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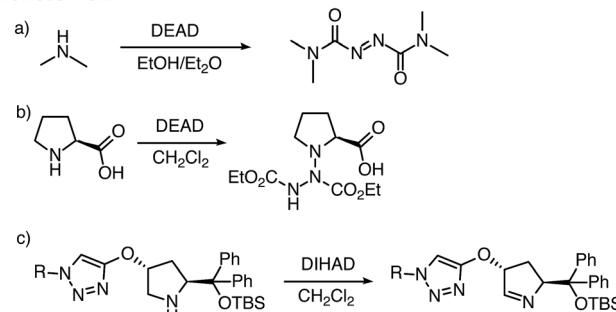
## Introduction

Imines serve as versatile building blocks in many synthetic transformations and, as a result, have been used in the construction of biologically active compounds, heterocycles, natural products, and agrochemicals.<sup>1</sup> Traditional approaches for the formation of imines involve condensation of primary amines with carbonyls.<sup>2</sup> This method suffers from limited scope and often requires unstable aldehydes and ketones. To overcome these issues, there has been a great deal of work devoted to developing amine dehydrogenation methods ranging from IBX oxidation to the bioinspired aerobic oxidation with transition metals.<sup>3</sup> Despite these works, there is still a large demand for general oxidative methods for the conversion of amines to imines.

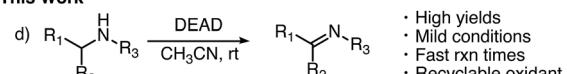
Azodicarboxylates have long been employed as electrophilic species in synthetic transformations ranging from the Mitsunobu reaction<sup>4</sup> and aminations<sup>5</sup> to [4 + 2] cycloaddition reactions.<sup>6</sup> They have also found application as ligands in the Cu catalyzed oxidation of alcohols and tetrahydronaphthalenes.<sup>7</sup> However, the abilities of these electrophilic azo species to act as general and broadly applicable oxidizing agents for amines has yet to be well documented or examined.<sup>8</sup>

In the mid 1900's, the examination of the reactivity of azodicarboxylates with aliphatic primary and secondary amines suggested they primarily provided substituted amides (Scheme 1a).<sup>9</sup> The most recent data on the reactivity of azodicarboxylates with amines comes from organocatalytic amination reactions where the azodicarboxylates often undergo side reactions with secondary amine catalysts. For example, it has been shown that L-proline reacts with diethyl azodicarboxylate (DEAD) to form a triazane species (Scheme 1b) and that diisopropyl azodicarboxylate (DIAD) is capable of deactivating

### Previous Work



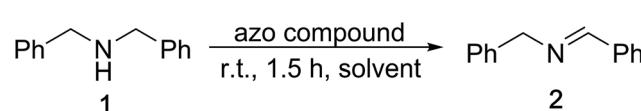
### This Work



Scheme 1 Reaction of DEAD with aliphatic secondary amines.

a Jørgensen–Hayashi catalyst containing a tethered base (Scheme 1c).<sup>10,11</sup> The ability of azodicarboxylates to oxidize amines as reported by Pericàs and as observed by our group in

Table 1 Optimization of Reaction Conditions



Entry	Azo compound	Solvent	NMR yield <sup>a,b</sup> (%)
1	DEAD	CDCl <sub>3</sub>	98
2	DEAD	Toluene-d <sub>8</sub>	84
3	DEAD	DMSO-d <sub>6</sub>	94
4	DEAD	Acetone-d <sub>6</sub>	94
5	DEAD	CD <sub>3</sub> CN	99
6	DIAD	CD <sub>3</sub> CN	91
7	PTAD	CD <sub>3</sub> CN	94
8	AIBN	CD <sub>3</sub> CN	0
9	NAB	CD <sub>3</sub> CN	0

<sup>a</sup> <sup>1</sup>H NMR yield. <sup>b</sup> 0.20 mmol amine, 0.24 mmol DEAD, 0.50 mL solvent.

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† Electronic supplementary information (ESI) available: Experimental procedures, analytical data, and NMR spectra. See DOI: 10.1039/c7ra09165f



Table 2 Secondary amine reaction scope

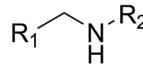
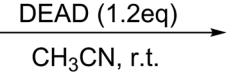
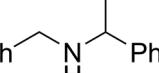
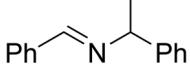
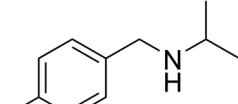
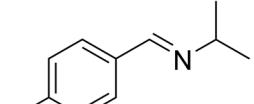
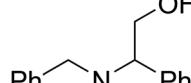
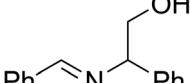
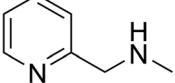
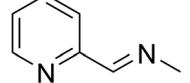
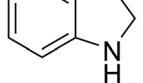
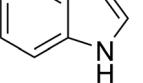
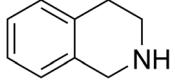
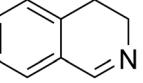
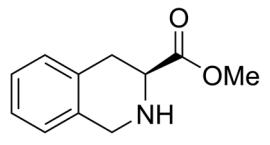
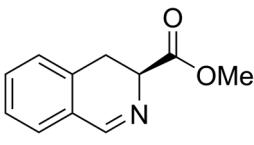
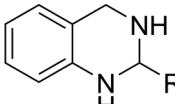
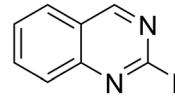
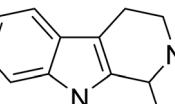
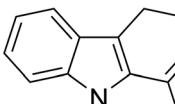
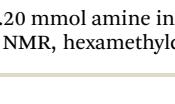
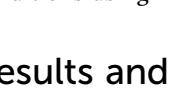
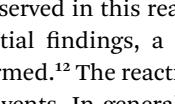
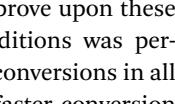
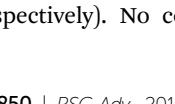
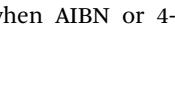
Substrate	Product <sup>a</sup>	Yield <sup>b</sup> (%)	Time (min)
			
1	2	96 <sup>c</sup>	90
		95 <sup>c</sup>	90
		95 <sup>c</sup>	90
5a R = H	6a R = H	88 <sup>c</sup>	90
5b R = OMe	6b R = OMe	90 <sup>c</sup>	90
5c R = NO <sub>2</sub>	6c R = NO <sub>2</sub>		
		82 <sup>c</sup>	90
7	8		
		85 <sup>c,d</sup>	90
9	10		
		98	20
11	12		
		77	20
13	14		
		84 <sup>c,e,f</sup>	20
15	16		



Table 2 (Contd.)

Substrate	Product <sup>a</sup>	Yield <sup>b</sup> (%)	Time (min)
		95 <sup>e</sup>	50
<b>17a</b> R = Cyclohexyl	<b>18a</b> R = Cyclohexyl	90 <sup>e</sup>	50
		95 <sup>e</sup>	50
<b>17b</b> R = Ph	<b>18b</b> R = Ph	80 <sup>e</sup>	50
		78	60
<b>17c</b> R = <i>p</i> -OMe-Ph	<b>18c</b> R = <i>p</i> -OMe-Ph	82	60
		70	60
<b>17d</b> R = <i>p</i> -NO <sub>2</sub> -Ph	<b>18d</b> R = <i>p</i> -NO <sub>2</sub> -Ph		
			
<b>19a</b> R = Ph	<b>20a</b> R = Ph		
			
<b>19b</b> R = <i>p</i> -OMe-Ph	<b>20b</b> R = <i>p</i> -OMe-Ph		
<b>19c</b> R = <i>p</i> -NO <sub>2</sub> -Ph	<b>20c</b> R = <i>p</i> -NO <sub>2</sub> -Ph		

<sup>a</sup> 0.20 mmol amine in 0.5 mL of CH<sub>3</sub>CN, 1.2 eq. DEAD. <sup>b</sup> Reported yields after purification by flash chromatography on silica. <sup>c</sup> Yields measured by <sup>1</sup>H NMR, hexamethyldisilane as internal standard. <sup>d</sup> In refluxing acetonitrile. <sup>e</sup> 2.2 eq. DEAD. <sup>f</sup> **21** observed in 14% yield at 20 min.

the development of other organocatalytic amination reactions has led us to explore the oxidizing abilities of azodicarboxylates. Herein we describe an efficient, atom economical, and general method for the oxidation of amines to imines under mild conditions using DEAD (Scheme 1d).

## Results and discussion

Initial studies on the oxidative abilities of azo compounds revealed that secondary amines could be readily oxidized by DEAD to form the corresponding imines. Reaction of dibenzylamine **1** with DEAD in CDCl<sub>3</sub> provided nearly quantitative conversion to dibenzylimine **2** in 1.5 h (Table 1, entry 1). The reduction of DEAD to diethyl hydrazodicarboxylate was also observed in this reaction. In an attempt to improve upon these initial findings, a screening of reaction conditions was performed.<sup>12</sup> The reaction was found to give high conversions in all solvents. In general, polar solvents provided faster conversion than non-polar solvents with acetonitrile providing the cleanest conversion (Table 1, entry 5).<sup>13,14</sup>

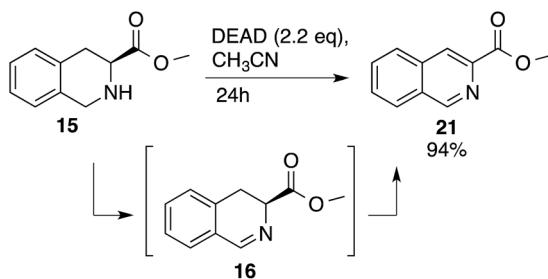
The oxidative abilities of various azo compounds were also explored (Table 1, entries 5–9). DEAD provided the highest conversion (99%), while DIAD and 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD) gave relatively high conversion (91% and 94% respectively). No conversion was observed when AIBN or 4-

nitroazobenzene (NAB) was employed as the oxidant. This suggests that an electrophilic azo species is required for the oxidation. Consequently, acetonitrile and DEAD were selected to explore the scope of this oxidative methodology. Using these conditions, we established the ability of this reaction to proceed on a larger scale (4.00 mmol **1**) with full conversion (see ESI for details†).

To determine the effectiveness of this oxidative method over a range of amines we examined alkylbenzylamines and dibenzylamines (Table 2). In most cases we observed high yields and full selectivity within 90 min. Full regioselectivity was observed for the secondary carbon of **3** and **5a–c**. Electron donating and electron withdrawing groups on the aromatic moiety had no significant influence on the yield or selectivity of the reaction (**5b** and **5c**). The amino alcohol **7** was converted to **8** with full chemoselectivity for the amine. Reactions between DEAD and amines **3**, **5**, and **7** demonstrate that less hindered sites are oxidized preferentially, suggesting a kinetic driving force.

Heteroaromatic amine **9** was found to provide the desired imine **10** in 85% yield in 90 min. To achieve the imine as the major product this reaction was conducted in refluxing acetonitrile, as lower temperatures resulted in a mixture of triazane species. Heterocyclic compounds **11** and **13** achieved >99% conversion within 20 min. The corresponding products were isolated in good to excellent yields (Table 2).<sup>15</sup> Methyl





Scheme 2 Aromatization of methyl tetrahydroisoquinolinecarboxylate 15.

tetrahydroisoquinolinecarboxylate (**15**) was employed to examine the selectivity between alpha- and benzyl- positions. At 20 min starting material had been consumed and imine **16** was observed in 84% yield with 14% of aromatized product **21** also present. Compound **21** was isolated in 94% yield after 24 hours (Scheme 2).

1,2,3,4-Tetrahydroquinazolines with both aryl and alkyl substituents at the 2-position (Table 2, **17a-d**) were found to readily undergo double oxidation to aromatic quinazoline derivatives **18a-d** with 2.2 equivalents of DEAD. In all cases high conversions and isolated yields were obtained. Phenyl substituted tetrahydro- $\beta$ -carboline **19a** provided the corresponding imine in >99% conversion and was isolated in 78% yield.  $\beta$ -Carboline derivatives containing electron donating and withdrawing groups showed equivalent conversions in 1 hour; however, isolated yields inversely correlate with the imine lability.

Encouraged by the broad scope of secondary amines that could be applied, we sought to extend the methodology to primary amines. Bulky benzyl amines **22** and **24** were found to favour amine oxidation over carboxylate substitution. Due to the difficulty associated with isolation of these labile primary imines, the species were hydrolyzed *in situ* and isolated as the corresponding ketones. The resulting products were successfully isolated in moderate yields (Table 3).

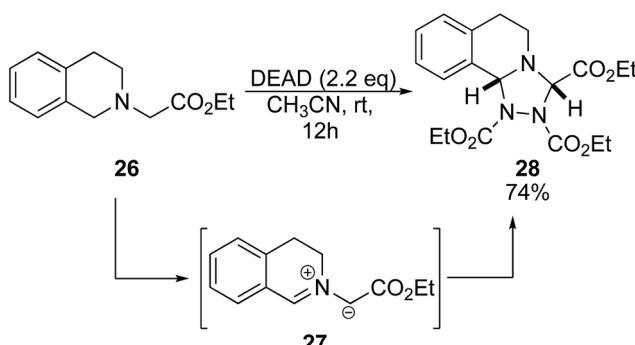
Previous studies of DEAD and tertiary amines show general dealkylation.<sup>6</sup> However, given the success of benzyl amines and  $\alpha$ -amino esters, we envisioned that the presence of an acidic proton on the tertiary amine would promote oxidation over dealkylation. When ethyl 3,4-dihydro-2(1H)-isoquinolinylacetate **26** was reacted with 2.2 eq. of DEAD, we observed production of triazolidine **28** (Scheme 3).<sup>16</sup> This product was likely obtained *via* a 1,3-dipolar cycloaddition of the azomethine ylide intermediate **27** with DEAD.<sup>17</sup> Scaffolds such as this are well known as antifungal drugs for medical and preservative purposes.<sup>18</sup> It is envisioned that this method could also serve to generate precursors for asymmetric N-heterocyclic carbenes.<sup>19</sup>

A key feature of this oxidation process is the ease of recovery of the spent oxidizing agent, hydrazodicarboxylate. This compound is insoluble in non-polar solvents and can be readily separated from the imine *via* crystallization from toluene. This process allows for 80% recovery of diethylhydrazodicarboxylate, which can be readily reoxidized to DEAD.

Based on our experimental results we propose a mechanism for the oxidation of amines by azodicarboxylates *via* a triazane

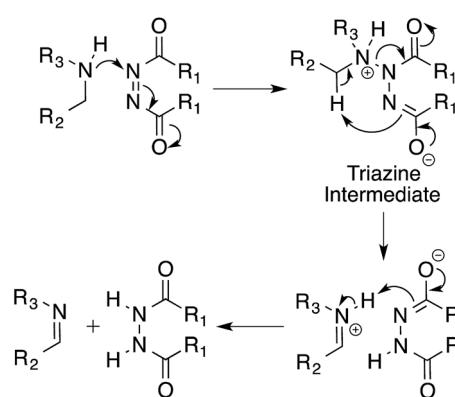
Table 3 Reaction scope studies with primary amines

Substrate	Product	Yield (%)
<b>22</b>	<b>23</b>	65
<b>24</b>	<b>25</b>	60



Scheme 3 Reaction of ethyl 3,4-dihydro-2(1H)-isoquinolinylacetate with DEAD.

intermediate (Scheme 4).<sup>20</sup> In this triazane pathway mechanism, the first step involves the nucleophilic attack of the amine on DEAD, taking advantage of the electrophilic nature of the azo



Scheme 4 Proposed mechanism.

species. The resulting triazane intermediate then undergoes an intramolecular elimination and subsequent proton transfer to produce the imine product. The details of this mechanism are currently under investigation.

## Conclusions

In this work we have described the first definitive demonstration of the oxidative abilities of azodicarboxylates with amines, greatly expanding their applicability in organic chemistry. This method not only provides access to versatile imine building blocks, but it also affords a rapid synthetic route to key alkaloid intermediates (e.g.  $\beta$ -carbolines, quinazolines) used across pharmaceutical and agrochemical synthesis. Additionally, the tandem oxidation/1,3-dipolar cycloaddition provides access to biologically relevant triazole scaffolds that may also serve as novel NHC scaffolds. The applicability of this reaction is accentuated by the ability to recover the spent oxidizing agent for regeneration and further use.

## Conflicts of interest

There are no conflicts to declare.

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12 No change in conversion was observed when the reaction was carried out under argon (Table 1, entry 2), eliminating the possibility of oxygen acting as a co-oxidant.

13 Alcohols were not used as solvents because it was known that alcohols can be oxidized in the presence of DEAD. See ref. 10.

14 A triazane species was observed as a minor side product (<2%) in  $\text{CDCl}_3$  but was absent in  $\text{CD}_3\text{CN}$ .

15 Isolated yields were poor in comparison to NMR conversion due to degradation of the imine on silica during purification.

16 The relative stereochemistry was determined by NOE experiments. For more details, see ESI.†

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20 The existence of a triazane species is supported by previous reports on the reaction of L-proline with azodicarboxylates. See ref. 10.

