Organic & Biomolecular Chemistry

Accepted Manuscript

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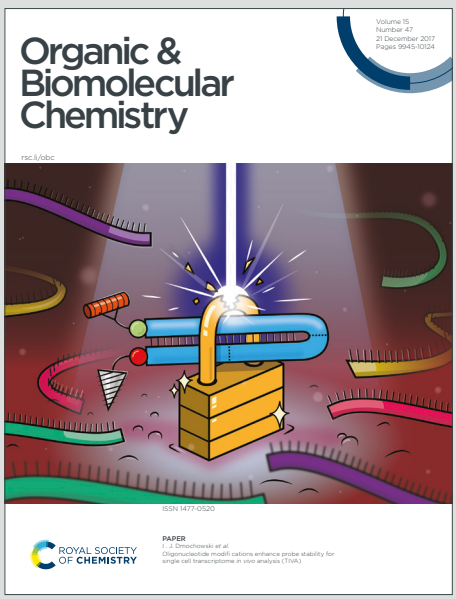

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DOI: 10.1039/D2OB01663J

COMMUNICATION

Aza-[4+2] Cycloadditions Employing Catalytically Derived *N*-Acyliminium Ions.

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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Herein, we report the development of a novel route to tricyclic lactam products via a facile *aza*-[4+2] cycloaddition of catalytically generated acyliminium ions. Employing a $Ca(NTf_2)_2$ / nBu_4NPF_6 catalyst system in low loadings, a range of diverse fused ring systems can be synthesised in predominantly good yields.

The development of new methods to access small, fused ring systems bearing multiple functional groups and synthetic handles remains an important goal within synthetic organic chemistry. 3-substitued isoindolones represent an important pharmacophore found in an increasing number of bioactive small molecules,[1, 2] with growing interest in tertiary substituted aza-cycles (Figure 1).

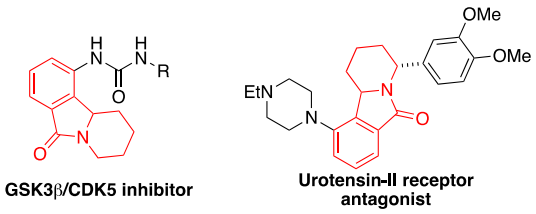

Figure. 1 Exemplar bioactive small molecules

Access to these fragments is typically through intramolecular cyclisation of pendant sp-rich functional groups,[3] mediated by both stoichiometric[4, 5] and catalytic Lewis acids (Figure 2).[6] Further cyclisation reaction employing stoichiometric Brønsted acids have also been reported.[7, 8] Additional methods include aza-Navarov cyclisation cascades[9] and tandem Aza-Prins/Friedel-Craft reactions.[10] Although these methods present elegant solutions, many of them take advantage of the inherent reactivity of a pendant functional group. This somewhat limits the scope of the reaction and builds in additional synthetic steps. Herein, we report our work in developing a [4+2] cycloaddition protocol to produce 6,5,6 fused tertiary aza-cycles in good to excellent yields.

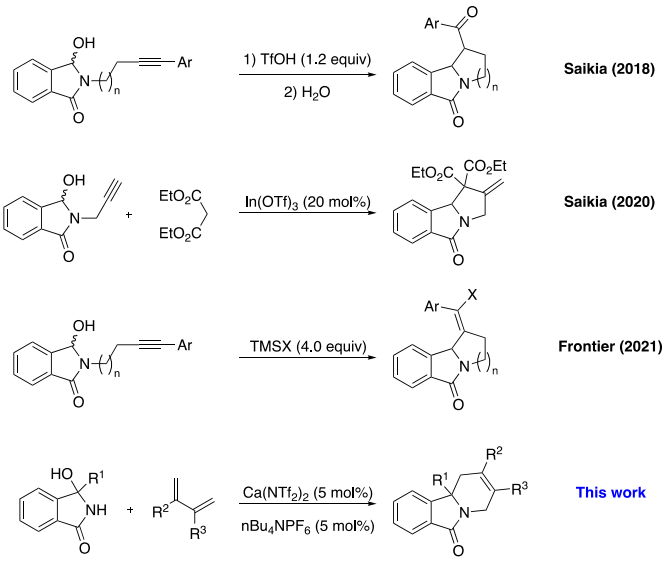

Figure 2. Recent methods to access isoindolone cores

Our work began by taking advantage of our previously reported methodology to access N-acyliminium ions via catalytic dehydration.[11-14] We therefore began our investigation using these conditions, employing hydroxyisoindolinone **1** and dimethylbutadiene (**2a**) as model substrates (Figure 3). As shown, optimisation of temperature, solvent, and catalyst loading led to conditions that afforded the [4+2] product in high isolated yield. In essence, the reaction proceeded in a range of solvents, with temperature being the variable that had the biggest impact. Furthermore, running the reaction in the absence of any part of the catalyst system was unsuccessful

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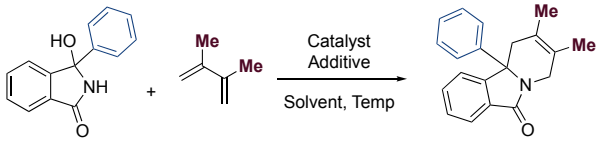
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

View Article Online DOI: 10.1039/D2OB01663J

a 1.5 equiv. diene used



1 2 3a

Entry	Catalyst	Additive	Loading	Temp	Solvent	Time (min)	Yield
1	$Ca(NTf_2)_2$	nBu_4NPF_6	10 mol%	65 °C	DCM	30	73%
2	$Ca(NTf_2)_2$	nBu_4NPF_6	10 mol%	65 °C	EtOAc	30	81%
3	$Ca(NTf_2)_2$	nBu_4NPF_6	10 mol%	65 °C	DCE	30	82%
4	$Ca(NTf_2)_2$	nBu_4NPF_6	10 mol%	65 °C	HFIP	30	57%
5	$Ca(NTf_2)_2$	nBu_4NPF_6	10 mol%	65 °C	Toluene	30	71%
6	$Ca(NTf_2)_2$	nBu_4NPF_6	10 mol%	40 °C	DCE	30	n.r
7	$Ca(NTf_2)_2$	nBu_4NPF_6	10 mol%	50 °C	HFIP	60	57%
8	$Ca(NTf_2)_2$	nBu_4NPF_6	10 mol%	80 °C	EtOAc	90	70%
9	$Ca(NTf_2)_2$	nBu_4NPF_6	10 mol%	80 °C	DCE	90	82%
10	$Ca(NTf_2)_2$	nBu_4NPF_6	10 mol%	80 °C	Toluene	90	76%
11	$Ca(NTf_2)_2$	nBu_4NPF_6	5 mol%	80 °C	DCE	60	82%
12	**$Ca(NTf_2)_2$**	**nBu_4NPF_6**	**5 mol%**	**80 °C**	**DCE**	**30**	**88%[a]**
13	$Ca(NTf_2)_2$	nBu_4NPF_6	1 mol%	80 °C	DCE	90	32%
14	$Ca(NTf_2)_2$	nBu_4NPF_6	1 mol%	80 °C	DCE	120	74%[a]
15	$Ca(NTf_2)_2$	-	5 mol%	80 °C	DCE	30	n.r
16	-	nBu_4NPF_6	5 mol%	80 °C	DCE	30	n.r
17	-	-	-	80 °C	DCE	30	n.r

Figure 3. Optimisation studies

With these conditions now optimised, we wanted to explore the substrate tolerance of the reaction, with particular emphasis on differing electronics. As shown (Figure 4), para-electron donating (**3b**) and withdrawing (**3c**) groups afforded the desired product in good yield, with a small reduction in yield observed in the trifluoromethyl substrate. *Meta*-electron withdrawing (**3d**) and *ortho, para*- (**3e**) electron donating groups both worked well, as did benzodioxole (**3f**). Heterocycles were also tolerated, with pyridyl (**3g, 3h**) and thiazole (**3i**) derivatives being synthesised in moderate yields.

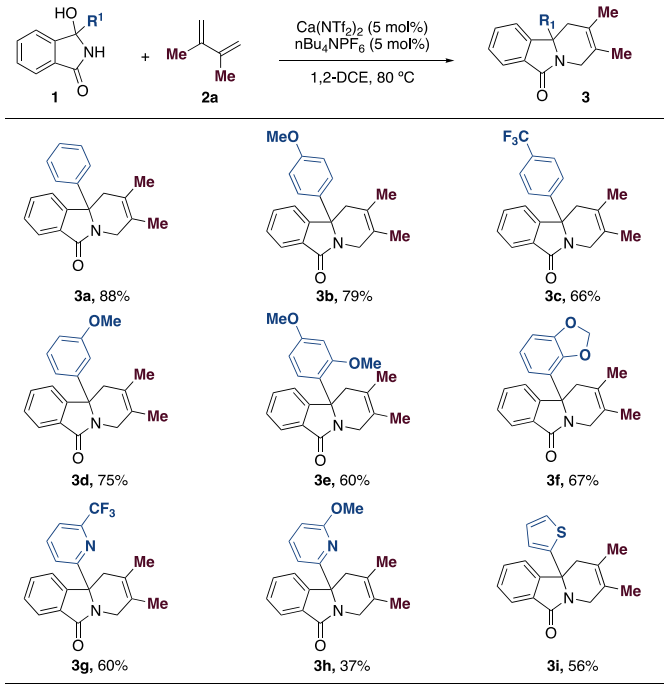


Figure 4. Dimethyl butadiene derived products

We also explored bis-phenyl diene **2b,** which was also well tolerated in most cases (Figure 5). The trifluromethyl group (**3l**) retarded the reaction, with prolonged reaction times and higher temperatures having little effect on the overall conversion.

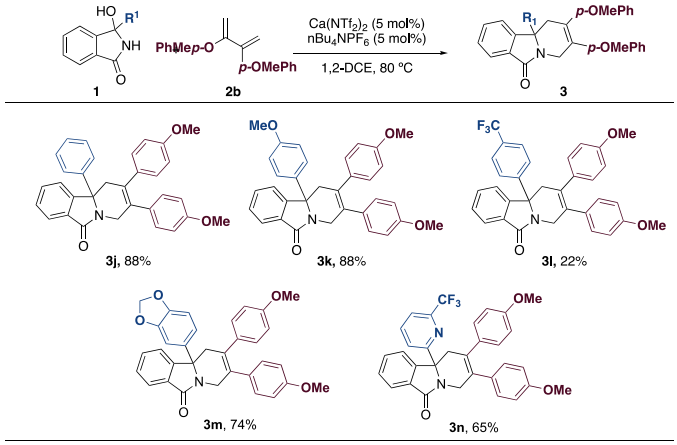


Figure 5. Further substrate scope

We next turned our attention to unsymmetrical dienes, as up to this point, we have employed dienes bearing the same group at each position. To this end, diene **4** was synthesised[15] and subjected to the above optimised conditions (Figure 6).

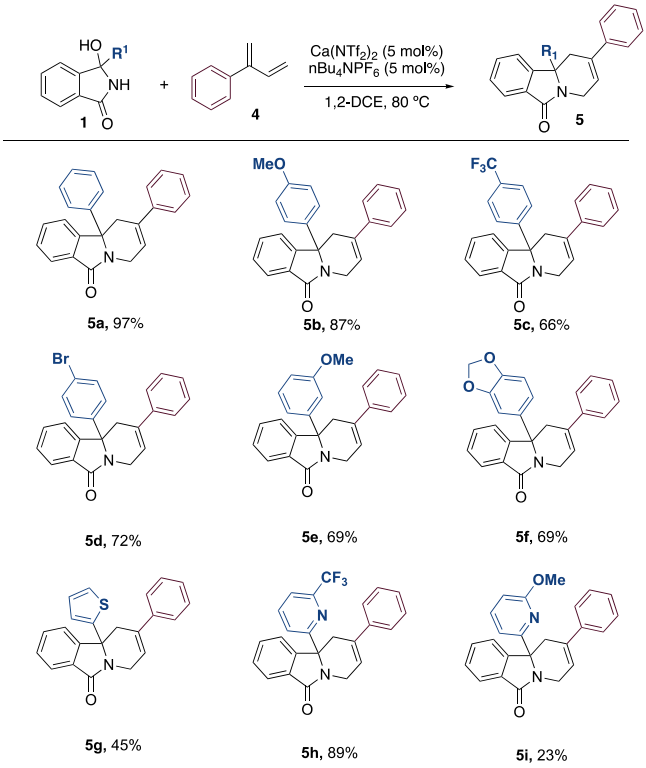


Figure 6. Unsymmetrical diene substrate scope

Once again, the reaction was tolerant to a variety of different functional groups including electron donating (**5b**) and withdrawing groups (**5c, 5d**), *meta* (**5e**) and acid sensitive (**5f**) functionalities. Furthermore, sulfur (**5g**) and nitrogen (**5h, 5i)** containing heterocycles provided the desired products in decent to good yields. In all cases, only a single isomer was observed and isolated, with no evidence of other isomers present, as determined by ^{1}H-NMR of the the crude reaction mixture.

Finally, we wanted to explore the synthetic utility of these compounds (Figure 7). To this end, **3a** was synthesised on gram scale in excellent yield. Subjecting **3a** to Upjohn dihydroxylation conditions (OsO_4 (cat), NMO) provided diol **6,** as a single diastereomer in good yield, while Prilezhaev epoxidation (*m*CPBA) gave epoxide **7,** once again as single diastereomer in excellent yield. Finally, lithium aluminium hydride reduction afforded the pyridoisoindole **8** in decent yield.

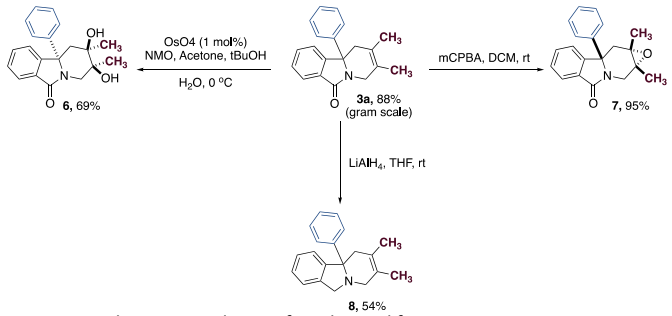


Figure 7. Synthetic manipulation of synthesised fragments

Conclusions

In conclusion, we have described the development of a novel *aza*-[4+2] cycloaddition reaction employing catalytically derived *N*-acyliminium ions. This reaction is tolerant to a wide range of functional groups and allows for the synthesis of diverse fused fragments from readily accessible hydroxyisoindolinones and dienes. Furthermore, the synthetic utility of the products has been demonstrated.

Conflicts of interest

There are no conflicts to declare”

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