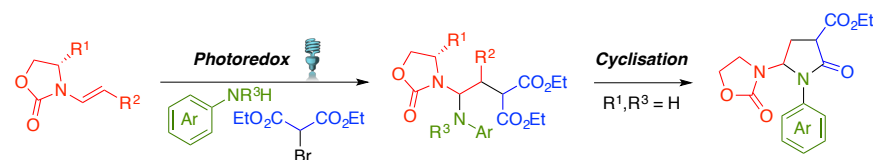# A photoredox approach to *N*-acyl-*N'*-aryl-*N,N'*-aminals using enamides, and their conversion to γ-lactams

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A photoredox catalytic approach to synthetically valuable *N*-acyl-*N'*-aryl-*N,N'*-aminals is described. This method uses the addition of a radical precursor to enamides, with subsequent interception of the cationic iminium intermediate with an arylamine. The reaction has been shown to be compatible with electron-rich and electron-deficient aryl amines, and moderate to good levels of diastereoselectivity can be attained using a chiral enamide. Furthermore, the *N*-acyl-*N'*-aryl-*N,N'*-aminal reaction products can be readily cyclized providing a novel synthetic route to valuable γ-lactams.

The *N*-acyl-*N'*-aryl-*N,N'*-aminal structural motif (Figure 1, **1**) is prevalent within a wide range of biologically important compounds. It is an essential motif within γ-lactams such as **2**, an important heterocycle within many biologically relevant drug candidates;[1] it is core within the dihydroquinazolones (**3**), a privileged heterocyclic structure in medicinal chemistry;[2] **1** is central to *gem*-diaminoacids (**4**), a significant class of amino acid isosters;[3] and finally, **1** is key to many natural product classes, such as the pyrroloindolines.[4]
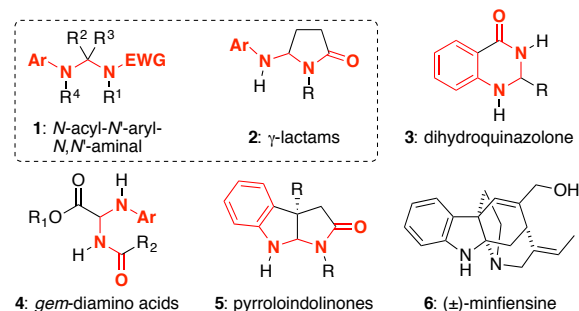

**Figure 1. Biologically relevant *N*-acyl-*N'*-aryl-*N,N'*-aminal.**

Typical approaches to the *N*-acyl-*N'*-aryl-*N, N'*-aminal motifs (**1**) whether cyclic or acyclic, have relied on the addition of an arylamine **7** to an *N*-acyliminium species **8**, or conversely, for example in the construction of pyrroloindolines, the addition of an amide or an equivalent (**9**) to a *N*-aryliminium such as **10** (Scheme 1). These approaches can be perceived as complementary, but their scope and functional group variability is ultimately predicated on the successful formation of an *N*-acyl and *N*-aryliminium species (**8** and **10**, respectively).[6] Additionally, the stability of **1** is predicated on the electron withdrawing group, as well as the electron density of the arylamine.

Scheme 1. Synthetic approaches to *N*-acyl-*N'*-aryl-*N,N'*-aminals (1).
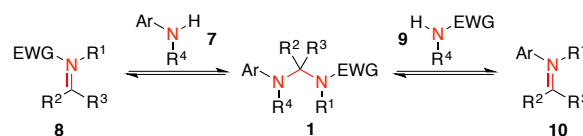
Previous work by Masson and co-workers[7a] has established that radical photoredox mediated addition of a CF_3 equivalent to electron rich styrene (**11**) derivatives followed by trapping of the intermediate carbocation by an electron-poor arylamine can lead to modest to good yields of the addition product **13** (Scheme 2).

**Scheme 2. Radical/cationic approach to *N*-acyl-*N'*-aryl-*N,N'*-aminals (17).**
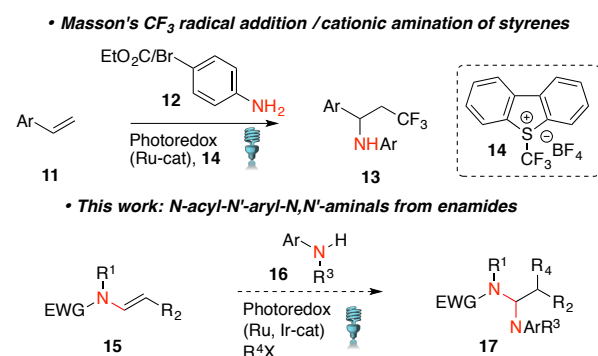
In this report the authors explored the use of easily oxidizable anilines such as *p*-anisidine where they observed poor or little conversion to the desired products. However, the authors could get the reaction to take place, without oxidation, by the

judicious choice of an electron-deficient aniline, e.g., *p*-bromoaniline and *p*-(ethoxycarbonyl)aniline.

Therefore, with this report in mind we sought to employ this radical/cationic pathway,[7b-d] via the use of photoredox catalysis[8] on enamides[9] in the presence of electron-poor and, importantly, electron-rich arylamines (**16**) to access these *N,N'*-aminals (**17**) (Scheme 2). The success of this approach would be predicated on ensuring the integrity[10] and compatibility of electron-rich and electron-poor arylamines; and while Masson and co-workers had previously shown the compatibility of enamides within this radical/cationic pathway,[7c,d] they have not, as yet, demonstrated this approach with arylamines and enamides to deliver *N,N'*-aminals. As a consequence, we now report our work on the synthesis of *N*-acyl-*N'*-aryl-*N,N'*-aminals such as **17** using this method, as well as the successful utilization of both electron-rich and electron-poor arylamines in the reaction pathway. Additionally, the synthetic utility of these product aminals will be highlighted by their successful cyclization yielding valuable γ-lactams.

We began our study by examining the use of arylamines in the photoredox addition of bromide **20** to enamides (Scheme 3). Using adapted conditions of Masson,[7c] we explored the Ir-catalysed (complex **22**) reaction of enamide **18** and bromide **20** with a large excess of the arylamine, aniline **19** (Table 1). Pleasingly, these conditions with 10 equiv. of **19** and after 18h reaction time, gave the desired product **21a** in a promising 56% isolated yield (entry 1).

**Scheme 3 and Table 1. Optimization of the synthesis of *N,N'*-aminal 21a.[a]**
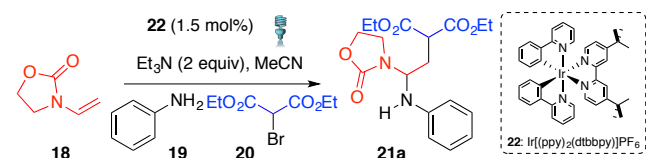
entry[a]	22 [mol %]	time [h]	equiv 19	yield [%][b]
1	2.5	18	10	56
2	2.5	18	5	62
3	1.5	18	5	60
4	1.5	6	5	61
5	1.5	3	5	72
6	1.5	3	2	38
7[c]	1.5	3	5	0

[a]Reactions were performed under an Ar atmosphere in MeCN (10 mL) with **22** (for mol % see Table), light (465 nm), **18** (1.00 mmol), **20** (2.00 mmol), Et₃N (2.00 mol) and the arylamine unless otherwise stated. [b]Isolated chemical yields. [c]In the absence of light (465 nm).

Isolation of the *N,N'*-aminal product **21** was non-trivial, and was further complicated by the reversibility of the nucleophile addition highlighted in Scheme 1. The identification of **21** was determined using a mixture of ¹H NMR and ¹³C NMR; with a key signal for the CH aminal being seen at δ 5.37 (t, *J* = 7.2 Hz, 1H). We were able to reduce the amount of **19** within the reaction mixture to 5 equiv (entry 2) as well as the amount of **22** (entry 3), and the reaction time to 3 h (entries 4 and 5); ultimately giving **21** in a higher isolated yield of 72%. A reduction to 2 equiv of **19** had a detrimental effect in yield (entry 6); and no conversion to the product **21** was observed in the absence of light (entry 7).

With conditions identified for the synthesis of **21a**, a range of electron-rich and electron-deficient anilines were examined to ascertain substrate scope (Scheme 4).

Scheme 4. Arylamine substrate scope.
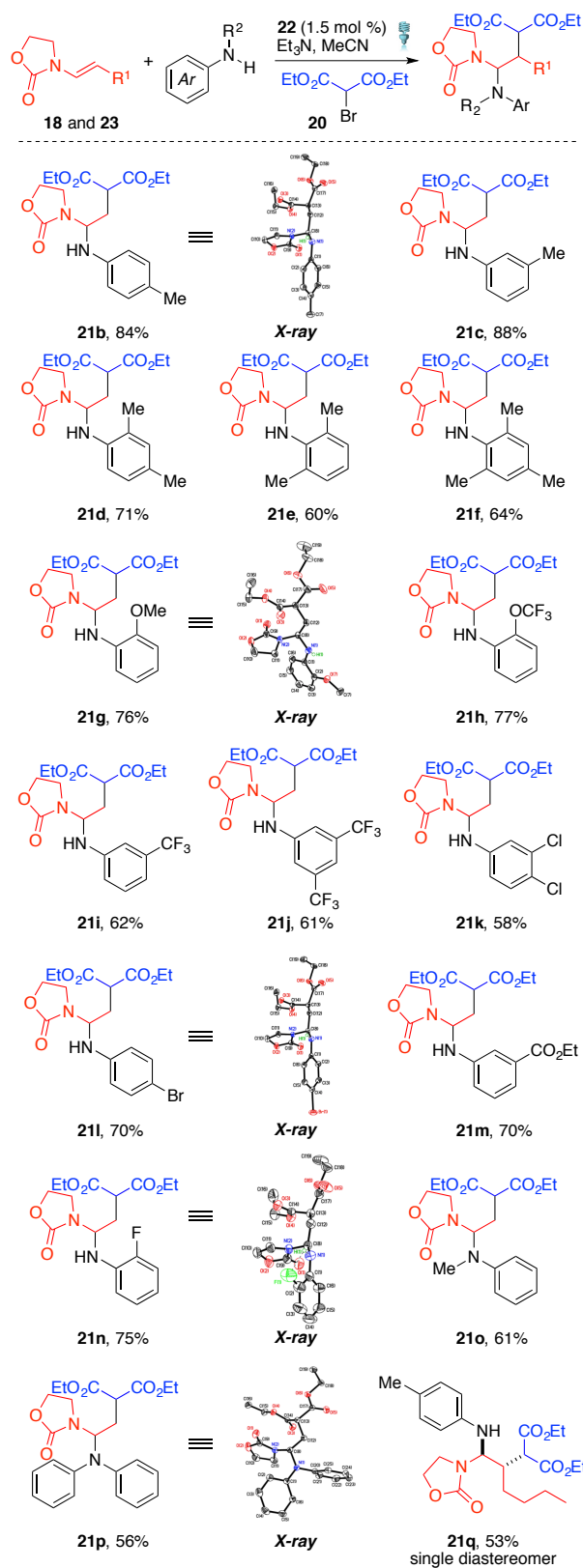
p-Toluidine delivered *N,N'*-aminal **21b** in a significantly higher yield (84%) than **21a**, presumably due to its increased nucleophilicity; additionally, we were able to obtain suitable crystals for single crystal X-ray analysis.[11] *m*-Toluidine also reacted, giving *N,N'*-aminal **21c** in 88% isolated yield. The 2,3- and 2,6-dimethylaniline gave the *N,N'*-aminals **21d** and **21e** in 71% and 60% yields, respectively; furthermore, sterically encumbered 2,4,6-trimethylaniline gave *N,N'*-aminal **21f** in 64% yield. o-Anisidine furnished *N,N'*-aminal **21g** in 76%, though, it was found that this product slowly degraded upon standing to give the imine, possibly due to the electron-rich nature of the aniline. However, we were able to obtain crystals of **21g**, suitable for single crystal X-ray analysis, which definitely assigned the structure as shown.[11] The 2-OCF$_3$ analogue **21h** could also be obtained in 77% isolated yield, and this product **21h** also demonstrated increased stability compared to **21g**. The reaction could accommodate electron-withdrawing groups, highlighted by 3-trifluoromethylaniline and 3,5-bistrifluoromethyl aniline, giving derivatives **21i** and **21j**, respectively. Anilines with halogen substitutions such as the 3,4-dichloro, 4-bromo, and 2-fluoroaniline all performed well in this reaction, with the latter two generating products with suitable crystals for single crystal X-ray analysis.[11] 3-(Ethoxycarbonyl)aniline also gave the desired *N,N'*-aminal **21m** in 70% isolated yield. *N*-Methylaniline was acceptable within these reaction conditions, with no observed oxidation of the *N*-methyl group,[12b] delivering *N,N'*-aminal **21o** in 61% yield; and diphenylamine gave *N,N'*-aminal **21p** in 56% isolated yield, illustrating that sterically encumbered anilines are also tolerated.[11] Finally, disubstituted *E*-enamide **23** was exposed to our conditions with *p*-toluidine. Pleasingly, this gave the *N,N'*-aminal **21q** in 53% isolated yield and essentially as a single diastereoisomer, in line with the results previously reported by Masson.[7c,d]

To the best of our knowledge, there have been limited investigations[7c,d] on the diastereoselectivity or the enantioselectivity of radical/cationic reactions with enamides, and none that involve the formation of *N,N'*-aminals.[12] As a consequence, we exposed chiral enamide **24** (Scheme 5; R^1 = Bn) to our conditions with three anilines.

**Scheme 5. Enamide (*S*)-24 and its influence on diastereoselectivity.**
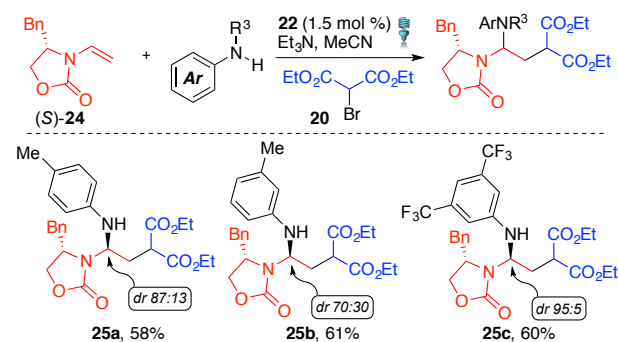
p-Toluidine and *m*-toluidine both gave their *N,N'*-aminal products **25a** and **25b**, respectively, in good isolated yields (58% and 61%, respectively) and appreciable levels of diastereoselectivity. This diastereoselectivity could be improved by the use of a more electron-withdrawing arylamine such as 3,5-bistrifluoromethyaniline, which gave the *N,N'*-aminal **25c** in 60% yield and essentially as one single enantiomer. Please

note that in all of the additions described, the separation of the two diastereomers could not be undertaken, and the diastereomeric ratio most likely represents an equilibrium (see Scheme 1).

To highlight the synthetic utility of these products, they were cyclized to their corresponding γ-lactams.[1,13] This was achieved *via* acid catalyzed cyclization with *N,N'*-aminals **21a-c**, **21i**, **21l** and **21n** (Scheme 6). In each case, the cyclization proved effective, but regrettably, modest diastereoselectivity was observed for all.[14] The major and minor diastereoisomers were identified using a combination of nOe experiments, and the major diastereoisomer in each is shown in Scheme 6; furthermore, the diastereomeric ratio for each could be determined using diagnostic signals around the γ-lactam ring.[15] Essentially, all cyclized products exhibited a slight preference for the anti-product, with the one exception being the *p*-tolyl γ-lactam **26b**. The diastereoselectivity ratio could also be partially influenced by the inclusion of an *ortho* substituent on the aryl ring, as exemplified by the 2-fluoroaryl γ-lactam **26f**.

Scheme 6. Synthesis of *N*-aryl γ-lactams.
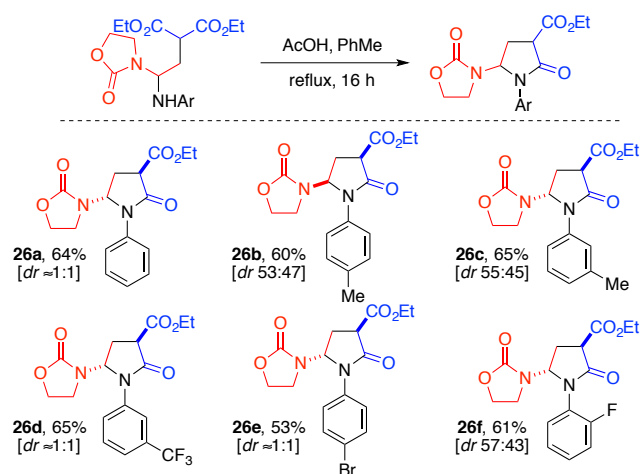
With this cyclization strategy in mind, we then applied it to the synthesis of γ-lactam **28**, as this would resemble the core structure of the gram-positive antibiotic Linezolid, and could plausibly function as new building block platform through palladium-catalyzed coupling of the bromide (Scheme 7).

Scheme 7. Formation of γ-lactam 28.
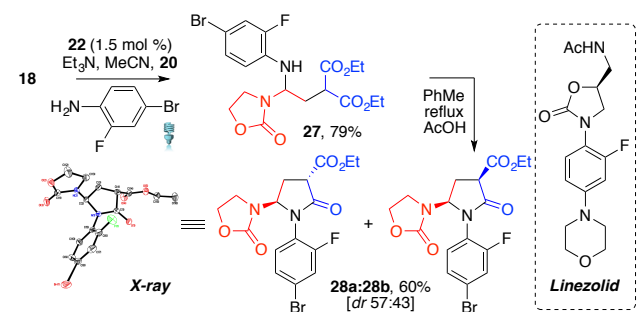
Treatment of enamide **18** with 2-fluoro-4-bromoaniline furnished the addition product **27** in good isolated yield, which upon treatment with acetic acid gave the aryl γ-lactam **21**. Pleasingly, this γ-lactam gave crystals upon standing that were identified as the major diastereoisomer **28a** after performing-

single crystal X-ray analysis.[11] Interestingly, upon dissolving the crystals in d-chloroform, this single diastereoisomer reverted back to the mixture indicated in Scheme 7. This evidence plausibly suggests that the diastereomeric ratio observed for the γ-lactam **28** (and **26a-f**) is an equilibrium mixture.

In summary, we have used a photoredox method for the synthesis of medicinally valuable *N*-acyl-*N'*-aryl-*N,N'*-aminals from readily available enamides. The process demonstrates that electron rich and poor arylamines are tolerant of the photoredox reaction conditions, and that moderate to good levels of diastereoselectivity can be achieved when using a chiral enamide. Additionally, we have demonstrated that these reaction products can be conveniently cyclized to give valuable γ-lactams. Our efforts in expanding this protocol using allenyl substrates is in progress, and will be reported on in due course.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:
Experimental procedures, characterization tables, NMR data, and X-ray table data for **21b**, **21lg**, **21l**, **21n**, **21p** and **28a** (PDF)

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Notes

The authors declare no competing financial interest.

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(15) Please see the Supporting Information.