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Interrupted intramolecular [3 + 2] to 5-*endo*-*dig* cyclization: [3 + 2] cycloaddition of nitrile ylides of diazo esters: photo-induced solvent-free *gem*-diamination to synthesize α-amino-α-substituted α-amino esters†

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In this work, we transition the blue LED-induced intramolecular [3 + 2] cycloaddition of nitrile ylides, generated from singlet carbenes of diazo esters, towards an intermolecular [3 + 2] cycloaddition with substituted isocyanates. This photolytic reaction efficiently yields α-amino-α-aryl α-amino esters through *gem*-diamination of readily available diazo esters, using diverse organonitriles and isocyanates as amine sources. The resulting α,α-disubstituted α-amino acids (α-AAs) are known to exhibit enhanced properties compared to conventional amino acids. These reactions, employing nitriles as stoichiometric reagents, are easily scalable to multigram quantities. Control experiments, coupled with density functional theory calculations, provide detailed insight into the reaction mechanism.

Introduction

α,α-Disubstituted α-amino acids are intriguing and biorelevant building blocks.[1] They not only enhance the chemical and metabolic stability of peptide backbones but also increase lipophilicity and induce unique conformations.[2–5] These amino acids exhibit diverse biological activities and are utilized for studying peptide structures, designing foldamers, and developing peptoid-based therapeutics.[6,7] Currently, 40–60% of new active pharmaceutical ingredients (APIs) suffer from poor aqueous solubility, leading to reduced bioavailability and drug efficacy.[8] The use of non-proteogenic α,α-disubstituted α-amino acids offers a potential solution to this issue.[9] Due to their presence in various natural products, they have attracted significant interest from pharmaceutical researchers as valuable building blocks for drug candidates.[10–12]

Some α,α-disubstituted α-amino acids arise from post-translational modifications, yet their synthesis, both chiral and achiral, remains challenging. This is largely due to steric hindrance from the four distinct non-hydrogen substituents at the quaternary carbon centre, necessitating multi-step syntheses that preserve the amino and carboxylate functionalities. Among these compounds, *gem*-diamino carboxylic acid derivatives are particularly important non-proteinogenic amino acids, commonly found in both natural and synthetic bioactive compounds. These derivatives are now recognized as crucial structural subunits in a variety of biologically active molecules (highlighted figure in Scheme 1a).[13–15]

The significance of bioactive building blocks has driven numerous synthetic studies. The traditional route, the Strecker synthesis (established in 1850), involves hydrocyanation of activated imines followed by hydrolysis to yield amino esters (Scheme 1b(i)).[16,17] Although an asymmetric variant was later introduced, the process suffers from low yields, toxic cyanides, and ketimine enolization as a side reaction.[18] The low electrophilicity of the iminyl carbon in ketimines further limits its application in synthesizing α,α-disubstituted-α-amino acids. Alternatively, Schiff base enolates have been used with various electrophiles to access these amino acids, though the iminyl carbon's electrophilicity remains critical for product formation (Scheme 1b(ii)).[19,20] Phase transfer-catalysed reactions of achiral Schiff bases offer a milder approach but require multiple steps to prepare the bases. Notably, two examples of *gem*-diamino carboxylic acid derivatives have emerged (Scheme 1c [i] and [ii]).[21,22] Zeng and colleagues used catalytic $Cu(OTf)_2$ and PPh_3 for the intermolecular amidation of α-acylimines (Scheme 1c[i]), while Antilla *et al.* employed chiral VAPOL

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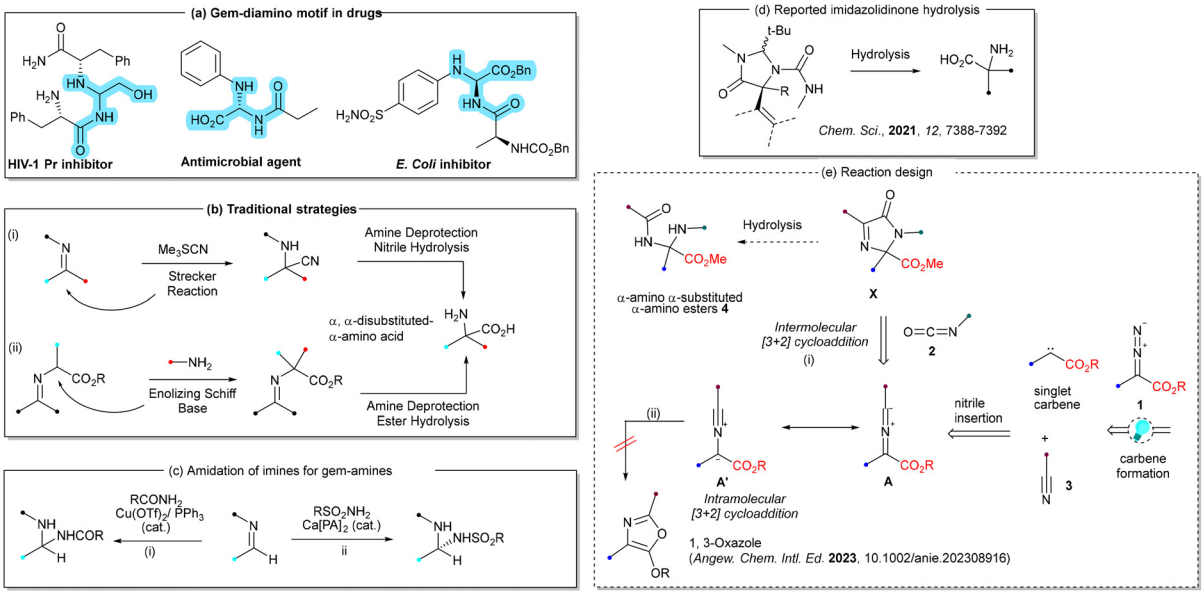


Scheme 1 (a) *gem*-Diamino carboxylic acid containing drug molecules. (b) Conventional strategies to construct α,α-disubstituted α-amino acids. (c) Amidation of imines for *gem*-amination. (d) Reported hydrolysis of imidazolidinones for the generation of substituted amino acids. (e) The design and concept of our interrupted intramolecular [3 + 2] cycloaddition of nitrile ylides A/A′ for the generation of α-amino-α-substituted amino acids.

calcium phosphate with sulfonamides for a similar transformation (Scheme 1c[ii]).[21,22]

In the past decade, advances in α,α-disubstituted-α-amino acid synthesis have emerged through metal-free C–H activation, organocatalysis, photo-electrocatalysis, and CO_2 fixation.[23–28]

Despite extensive efforts, the synthesis of α-amino-α-aryl α-amino esters remains elusive. Traditional methods like electrophilic amination of Schiff base enolates and nucleophilic Strecker reactions have proven ineffective. Reported imine amidations only produce tertiary carbons, leaving quaternary centers inaccessible. Therefore, a new approach is necessary.

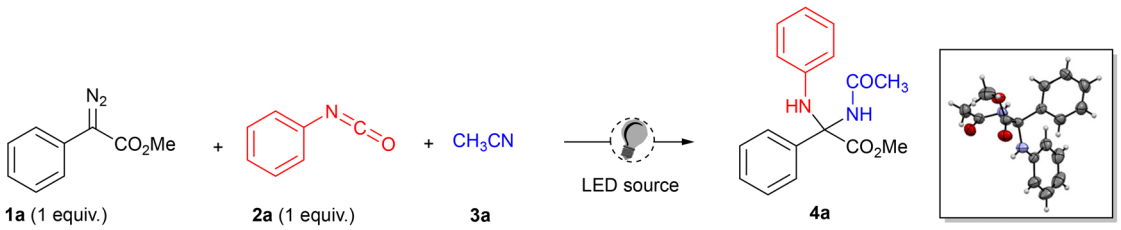
Imidazolidinones are known to hydrolyze into disubstituted α-amino acids (Scheme 1d).[29,30] We propose that dihydro-imidazolidinone **X** could serve as a precursor, generating the desired α-amino-α-aryl α-amino esters upon hydrolysis (Scheme 1e[i]), provided suitable functionalities are installed. Precursor **X** could be synthesized *via* a [3 + 2] cycloaddition between substituted isocyanates and nitrile ylides **A**, derived from diazo esters **1**. Recently, we reported that under blue LED light, nitrile ylide **A′** is formed by inserting alkyl nitriles into singlet carbenes from diazo esters, followed by an intramolecular [3 + 2] cycloaddition to yield 1,3-oxazoles (Scheme 1e[ii]).[31] Here, we aim to interrupt this intramolecular cycloaddition by trapping nitrile ylide **A** with aryl isocyanates, promoting intermolecular [3 + 2] cycloaddition to access α-amino-α-aryl α-amino esters (Scheme 1e[i]).

We present a novel, modular, solvent-free, and eco-friendly synthesis of α-amino-α-aryl α-amino esters *via* geminal diamination of diazo esters with alkyl nitriles (including acetonitrile) and substituted isocyanates as aminating agents under blue LED light (456 nm) at room temperature (Scheme 1e[i]). The key step is an intermolecular [3 + 2] cycloaddition between nitrile ylides **A** and isocyanates. Control experiments helped elucidate the reaction mechanism.

Results and discussion

As a proof of concept, phenyl diazoacetate **1a** (1 equiv.) was reacted with phenyl isocyanate **2a** (1 equiv.) in acetonitrile **3a** (50 equiv.) under blue LED light (456 nm, ~34 W, see the ESI† for details) at room temperature for 6–7 hours (Scheme 2). Thin layer chromatography revealed the formation of a major product, which was isolated and identified as α-amino-α-phenyl α-amino ester **4a**, with a 72% yield. The structure was confirmed by single-crystal X-ray analysis (Scheme 2). Interestingly, acetonitrile and phenyl isocyanate were the amine sources. When tested with other LEDs (white, red, green, and violet), none were as efficient as the blue LED. Solvent mixtures (THF, DCM, toluene, and DCE with acetonitrile) were also less effective and pure acetonitrile afforded the best results. To minimize acetonitrile use due to toxicity concerns, the reaction was optimized with 1–4 equivalents of acetonitrile, with 4 equivalents providing the best yield of 76% (Scheme 2). The final protocol involved irradiating **1a** and **2a** with a blue LED for 7 hours at room temperature in 4 equivalents of acetonitrile, yielding **4a**.

After optimizing the reaction conditions, we explored the scope of our protocol for synthesizing various α-amino-α-aryl α-amino esters **4** (Scheme 3). A variety of diazo esters **1** and aryl isocyanates **2** were reacted with stoichiometric acetonitrile **3a** or propionitrile **3b** under blue LED irradiation at room temperature in open air. Depending on the physical state of



Entry	LED source	CH_3CN	Yield (%)[a]
1	Blue	50 equiv.	84
2	Red	"	12
3	Green	"	43
4	Violet	"	56
5	Blue	4 equiv.	76

[a] Isolated Yield

Scheme 2 Proof-of-concept studies for the synthesis of **4a** followed by the optimisation of the process.

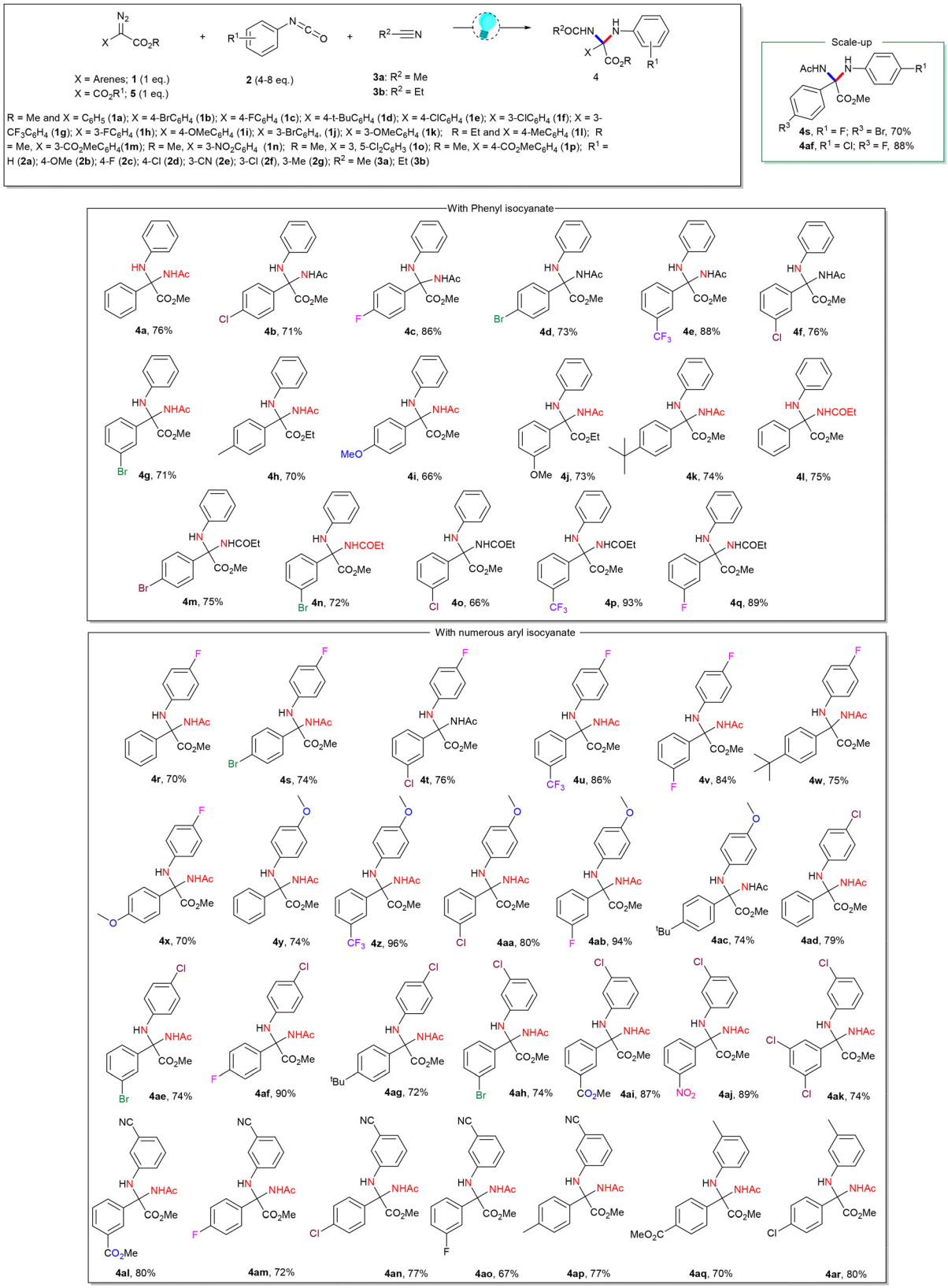
the diazo esters, 3 equivalents of nitriles were used for liquid diazo esters, and 5 equivalents for solid ones. Initially, diazo esters **1a–1p** were reacted with phenyl isocyanate **2a**, affording products **4a–4q** in 66–93% yields (Scheme 3). Yields varied with the substitution pattern of the aryl diazo esters; electron-withdrawing groups (*e.g.*, *para*- and *meta*-fluoro, and *meta*-trifluoromethyl) gave higher yields than electron-donating ones. This may be due to better stabilization of singlet carbenes by electron-withdrawing substituents. Both acetonitrile and propionitrile worked well, providing products **4l–4q** in moderate to excellent yields. Notably, benzyl and phenyl nitrile reactions yielded 1,3-oxazoles *via* intramolecular [3 + 2] cycloaddition. To further test the robustness of our protocol, various aryl isocyanates **2b–2g** were reacted with substituted diazo esters **1a–1q** (Scheme 3). Gratifyingly, products **4r–4ar** were obtained in moderate to excellent yields. Electron-poor diazo esters (*e.g.*, **1c**, **1g**, **1h** and **1t**) combined with electron-rich isocyanates (*e.g.*, **2b**, **2d**, **2f** and **2g**) afforded high yields (>88%). The reaction tolerated *para*- and *meta*-substituted aryl isocyanates, generating compounds **4ag–4ar**. Sensitive groups like $-NO_2$ (**1n**), $-CO_2Me$ (**1l** and **1m**), and –CN (**2e**) were compatible, producing compounds **4aj** and **4al–4ap** in good yields. The reaction of 3,5-dichlorophenyl diazoacetate **1o** with 3-chlorophenyl isocyanate **2f** in acetonitrile produced **4ak** in 74% yield. Similarly, 3-tolyl isocyanate **2g** reacted with diazo esters **1e** and **1p** to give **4aq** and **4ar**. Interestingly, reactions of diazo esters **1a–1d** with *o*-tolyl isocyanate **2h** did not yield the desired products, instead isolating 1,3-oxazoles **7a–7d**, likely due to steric hindrance from *ortho*-aryl substituents. To demonstrate scalability, reactions of **1b** and **1c** with **2c** and **2d** were performed on a gram scale, affording products **4s** and **4af** in 70% and 88% yield, respectively. The final products were isolated *via* recrystallization from isopropanol.

Next, we wanted to investigate numerous other diazo esters as a suitable substrate for our reaction. Accordingly, dimethyl-2-diazomalonate **5a**, diethyl diazomalonate **5b** and diisopropyl diazomalonate **5c** when reacted with 4-chlorophenylisocyanate **2d** in acetonitrile **3a** afforded the desired α,α-dicarbonylated aminals **4as–4au** in excellent yields (Scheme 4). The resulting α,α-dicarbonylated aminals belong to a class of chemicals that exhibit high potential as synthetic building blocks for diverse frameworks, including bioactive compounds.[32,33] However, unlike ours, the reported strategies are either multistep and or demonstrate installation of the same two amino moieties.[34–42] In another example, the reaction of methyl-2-diazopropanoate **5d** with 3-cyanophenyl isocyanate **2e** generated the desired final compound **4av** in 67% yield (Scheme 4). It is noteworthy that ethyl-2-diazoacetate **5e**, methyl diazopropanoate **5f** and methyl-2-diazobutanoate **5g** failed to generate the α-amino-α-aryl α-amino esters **4**.

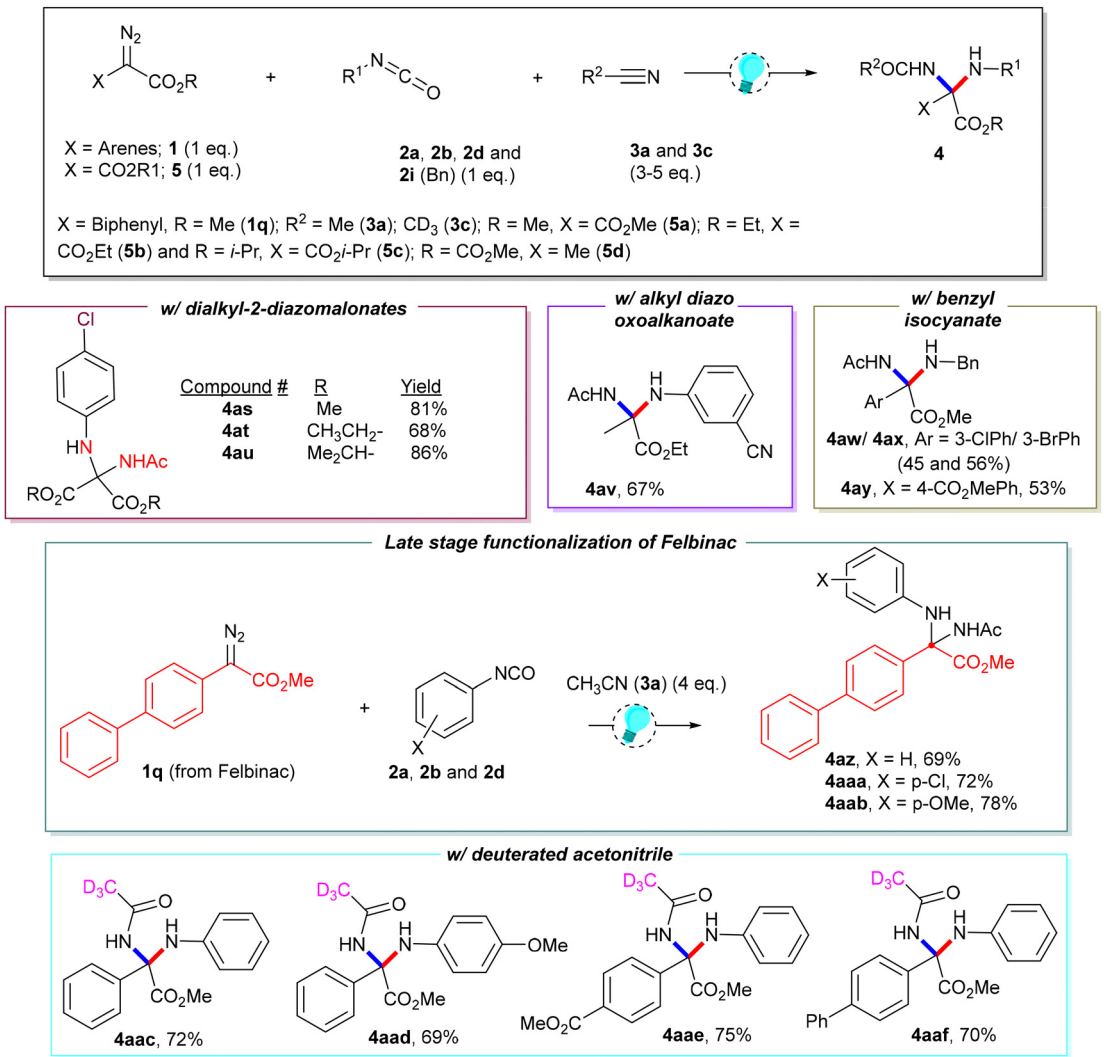
Next, we wanted to assess the compatibility of our protocols with alkyl isocyanates. Accordingly, benzyl isocyanate **2i** afforded the desired products **4aw–4ay** in 45 to 56% yields (no 1,3-oxazole detected) with **1f**, **1j** and **1p** (Scheme 4).

The utility of our newly developed double C–N bond formation strategy was demonstrated through the functionalization of felbinac, a nonsteroidal anti-inflammatory drug (NSAID) used to treat muscle inflammation and arthritis (Scheme 4).[43,44] Felbinac is typically functionalized at the carboxylic acid or biphenyl moiety, but there are no reports of benzylic functionalization.[45,46] We methylated felbinac, installed a diazo group, and used the resultant substrate **1q** (see the ESI†). Under optimized conditions, reactions of **1q** with isocyanates **2a**, **2b**, **2d**, and acetonitrile **3a** yielded methyl 2-([1,1′-biphenyl]-4-yl)-2-acetamido-2-(arylamino) acetates **4az**, **4aaa**, and **4aab** in 69–78% yields, demonstrating late-stage felbinac functionalization (Scheme 4).

In medicinal chemistry, analysing isotopically labelled molecules is essential for understanding mechanisms of action, metabolism, and toxicity *in vivo* and *in vitro*. This strategy was applied to synthesize isotope-labelled α-amino-α-aryl α-amino esters (Scheme 4). Reactions of deuterated acetonitrile **3c** with aromatic diazo esters **1a**, **1p**, and **1q**, along with isocyanates **2a** and **2b**, produced deuterium-labeled α-amino-α-aryl α-amino esters **4aac–4aaf**, including the deuterated felbinac derivative **4aaf**, in 69–75% yields (Scheme 4).



Scheme 3 Synthesis of diversely substituted α-amino-α-substituted amino esters.



Scheme 4 Application of our geminal diamination of aryl diazo esters on numerous diazo esters using deuterated acetonitrile, and the expedient functionalisation of felbinac.

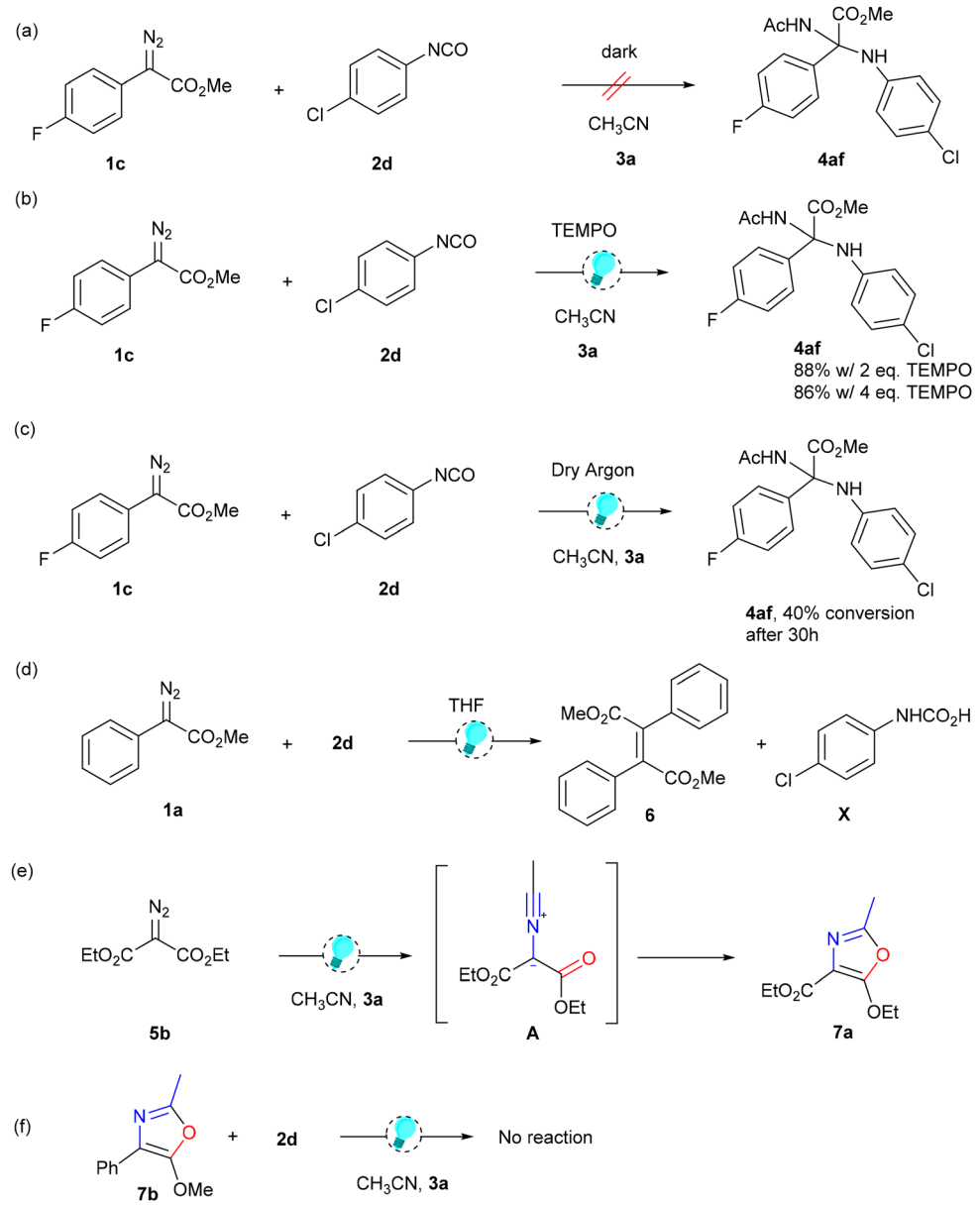
It is noteworthy that the reactions with ethyl 2-diazoacetate resulted in the dimerization of the diazo ester whereas with ethyl 2-diazo-3-oxobutanoate, we have primarily obtained an oxazole as the major product as reported earlier.[31]

To elucidate the reaction mechanism, several experiments were conducted (Scheme 5). First, the reaction of 4-fluorophenyl diazo ester **1c** with 4-chlorophenyl isocyanate **2d** in acetonitrile **3a** under dark conditions failed to yield any product, confirming that blue LED light is essential for generating the singlet carbene (Scheme 5a). Next, performing the same reaction with 2 or 4 equivalents of the radical trapping agent TEMPO afforded **4ad** in 88% and 86% yields, respectively, similar to the reaction without TEMPO (78%). This suggests no radical involvement as TEMPO did not inhibit product formation (Scheme 5b).

Additionally, the reaction under dry argon was slow, reaching only 40% conversion after 30 hours, indicating that air or moisture aids the reaction (Scheme 5c). When phenyl diazoacetate **1a** and 4-chlorophenyl isocyanate **2d** were reacted in tetrahydrofuran (THF) under a blue LED, dimerization of **1a** occurred, forming **6** and the hydrolyzed product of **2d** (Scheme 5d). This suggests that acetonitrile **3a** facilitates the formation of a nitrile ylide and its absence leads to dimerization.

Furthermore, irradiation of diethyl diazo malonate **5b** with **3a**, without isocyanates, exclusively formed 1,3-oxazole **7** through intramolecular [3 + 2] cycloaddition (Scheme 5e), implying that aryl isocyanates act as dipolarophiles for the intermolecular [3 + 2] cycloaddition in our reaction. Finally, reacting **7b** with **2d** under optimized conditions failed to produce **4ad**, confirming that **7** is not involved in the formation of **4** (Scheme 5f).

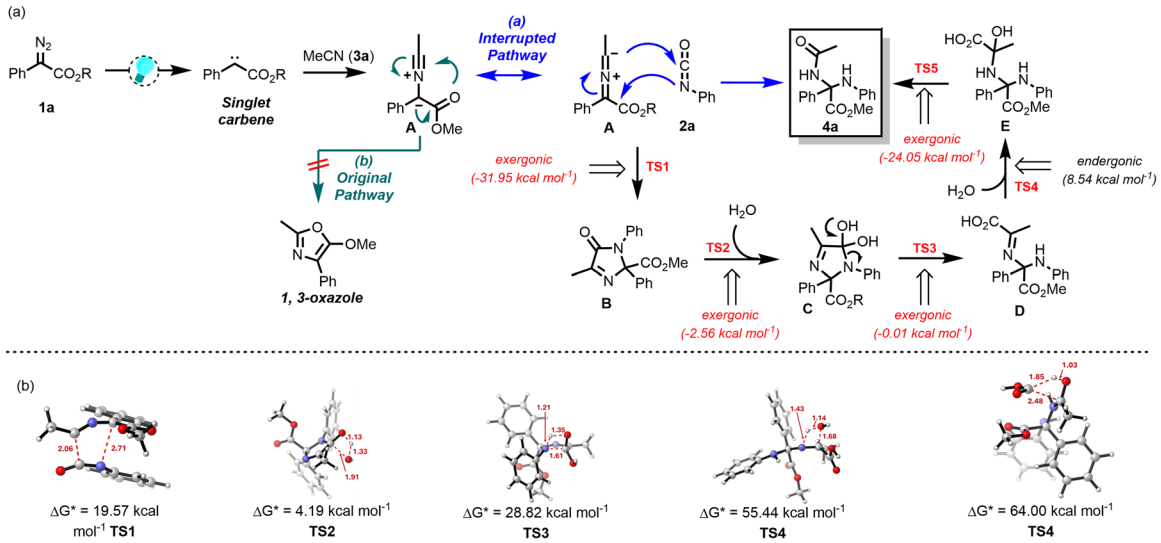
The mechanism underlying the synthesis of α-amino α-aryl amino esters as realised from the control experiments and previous reports suggested an interrupted intra- to intermolecular [3 + 2] cycloaddition of nitrile ylide **A** and appropriate isocya-



Scheme 5 Control experiments to delineate the mechanism for the formation of α-amino-α-aryl amino esters **4**.

nates **2** (Scheme 6a). The original pathway generated 1,3-oxazoles (Scheme 6b) whereas the introduction of **2** steered the transformation towards the formation of **4** (Scheme 6a). To further elucidate this, gas phase DFT calculations were performed using the Gaussian 09 package at the M06-2X/6-31**G level of theory.[47] In accordance with the expectation, the intermolecular [3 + 2] cycloaddition of the nitrile ylide **A** (obtained from the insertion of the acetonitrile **3a** onto the singlet carbene from **1a**) with phenyl isocyanate **2a** to form the imidazolidinone intermediate **B** is highly exergonic (−31.95 kcal mol^{-1}) and happens through a transition state **TS1** with a moderate activation barrier (19.57 kcal mol^{-1}) (Scheme 6a). The hydrolysis of the amide carbonyl of **B** to generate **C** is mildly exergonic (−2.56 kcal mol^{-1}) through the transition state **TS2** with a low activation energy barrier of 4.19 kcal mol^{-1} (Scheme 6a). Intermediate **C** opens to afford imine **D**. This is again mildly exergonic (−0.01 kcal mol^{-1}) through the transition state **TS3** with a high activation energy (28.82 kcal mol^{-1}). While subsequent imine hydrolysis of **D** to **E** is an endergonic process (8.54 kcal mol^{-1}) through **TS4** with a substantially high activation energy of 55.44 kcal mol^{-1}, the data are reasonable for the progress of the reaction (Scheme 6a). Finally, an exergonic decarboxylation of **E** (−24.05 kcal mol^{-1}) through **TS5** (64 kcal mol^{-1}) afforded the final product **4a** (Scheme 6a).

Interestingly, the reaction of **1a** with phenyl isothiocyanate **2j** and acetonitrile **3a** (8 equivalents) produced a 1 : 1 mixture of 1,3-isoxazole **7b** and 2,3-dihydroazete **8a**, instead of the

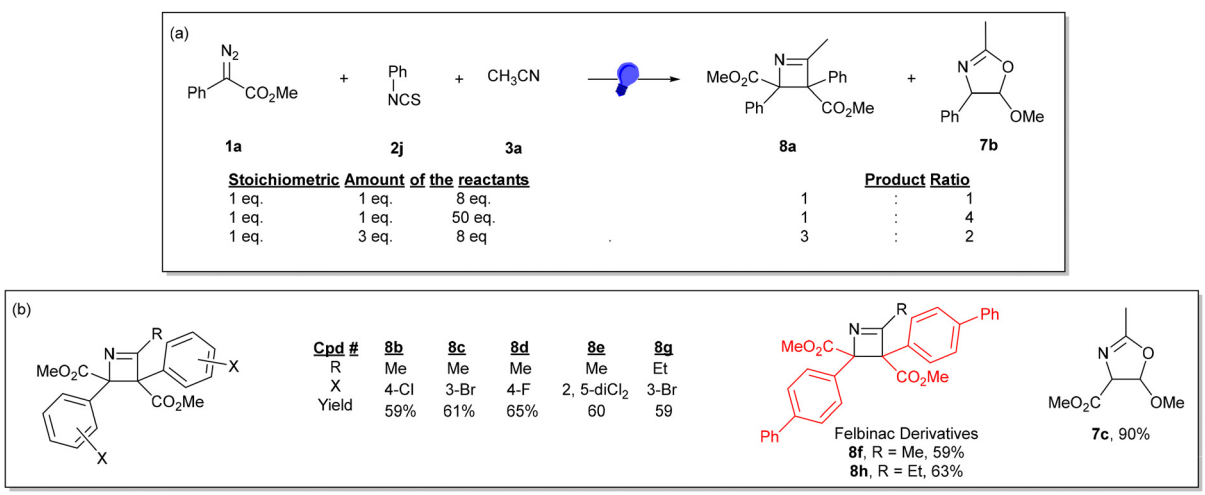


Scheme 6 (a) The reaction mechanism for the generation of α-amino-α-aryl amino esters and calculated reaction coordinates as determined at the M06-2X/6-31**G level of theory. Gibbs free energy values were calculated from frequency calculations. (b) The original intramolecular [3 + 2] cycloaddition to afford 1,3-oxazoles.

expected **4a** (Scheme 7a). We believe the generation of **8a** is the result of a [3 + 1] cycloaddition between the nitrile ylide **A** and the singlet carbene from **1a**, where **2j** acted as an additive to stabilize the singlet carbene. However, in this case, the intramolecular [3 + 2] cycloaddition could not be entirely inhibited. Increasing the volume of **3a** to 50 equivalents yielded **7b** as the major product (Scheme 7). To improve the yield of **8a**, the reaction was attempted with varying amounts of **2j** (2, 3, and 5 equivalents), and the best result of 55% of **8a** in a 3 : 2 ratio with **7b** was obtained using 3 equivalents of **2j** and 8 equivalents of **3a** (Scheme 7a).

Furthermore, various electron-rich and electron-poor diazo esters (**1c**, **1e**, **1k**, **1r**, and **1t**) reacted with **3a** or **3b** (8 equivalents) in the presence of 3 equivalents of **2j** to generate the desired 2,3-dihydroazetes **8b–8h** in 59–65% yields (Scheme 7b). Notably, the drug molecule felbinac was functionalized to 2,3-dihydroazete analogs **8f** and **8h** in 59% and 63% yields, respectively. However, the reaction of dimethyl malonate diazo ester **5a** led exclusively to 1,3-oxazole **7c**.

This is significant because four-membered aza-heterocycles are common in natural products and bioactive compounds, typically featuring a β-lactam or azetidine core, such as mugineic acid (an iron transporter) or azetidine-2-carboxylic acid (Aze), found in nicotianamine (Scheme 7).[48–52] These compounds are also known to inhibit the HCMV serine protease enzyme.[53] The 2,3-dihydroazetes are unique four-membered aza-heterocycles, being more rigid and less basic than azetidines due to the presence of an sp^2 carbon in the ring.[54–56]



Scheme 7 (a) Synthesis of 2,3-dihydroazete derivatives *via* blue LED induced competitive interrupted intramolecular [3 + 2] cycloaddition to intermolecular [3 + 1] cycloaddition. (b) Four-membered aza-heterocycles as natural products and drug molecules.

Though a few syntheses of 2,3-dihydroazetes exist, mild, metal- and acid/base-free synthesis under solvent-free conditions remains unreported.

Conclusion

Herein, we have presented a modular, robust and ecofriendly photolytic synthesis of α-amino-α-aryl α-amino esters *via gem*-diamination of appropriate diazo esters through an intermolecular 5-*endo-dig* cyclization: [3 + 2] cycloaddition between nitrile ylides **A** of diazo esters and aryl isocyanates **2**. A blue LED induced singlet carbene generation (from diazo esters **1**) followed by nitrile **3** insertion into the carbene, affording **A**. Subsequent hydrolysis of the [3 + 2] cycloadduct provided the desired compounds **4**. Control experiments delineated the reaction mechanism.

Data availability

The data supporting this article have been included as part of the ESI.†

Conflicts of interest

There are no conflicts to declare.

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