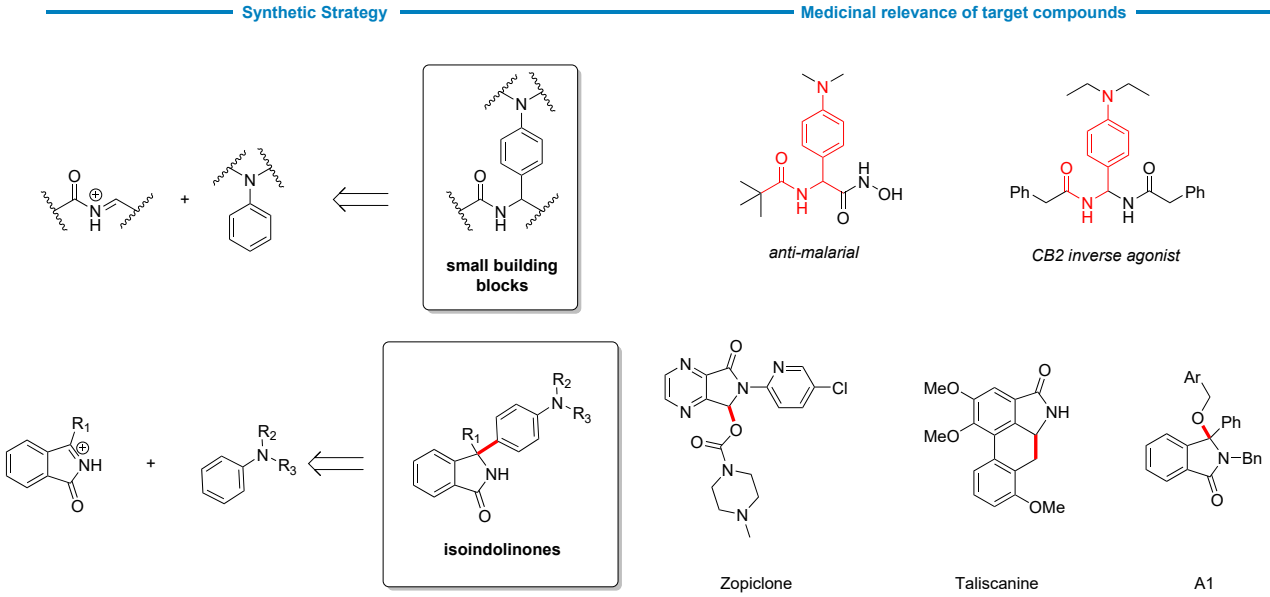
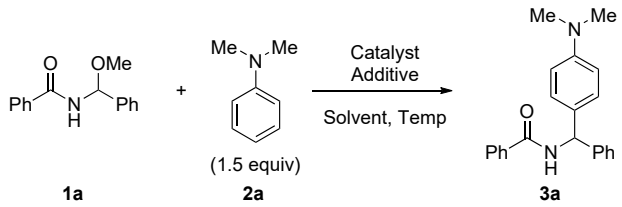


Figure 1. Universal approach to access small building blocks and isoindolinone derivatives
N-acyliminium ions allow functionalization alpha to amides.

(**4f**). We then studied the reactivity by varying the aldehyde component of the N,O-acetal. Again, the reaction was tolerated to halo-substituted aromatic **4g** and electron-withdrawing groups **4h**, **4i**, and **4j**. The meta-substituted nitrile functionality **4k** was also well tolerated. Furthermore, heterocycles **4l** also worked well.

To ensure that our methodology was not only modular but also amenable to other sources of *N*-acyliminium ions, we wanted to explore whether we could functionalize the medicinally relevant isoindolinones using the same conditions (Figure 4). To our delight, when our optimized conditions were employed to the reaction

Table 1. Optimization study



Entry	Catalyst	Additive	Loading (mol %)	Temp (°C)	Solvent	Time (h)	Yield[a]
1	$Ca(NTf_2)_2$	nBu_4NPF_6	10	80	1,2-DCE	2	83%
2	$Ca(NTf_2)_2$	nBu_4NPF_6	5	80	1,2-DCE	2	82%
3	$Ca(NTF_2)_2$	nBu_4NPF_6	1	80	1,2-DCE	12	73%
4	$Ca(NTF_2)_2$	nBu_4NPF_6	5	80	EtOAc	2	decomp.
5	$Ca(NTF_2)_2$	nBu_4NPF_6	5	80	HFIP	2	decomp.
6	$Ca(NTF_2)_2$	nBu_4NPF_6	5	80	toluene	2	decomp.
7	$Ca(NTF_2)_2$	nBu_4NPF_6	5	40	1,2-DCE	2	n.r
8	$Ca(NTF_2)_2$	–	5	80	1,2-DCE	2	n.r
9	–	nBu_4NPF_6	5	80	1,2-DCE	2	n.r

n.r, no reaction; decomp., decomposition.
[a]Isolated yields.

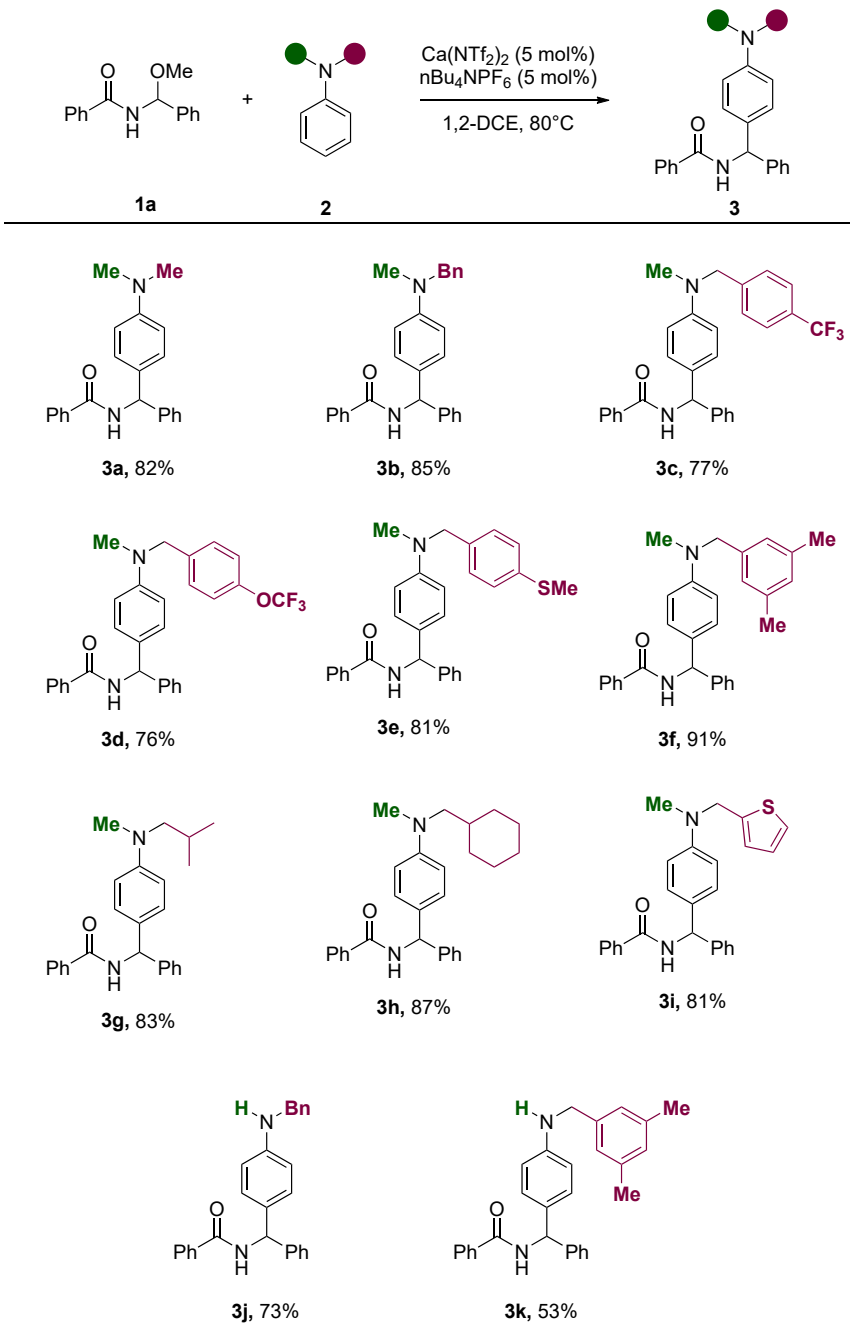


Figure 2. Scope of aniline derivatives

of 5a with di-methylaniline 2a, we were able to form the desired product in high yield (6a). We then began to probe the substrate scope of various 3-hydroxyisoindolinones (5). The reaction was tolerant to electron-donating 6b and halo-substituted isoindolinones 6c. Otho-substituted aromatics were also well tolerated (6d). The reaction was also tolerant to oxygen-containing heterocycles 6e and 6f, sulfur-containing heterocycle 6g, unsaturated traditionally difficult Lewis basic heterocycles 6h,6i, and saturated heterocycle 6j. Unfortunately, when subjecting our conditions to electron-withdrawing derivatives, only trace amounts

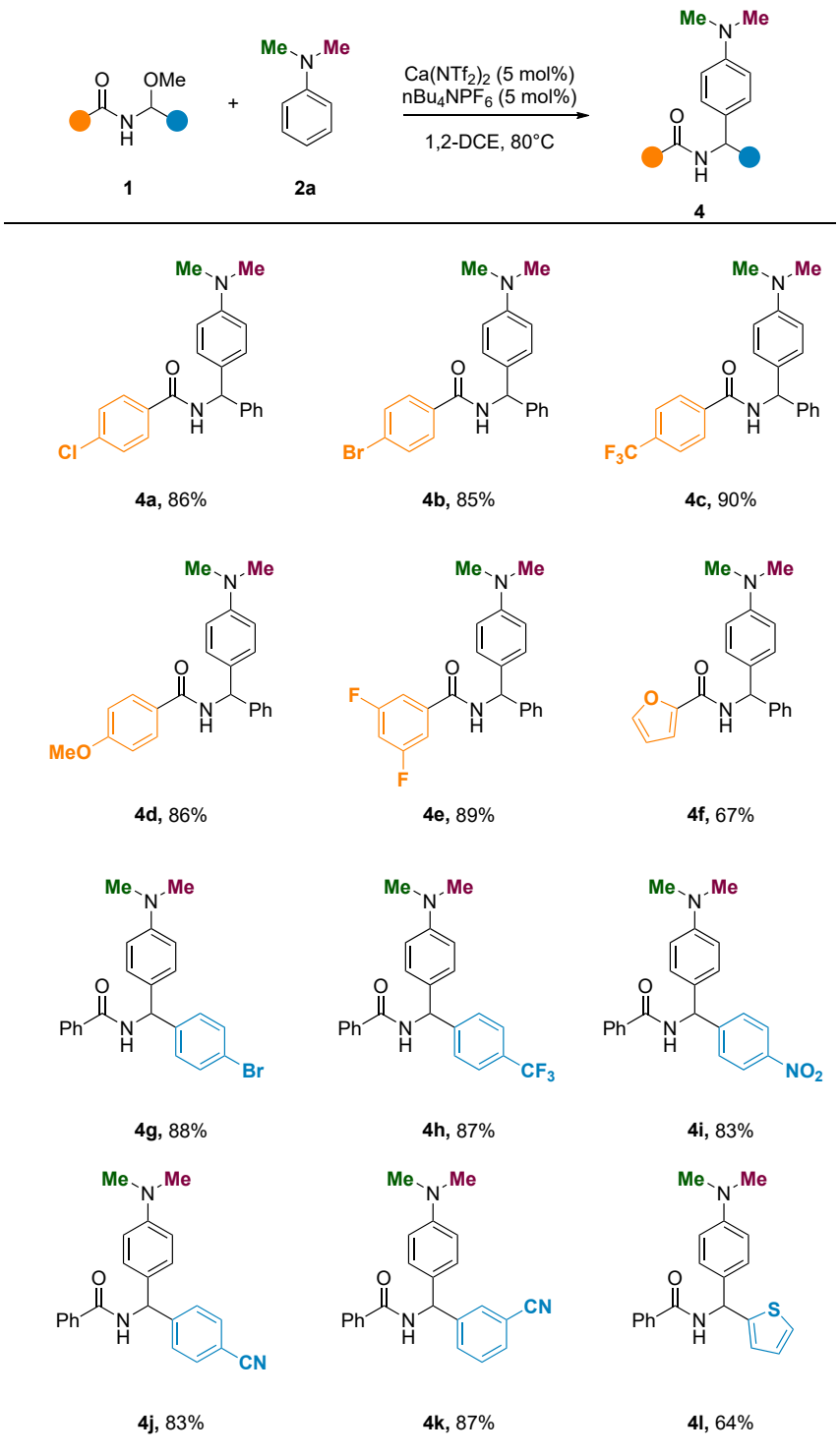


Figure 3. Scope of N-acyl-N,O-acetal

of product was detected (6k, 6l), with the mass balance being unreacted starting material. Increasing the catalyst loading and temperature had little effect on the reaction outcome.

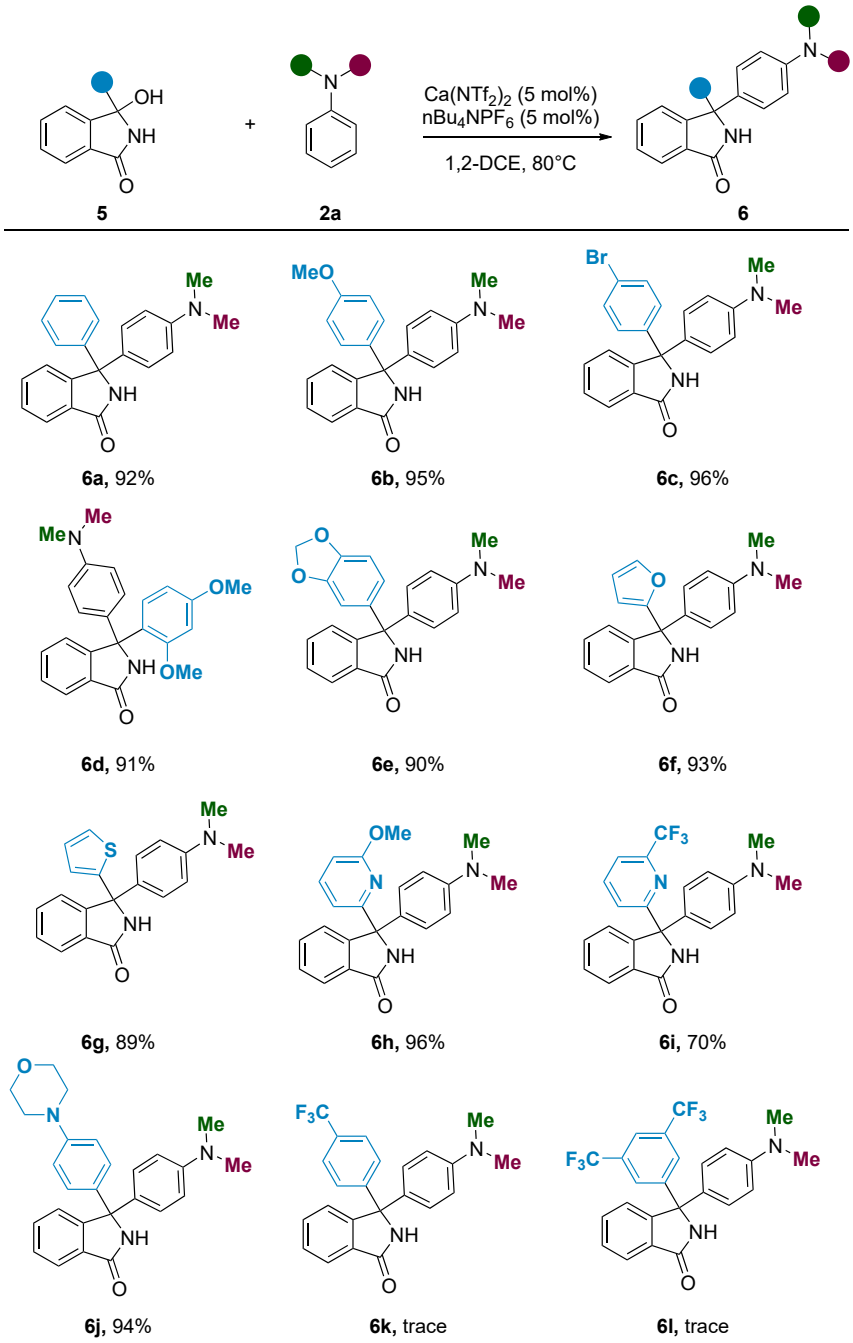


Figure 4. Substrate scope varying the isoindolinone

We then explored the reactivity of various aniline derivatives toward the isoindolinone-derived *N*-acyliminium ions (Figure 5). The reaction was tolerant to electron-rich **7b**,**7c** and electron-deficient **7d**, **7e**, and **7f** aniline derivatives. Saturated groups were again well tolerated (**7g** and **7h**) along with traditionally difficult heterocycle **7i**. Finally, secondary aniline derivatives worked well producing benzyl-substituted **7j** and methyl-substituted **7k** scaffolds in high yields.

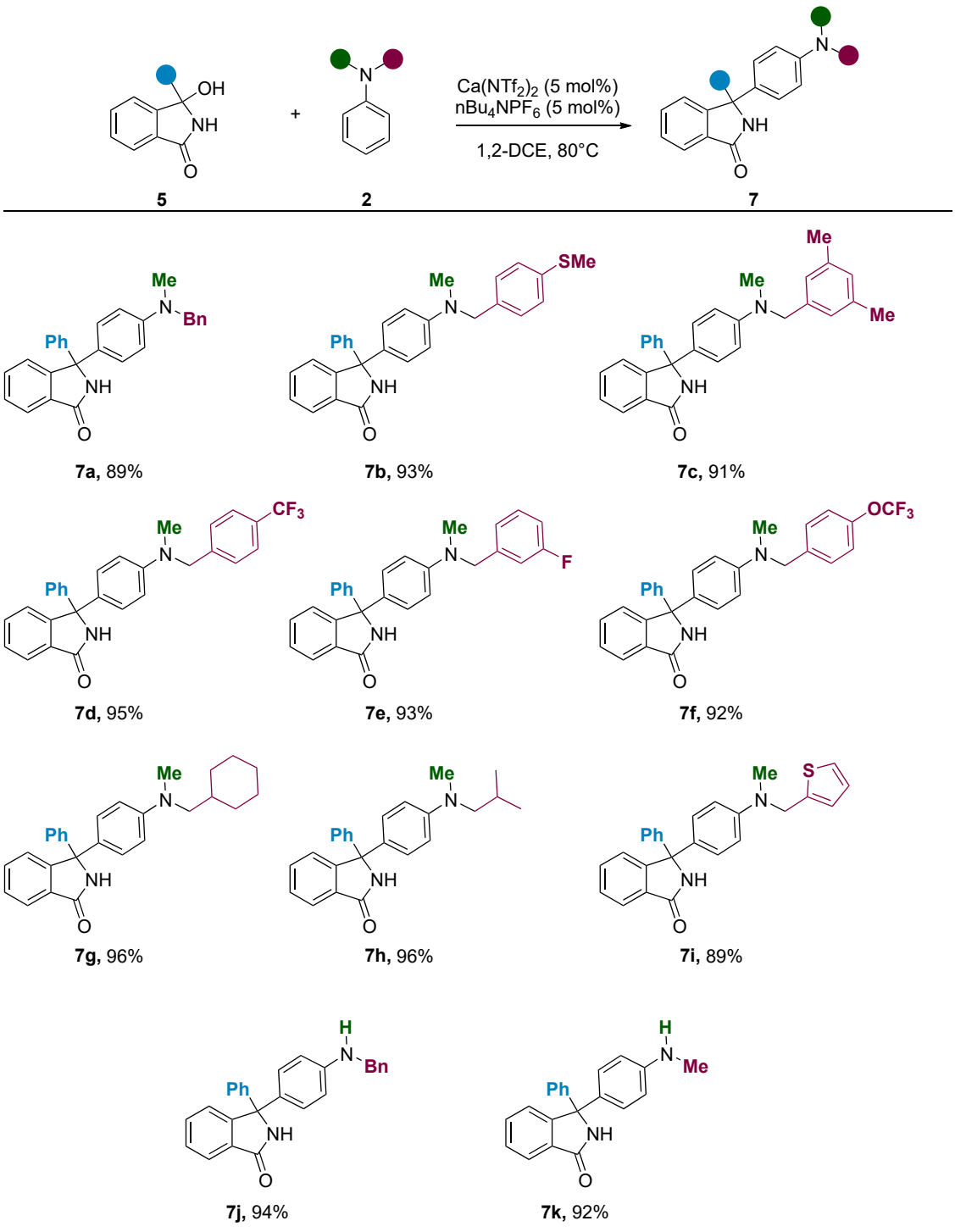


Figure 5. Substrate scope varying aniline derivatives with isoindolinones

Potential mechanism

Based on previous reports,[12] a plausible reaction mechanism is depicted below (Figure 6). The proposed active catalyst [PF_6CaNTf_2] **A** is formed by anion metathesis.

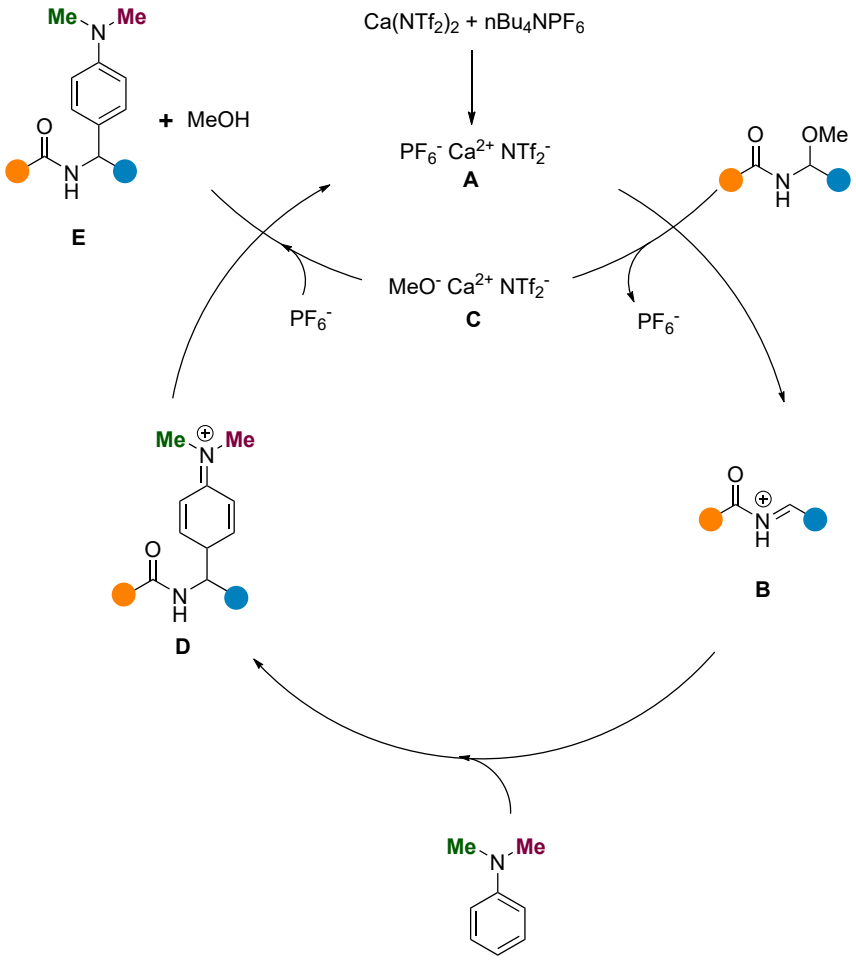


Figure 6. Plausible catalytic cycle

Coordination of the N-acyl-N,O-acetal to **A** generates *N*-acyliminium **B**, liberating the non-coordinating PF_6^- anion and intermediate **C**. Addition of the aniline derivative via **D** followed by re-aromatization generates product **E**, which subsequently liberates the alcohol byproduct and regenerates the active catalyst.

In summary, we have developed a unified calcium-catalyzed addition of aniline derivatives into *N*-acyliminium ions. The reaction is highly modular and tolerant to various *N*-acyliminium ion precursors, which can be used to access both small building blocks and highly functionalized medicinally relevant isoindolinone derivatives. We anticipate that this methodology will be of interest to organic chemists who require access to small building blocks and medicinal chemists working within drug discovery.

EXPERIMENTAL PROCEDURES

Resource availability

Lead contact

Further information and requests for resources and reagents should be directed to and will be fulfilled by the lead contact, Mark McLaughlin (m.mclaughlin3@lancaster.ac.uk).

Materials availability

All data supporting this study are available in the supplemental information or are available upon request from the lead author.

Data and code availability

Data are available from the lead contact upon reasonable request. See Figures S1–S44 for nuclear magnetic resonance (NMR) spectra.

General procedure

To a 4 mL vial capped with a Teflon cap was added the corresponding N-acyl,N-*O*-acetal (**1**) or 3-hydroxyisoindolinone (**5**) (1 equiv), aniline derivative (**2**) (1.5 equiv), $Ca(NTf_2)_2$ (5 mol %) and nBu_4NPF_6 (5 mol %) in 1,2-DCE (0.2 M). The reaction was stirred at 80°C until TLC analysis indicated full conversion to the product (typically 12 h). The solution was then concentrated and purified by FCC (EtOAc:Hept) to afford the pure compound.

Further details can be found in the supplemental experimental procedures.

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.xcrp.2022.101234.

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AUTHOR CONTRIBUTIONS

M.G.M. conceived the study. A.J.B. conducted the experiments. Both authors wrote the paper.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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