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## Catalyst-free cycloaddition of 1,3-diene-1-carbamates with azodicarboxylates: a rapid click reaction

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### ABSTRACT

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Novel click reactions are of continued interest in many scientific research areas and applications. Herein, we report a novel practical, catalyst-free, azo-Diels-Alder reaction between dienecarbamates and azodicarboxylates exhibiting a remarkable functional group tolerance. The availability of starting materials, mild reaction conditions, chemoselectivity and scalability make this cycloaddition a viable supplement to the other reactions in “click” chemistry.

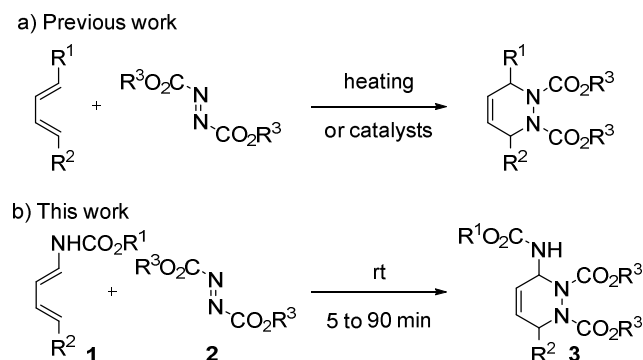
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## 1. Introduction

Click chemistry has become a powerful chemical tool in various research areas such as organic chemistry,<sup>1</sup> drug discovery,<sup>2</sup> bioconjugation,<sup>3</sup> radiochemistry,<sup>4</sup> and chemical biology.<sup>2a,5</sup> As defined by Sharpless,<sup>6</sup> a click reaction proceeds rapidly under mild conditions to produce building blocks with high selectivity, specificity, and yield, without byproducts. The starting materials must be readily available, and the reaction should have broad functional group tolerance and scope. Typical examples of such reactions include: (1) cycloaddition reactions (1,3-dipolar cycloadditions and hetero-Diels-Alder reactions), (2) nucleophilic ring-opening reactions of strained heterocyclic electrophiles (such as epoxides, aziridines and, aziridinium ions), (3) carbonyl chemistry (formation of imines, oxime ethers, hydrazones and amides), (4) additions to carbon-carbon multiple bonds (epoxidation, aziridination, Michael addition), (5) thiol-ene additions and (6) azide-phosphine reaction (Staudinger ligation).<sup>1-7</sup> Despite the significant advance made in this field over the past decade, there is still a demand for the development of novel click reactions, especially ones requiring no catalyst to complement the existing arsenal.

For many years, stable azodicarboxylates have been recognized as highly reactive dienophiles in the azo-Diels-Alder (azo-DA) reaction (Scheme 1a) and have been broadly used for the synthesis



**Scheme 1.** Development of click azo-DA reaction.

of key intermediates for the preparation of natural and pharmaceutical products (Figure 1).<sup>8</sup> Several catalytic enantioselective cycloadditions using chiral Lewis or Brønsted acid catalysts have been also reported.<sup>8,9</sup> In addition, the easy synthesis of these azodicarbonyl compounds incorporating biological molecules makes them valuable reagents for the bioconjugation.<sup>10</sup>

However, despite their potential usefulness, the azo-DA reactions have rarely been utilized as click reactions because of the requirement of catalysts or heating.<sup>11</sup> In this context, we envisioned that the use of electron-rich diene partners for the DA

**Figure 1.** Natural products and bioactive compounds.

reaction with might be a solution to improve efficiency of this cycloaddition.<sup>6</sup> Based on this consideration and our previous work in cycloaddition reactions,<sup>12</sup> we considered that stable dienecarbamates<sup>12a,d</sup> could be well adapted to our goal. Indeed, these compounds are easily synthesizable<sup>13</sup> and highly reactive diene partners in various cycloadditions as demonstrated by Overman.<sup>14,15</sup> Herein, we report a novel fast and efficient azo-DA reaction between stable dienecarbamates **1** and azodicarboxylates **2** resulting in an efficient synthesis of hydropyridazines which are often present in various biologically active compounds.<sup>8,9</sup> (Scheme 1b). The reaction shows a broad substrate scope and functional group compatibility.

## 2. Results and Discussion

Our initial experiment started with the reaction between benzyl (penta-1,3-dien-1-yl)carbamate (**1a**) and the commercially available dibenzyl azodicarboxylate (**2a**) in CH<sub>2</sub>Cl<sub>2</sub> at room temperature. This resulted in the formation of desired hydropyridazine **3a** in 81% yield with excellent diastereoselectivity (>95:5 dr) within 60 min (Table 1, entry 1). The relative stereochemistry of **3a** was unequivocally assigned as *cis* based on single crystal X-ray diffraction data (*cf* Supporting information).<sup>16</sup> Encouraged by this promising result, we screened several other solvents to optimize reaction conditions. Interestingly, the reaction rates varied noticeably depending on the solvent used. Toluene was superior to more polar aprotic solvents such as THF and CH<sub>3</sub>CN. The cycloadditions proceeded significantly faster in the presence of protic solvents.

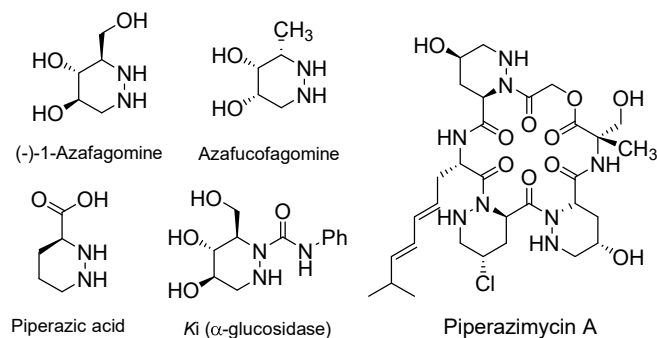
**Table 1.** Survey of conditions for azo-DA reaction.<sup>a</sup>

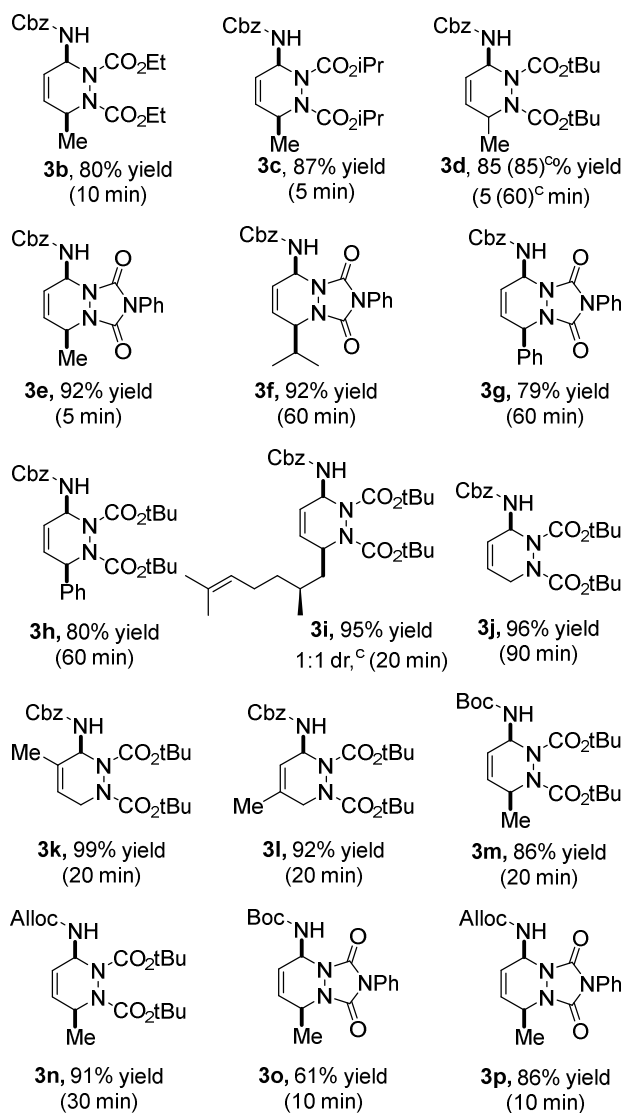
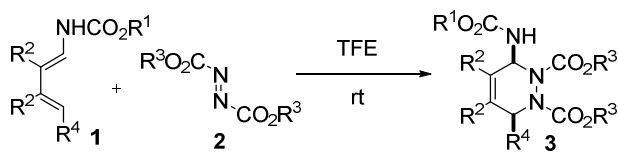
Entry	Solvent	Time (min)	Yield
1	CH <sub>2</sub> Cl <sub>2</sub>	60	82
2	Toluene	60	84
3	CH <sub>3</sub> CN	90	73
4	THF	210	85
5	MeOH	20	64
6	TFE	10	87
7	HFIP	10	89
8	TFE/H <sub>2</sub> O (2:1)	20	67

<sup>a</sup> General Conditions: dienecarbamate **1a** (0.1 mmol) and dibenzyl azodicarboxylate **2a** (0.1 mmol) in solvent (1.0 mL).

<sup>b</sup> Yields refer to chromatographically pure product.

**Table 2.** Substrate scope of 1,3-diene-1-carbamates **1** and azodicarboxylates **2**.<sup>a,b</sup>





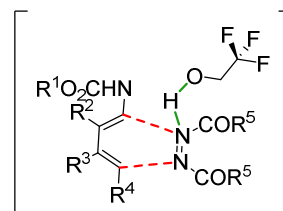
<sup>a</sup> General Conditions: dienecarbamates **1** (0.1 mmol) and azodicarboxylates **2** (0.1 mmol) in TFE (1.0 mL) at room temperature.

<sup>b</sup> Yields refer to chromatographically pure product.

<sup>c</sup> With 1 mmol of **1a** and **2d**.

<sup>d</sup> dr determined by <sup>1</sup>H-NMR analysis of crude mixtures<sup>c</sup>

Trifluoroethanol (TFE) or hexafluoro-2-propanol (HFIP) were shown to be the best choice in terms of both the reaction rate and yield, affording the desired product in 87 and 89% yield, respectively, in about 10 min (entries 6 and 7).<sup>17</sup> The origin of the rate enhancement might be attributed to the formation of hydrogen bonds between the fluorinated solvents and nitrogen atoms of **2**, thereby lowering their LUMO and enhancing their reactivity (Figure 2). Taking this in consideration, TFE was chosen as the reaction solvent because it is four times less expensive than HFIP. We were pleased to observe that this cycloaddition tolerates water, which is an important criterion for applications in bioconjugation. It is noteworthy that the reaction can be carried out without the use of inert atmosphere since it can be performed in an open flask.



**Figure 2.** Activation model via a putative transition state.

With the optimal conditions in hand, the scope of this azo-DA reaction was studied using a range of commercially available azodicarboxylates with different ester substituents (Table 2). The diethyl azodicarboxylate (**2b**), worked equally well than **2a**, affording corresponding cycloadduct **3b** in an excellent yield. Notably, the sterically encumbered, di-isopropyl azodicarboxylate (**2c**) and di-*tert*-butyl azodicarboxylate (**2d**), also reacted in less than 5 min, indicating that the reaction is not sensitive to steric hindrance. Interestingly, the more reactive dienophiles 4-phenyl-1,2,4-triazoline-3,5-dione (**2e**)<sup>11</sup> did not react more rapidly with **1a** than other azodicarbonyl derivatives.

**Table 3.** Robustness screening.<sup>a</sup>

Entry	Additive <b>4</b>	Conversion
1	none	94
2		94
3		88
4		81
5		79
6		83
7		83
8		67
9		60

<sup>a</sup> General Conditions: dienecarbamate **1a** (0.1 mmol), dibenzyl azodicarboxylate **2a** (0.1 mmol), additive and *p*-nitroanisole in TFE (1.0 mL) at room temperature.

<sup>b</sup> Conversions were measured by <sup>1</sup>H NMR using *p*-nitroanisole as an internal standard.

To further evaluate the scope of this reaction, a variety of dienecarbamates were employed. As shown in Table 4, the

dienecarbamate bearing alkyl (such as isopropyl) or aryl (such as phenyl) groups at the C-4 position were converted into corresponding cycloadducts **3f** and **3g** in good yields, albeit with longer reaction time. Noteworthy is that the chiral dienecarbamates derived from (*S*)-citronellol formed a 1:1 mixture of diastereomers **3h** in excellent yield. Unsubstituted C-4 dienecarbamates were also investigated and cycloadduct **3j** with no substituent was obtained in 96% yield after 1h30. By contrast, the reaction was slightly faster with the unsubstituted C-4 dienecarbamates bearing a methyl group at the C-2 or C-3 position. Finally, varying the nature of the carbamate had slight influence on the reaction rate and the yield (**3m** to **3p**, Table 2).

To further demonstrate the usability of the developed method, the reaction was performed on a 1 mmol scale. Although a longer reaction time was required for completion, the desired dihydropyridazine **3d** was isolated in excellent yield (Table 2, **3d**). Next, we sought to evaluate the functional group tolerance and applicability of this method further. Inspired by Glorius' work,<sup>18</sup> a rapid screen was performed in the presence of a variety of small biomolecules and additives containing common functional groups (Table 3). Several useful functional groups such as aldehydes, alcohols, carboxylic acids, carbamates, amides, alkenes, alkynes and amines were evaluated. The cycloaddition proceeds well in the presence of cytosine (**4a**), methyl  $\alpha$ -D-glucopyranoside (**4b**), *N*-Cbz glycine (**4c**) and *N*-Cbz-L-Phenylalanine-amide (**4f**), while *N*-carbobenzyl-L-tryptophan (**4e**) and *N*-Cbz-D-serine methyl ester (**4f**) moderately affected the amount of **3e** detected.

### 3. Conclusion

In summary, a simple and efficient azo-Diels-Alder click reaction which has been described enables access to a range of functionalized dihydropyridazines. The reaction has good substrate scope and tolerates a wide range of functional groups. The rate of this azo-cycloaddition reaction between dienecarbamates and azodicarboxylates was found to be very high. We believe that this click reaction should find broad applications in synthetic organic chemistry, as well as chemical biology.

## 4. Experimental Section

### 4.1 General methods and materials

Moisture sensitive reactions were carried out under argon atmosphere in flame-dried glassware with magnetic stirring bar. Solvents used in the reactions were dried with activated 4Å molecular sieves. Analytical thin layer chromatography (TLC) was purchased from Merck KGaA (silica gel 60 F254). Visualization was accomplished by irradiation with a UV light at 254 nm. Flash column chromatography was carried out using kieselgel 35-70  $\mu$ m particle sized silica gel (200-400 mesh). Chromatography was performed using silica gel 60 (0.040-0.063 mm) from Merck. <sup>1</sup>H NMR and <sup>13</sup>C spectra were recorded with Bruker 500 MHz and 300 MHz instruments. Data for <sup>1</sup>H NMR are reported as follows: chemical shift ( $\delta$  ppm), multiplicity (app = apparently, s = singlet, d = doublet, t = triplet, q = quartet, sext = sextet, m = multiplet), coupling constant (Hz), integration. Data for <sup>13</sup>C NMR are reported in terms of chemical shift ( $\delta$  ppm). The following calibration values have been used for <sup>1</sup>H NMR: CDCl<sub>3</sub> (7.26 ppm), CD<sub>3</sub>CN, (1.94 ppm); for <sup>13</sup>C NMR: CDCl<sub>3</sub> (77.0 ppm), CD<sub>3</sub>CN (1.3 and 118.3 ppm). Mass spectra were obtained from an AEI MS-9 using electron spray ionization (ESI). The HRMS data were measured on a MALDI-TOF instrument for high resolution mass spectra. Infrared spectra were recorded on neat samples, on a Perkin Elmer Spectrum BX FT-IR spectrometer and the characteristic IR absorption frequencies are

reported in cm<sup>-1</sup>. Melting points were recorded using Reichert melting point apparatus and temperatures were uncorrected. All reagents were obtained from commercial supplier and used as received unless otherwise noted. Dienecarbamates were prepared according to literature procedure.

#### 4.1.1 Typical Procedure for cycloaddition reaction

A reaction tube was equipped with a stirring bar and was thoroughly flame dried under high vacuum and flushed with argon. Dienecarbamate **1** (0.1 mmol) and azodicarboxylate **2** (0.1 mmol) were then loaded and dissolved in freshly dry 2,2,2-trifluoroethanol (1.0 mL). The resultant mixture was stirred at RT until complete conversion of substrates. After this time, TFE was removed and the crude product was purified by flash chromatography employing mixtures of *n*-heptane:ethyl acetate 7/3 as eluents to afford the corresponding pure compound **3**.

#### 4.1.2 Dibenzyl 3-(((benzyloxy)carbonyl)amino)-6-methyl-3,6-dihydropyridazine-1,2-dicarboxylate (**3a**)

Prepared according to the typical procedure described above. Reaction on 21.7 mg (0.10 mmol) of dienecarbamate (**1a**) to afford 47.9 mg of a colorless oil, 87% yield. <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>CN)  $\delta$  7.48 – 7.13 (m, 15H), 6.39 (d, *J* = 8.4 Hz, 1H), 6.18 (s, *J* = 8.4 Hz, 1H), 5.85 (ddd, *J* = 9.9, 4.5, 1.7 Hz, 1H), 5.76 (d, *J* = 10.0 Hz, 1H), 5.27 – 4.83 (m, 6H), 4.26 (s, 1H), 1.57 (d, *J* = 6.4 Hz, 3H); <sup>13</sup>C NMR (75 MHz, CD<sub>3</sub>CN)  $\delta$  156.5, 156.4, 155.5, 137.9 (rot. 1), 137.6 (rot. 2), 135.4, 133.4 (rot. 1), 133.0 (rot. 2), 129.5, 129.4, 129.3, 129.2, 129.0, 128.9, 128.8, 128.5 (rot. 1), 128.3 (rot. 2), 126.9, 123.9 (rot. 1), 123.5 (rot. 2), 68.9, 68.0 (rot. 1), 67.9 (rot. 2), 67.8, 67.3, 67.2, 63.2 (rot. 1), 61.5 (rot. 2), 60.8, 53.1, 52.3, 51.2, 24.4, 20.3, 17.8; IR (neat)  $\nu$  (cm<sup>-1</sup>): 3331, 2915, 1718, 1498, 1455, 1401, 1303, 1259, 1217, 1043, 1012, 797, 736, 696; HRMS (ESI+, *m/z*): [M+Na]<sup>+</sup> calculated for C<sub>29</sub>H<sub>29</sub>N<sub>3</sub>O<sub>6</sub>Na<sup>+</sup>: 538.1949, found 538.1949

#### 4.1.3 Diethyl 3-(((benzyloxy)carbonyl)amino)-6-methyl-3,6-dihydropyridazine-1,2-dicarboxylate (**3b**)

Prepared according to the typical procedure described above. Reaction on 21.7 mg (0.10 mmol) of dienecarbamate (**1a**) to afford 31.3 mg of a colorless oil, 80% yield. <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>CN)  $\delta$  7.46 – 7.23 (m, 5H), 6.30 (d, *J* = 8.6 Hz, 1H), 6.21 – 5.93 (m, 1H), 5.91 – 5.80 (m, 1H), 5.75 (d, *J* = 10.0 Hz, 1H), 5.11 (s, 2H), 4.37 – 3.94 (m, 5H), 1.57 (d, *J* = 6.7 Hz, 3H), 1.40 – 1.03 (m, 6H); <sup>13</sup>C NMR (75 MHz, CD<sub>3</sub>CN)  $\delta$  156.4, 135.5, 129.5, 129.0, 128.8, 127.0, 123.9, 67.3, 63.7, 63.5, 62.6, 62.4, 61.4, 60.6, 52.9, 52.1, 20.4, 14.9, 14.8; IR (neat)  $\nu$  (cm<sup>-1</sup>): 3332, 2963, 2932, 1713, 1523, 1404, 1376, 1304, 1259, 1222, 1077, 1043, 1017, 797, 698; HRMS (ESI+, *m/z*): [M+Na]<sup>+</sup> calculated for C<sub>19</sub>H<sub>25</sub>N<sub>3</sub>O<sub>6</sub>Na<sup>+</sup>: 414.1636, found 414.1637.

#### 4.1.4 Diisopropyl 3-(((benzyloxy)carbonyl)amino)-6-methyl-3,6-dihydropyridazine-1,2-dicarboxylate (**3c**)

Prepared according to the typical procedure described above. Reaction on 21.7 mg (0.10 mmol) of dienecarbamate (**1a**) to afford 36.5 mg of a colorless oil, 87% yield. <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>CN)  $\delta$  7.37 (m, 5H), 6.26 (d, *J* = 8.4 Hz, 1H), 6.09 (d, *J* = 7.3 Hz, 1H), 5.82 (dd, *J* = 9.8, 4.2 Hz, 1H), 5.73 (d, *J* = 10.0 Hz, 1H), 5.17 – 5.01 (m, 2H), 4.95 – 4.72 (m, 2H), 4.20 (s, 1H), 1.56 (d, *J* = 6.6 Hz, 3H), 1.36 – 1.03 (m, 12H); <sup>13</sup>C NMR (75 MHz, CD<sub>3</sub>CN)  $\delta$  156.4, 138.0, 135.7, 133.6, 129.5, 129.0, 128.9, 128.8, 127.0, 124.0, 71.5 (rot. 1), 71.3 (rot. 2), 70.1 (rot. 1), 69.8 (rot. 2), 67.3, 61.2 (rot. 1), 60.5 (rot. 2), 52.7, 52.1 (rot. 1), 51.9 (rot. 2), 23.7, 22.3, 22.2, 20.5, 17.9; IR (neat)  $\nu$  (cm<sup>-1</sup>): 3332, 2981, 2936, 2370, 1711, 1521, 1455, 1374, 1302, 1260, 1223, 1104, 1039, 798, 697; HRMS (ESI+, *m/z*): [M+Na]<sup>+</sup> calculated for C<sub>21</sub>H<sub>29</sub>N<sub>3</sub>O<sub>6</sub>Na<sup>+</sup>: 442.1949, found 442.1946.

#### 4.1.5 Di-tert-butyl 3-(((benzyloxy)carbonyl)amino)-6-methyl-3,6-dihydropyridazine-1,2-dicarboxylate (**3d**)

Prepared according to the typical procedure described above. Reaction on 21.7 mg (0.10 mmol) of dienecarbamate (**1a**) to afford 38.1 mg of a colorless oil, 85% yield. <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>CN) δ 7.54 – 7.18 (m, 5H), 6.20 (d, *J* = 8.9 Hz, 1H), 6.05 (d, *J* = 3.8 Hz, 1H), 5.81 (dd, *J* = 9.8, 4.0 Hz, 1H), 5.71 (d, *J* = 9.9 Hz, 1H), 5.10 (s, 2H), 4.16 (q, *J* = 6.4 Hz, 1H), 1.54 (d, *J* = 6.6 Hz, 3H), 1.43 (s, 10H), 1.37 (s, 8H); <sup>13</sup>C NMR (75 MHz, CD<sub>3</sub>CN) δ 156.4, 135.9, 129.5, 129.0 (rot. 1), 128.9 (rot. 2), 128.8 (rot. 1), 128.7 (rot. 2), 127.2, 124.3, 124.1, 80.8, 67.2, 61.1, 60.2, 52.5, 51.9, 28.6 (2 C), 28.4 (4 C), 24.4, 21.4 (rot. 1), 20.7 (rot. 2), 20.5; IR (neat) ν (cm<sup>-1</sup>): 3340, 2978, 2933, 1714, 1499, 1393, 1367, 1312, 1255, 1159, 1046, 852, 754, 698; HRMS (ESI+, *m/z*): [M+Na]<sup>+</sup> calculated for C<sub>23</sub>H<sub>33</sub>N<sub>3</sub>O<sub>6</sub>Na<sup>+</sup>: 470.2262, found 470.2264.

#### 4.1.6 Benzyl (8-methyl-1,3-dioxo-2-phenyl-2,3,5,8-tetrahydro-1H-[1,2,4]triazolo[1,2-*a*]pyridazin-5-yl)carbamate (**3e**)

Prepared according to the typical procedure described above. Reaction on 21.7 mg (0.10 mmol) of dienecarbamate (**1a**) to afford 36.2 mg of a colorless oil, 92% yield. <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>CN) δ 7.59 – 7.29 (m, 10H), 6.40 (s, 1H), 6.09 (d, *J* = 9.6 Hz, 1H), 5.93 (dd, *J* = 11.2, 1.1 Hz, 1H), 5.85 (dd, *J* = 10.8, 3.3 Hz, 1H), 5.10 (s, 2H), 4.48 – 4.34 (m, 1H), 1.60 (d, *J* = 6.7 Hz, 3H); <sup>13</sup>C NMR (75 MHz, CD<sub>3</sub>CN) δ 156.1, 137.9, 131.9, 130.1, 130.0 (2 C), 129.5, 129.3 (2 C), 129.0 (2 C), 128.7, 127.3, 122.8, 67.4, 59.6, 52.9, 45.6, 30.4, 24.4, 19.2; IR (neat) ν (cm<sup>-1</sup>): 3313, 2930, 1781, 1718, 1503, 1415, 1292, 1222, 1146, 1039, 768, 691; HRMS (ESI+, *m/z*): [M+Na]<sup>+</sup> calculated for C<sub>21</sub>H<sub>20</sub>N<sub>4</sub>O<sub>4</sub>Na<sup>+</sup>: 415.1377, found 415.1377.

#### 4.1.7 Benzyl (8-isopropyl-1,3-dioxo-2-phenyl-2,3,5,8-tetrahydro-1H-[1,2,4]triazolo[1,2-*a*]pyridazin-5-yl)carbamate (**3f**)

Prepared according to the typical procedure described above. Reaction on 24.5 mg (0.10 mmol) of dienecarbamate to afford 38.9 mg of a colorless oil, 92% yield. <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>CN) δ 7.59 – 7.41 (m, 5H), 7.40 – 7.28 (m, 5H), 6.14 (s, 1H), 6.11 – 6.02 (m, 2H), 5.96 (ddd, *J* = 10.7, 3.9, 2.1 Hz, 1H), 5.11 (s, 2H), 4.34 (dq, *J* = 4.7, 2.1 Hz, 1H), 2.89 (heptd, *J* = 7.0, 4.5 Hz, 1H), 1.05 (d, *J* = 7.2 Hz, 3H), 0.96 (d, *J* = 6.8 Hz, 3H); <sup>13</sup>C NMR (75 MHz, CD<sub>3</sub>CN) δ 156.0, 153.2, 152.7, 137.9, 132.6, 130.0, 129.4, 129.2 (2C), 129.0, 128.7, 127.3 (2C), 126.5 (2C), 125.2 (2C), 67.4, 61.2, 60.0, 30.6, 19.1, 16.8; IR (neat) ν (cm<sup>-1</sup>): 3310, 2966, 1778, 1703, 1502, 1456, 1415, 1219, 1145, 1081, 1040, 767; HRMS (ESI+, *m/z*): [M+H]<sup>+</sup> calculated for C<sub>23</sub>H<sub>25</sub>N<sub>4</sub>O<sub>4</sub>: 421.1882, found 421.1876.

#### 4.1.8 Benzyl (1,3-dioxo-2,8-diphenyl-2,3,5,8-tetrahydro-1H-[1,2,4]triazolo[1,2-*a*]pyridazin-5-yl)carbamate (**3g**)

Prepared according to the typical procedure described above. Reaction on 27.9 mg (0.10 mmol) of dienecarbamate to afford 36.0 mg of a colorless oil, 79% yield. <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>CN) δ 7.57 – 7.25 (m, 15H), 6.53 (s, 1H), 6.19 (d, *J* = 9.6 Hz, 1H), 5.95 (s, 2H), 5.42 (s, 1H), 5.13 (s, 2H); <sup>13</sup>C NMR (75 MHz, CD<sub>3</sub>CN) δ 156.23, 153.51, 138.57, 137.88, 132.47, 130.50, 130.08, 130.01 (2 C), 129.60 (2 C), 129.48, 129.31, 129.27 (2 C), 128.99 (3 C), 128.79 (2 C), 127.61, 127.17, 123.39, 67.52, 60.38, 59.77; IR (neat) ν (cm<sup>-1</sup>): 3302, 3034, 2928, 1781, 1709, 1502, 1456, 1413, 1220, 1144, 1082, 1039, 840, 767, 756, 697; HRMS (ESI+, *m/z*): [M+Na]<sup>+</sup> calculated for C<sub>26</sub>H<sub>22</sub>N<sub>4</sub>O<sub>4</sub>Na<sup>+</sup>: 477.1533, found 477.1534.

#### 4.1.9 Di-tert-butyl 3-(((benzyloxy)carbonyl)amino)-6-phenyl-3,6-dihydropyridazine-1,2-dicarboxylate (**3h**)

Prepared according to the typical procedure described above. Reaction on 27.9 mg (0.10 mmol) of dienecarbamate to afford

41.0 mg of a colorless oil, 80% yield. <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>CN) δ 7.56 – 7.14 (m, 10H), 6.31 (s, 1H), 6.22 (s, 1H), 5.84 (dd, *J* = 9.4, 4.0 Hz, 1H), 5.64 (d, *J* = 9.9 Hz, 1H), 5.16 (s, 2H), 5.10 (s, 1H), 1.48 (s, 10H), 1.29 – 0.94 (m, 8H); <sup>13</sup>C NMR (75 MHz, CD<sub>3</sub>CN) δ 156.45, 140.81, 134.30, 129.51, 129.35 (2 C), 129.26, 129.10, 128.99, 128.84, 128.59, 128.14 (2 C), 127.98 (2 C), 122.88, 81.11, 67.33, 67.05, 60.93, 60.82, 60.56, 28.40 (4 C), 28.18 (2 C); IR (neat) ν (cm<sup>-1</sup>): 3331, 2978, 2929, 1717, 1716, 1496, 1392, 1368, 1319, 1257, 1156, 1047, 759, 699; HRMS (ESI+, *m/z*): [M+Na]<sup>+</sup> calculated for C<sub>28</sub>H<sub>35</sub>N<sub>3</sub>O<sub>6</sub>Na<sup>+</sup>: 532.2418, found 532.2415.

#### 4.1.10 Di-tert-butyl 3-(((benzyloxy)carbonyl)amino)-6-((*S*)-2,5-dimethylhex-4-en-1-yl)-3,6-dihydropyridazine-1,2-dicarboxylate (**3i**)

Prepared according to the typical procedure described above. Reaction on 32.7 mg (0.10 mmol) of dienecarbamate to afford 52.9 mg of a colorless oil, 95% yield as a mixture of diastereoisomers. <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>CN) δ 7.48 – 7.22 (m, 5H), 5.96 (s, 2H), 5.80 – 5.60 (m, 1H), 5.44 (d, *J* = 10.0 Hz, 1H), 5.25 – 4.99 (m, 3H), 4.55 (dd, *J* = 22.5, 9.4 Hz, 1H), 2.07 – 1.97 (m, 1H), 1.81 (s, 1H), 1.66 (s, 3H), 1.59 (s, 3H), 1.53 – 1.33 (m, 21H), 1.31 – 1.06 (m, 2H), 0.98 – 0.88 (m, 2H); <sup>13</sup>C NMR (75 MHz, CD<sub>3</sub>CN) δ 156.44, 133.25 (dia. 1), 132.98 (dia. 2), 132.57 (dia. 1), 132.44 (dia. 2), 129.40, 128.82, 128.61, 127.18 (dia. 1), 127.10 (dia. 2), 126.99, 125.93, 82.51, 66.94, 62.42 (dia. 1), 61.74 (dia. 2), 54.32 (dia. 1), 54.22 (dia. 2), 53.31 (dia. 1), 53.13 (dia. 2), 40.09 (dia. 1), 39.64 (dia. 2), 39.46 (dia. 1), 39.17 (dia. 2), 38.84, 30.51, 28.63, 28.44 (6 C), 26.52 (rot. 1), 26.47 (rot. 2), 25.91 (rot. 1), 25.88 (rot. 2), 24.40, 20.52, 18.77, 17.80; IR (neat) ν (cm<sup>-1</sup>): 3335, 2966, 2926, 1713, 1500, 1455, 1392, 1367, 1307, 1259, 1152, 1054, 803, 697; HRMS (ESI+, *m/z*): [M+Na]<sup>+</sup> calculated for C<sub>31</sub>H<sub>46</sub>N<sub>3</sub>O<sub>6</sub>Na<sup>+</sup>: 580.3357, found 580.3361; [α]<sub>D</sub><sup>22</sup> ([c] = 0.1 g/L, CHCl<sub>3</sub>) -2.0°.

#### 4.1.11 Di-tert-butyl 3-(((benzyloxy)carbonyl)amino)-3,6-dihydropyridazine-1,2-dicarboxylate (**3j**)

Prepared according to the typical procedure described above. Reaction on 20.3 mg (0.10 mmol) of dienecarbamate to afford 41.5 mg of a colorless oil, 96% yield. <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>CN) δ 7.52 – 7.24 (m, 5H), 6.29 (d, *J* = 9.6 Hz, 1H), 6.07 (d, *J* = 8.3 Hz, 1H), 5.96 (ddd, *J* = 10.0, 5.2, 2.3 Hz, 1H), 5.81 (ddd, *J* = 10.0, 4.5, 2.3 Hz, 1H), 5.18 – 5.00 (m, 2H), 4.29 (ddd, *J* = 18.1, 4.5, 2.2 Hz, 0.8H, rot.1), 4.19 (d, *J* = 14.1 Hz, 0.2H, rot.2), 3.75 (d, *J* = 18.1 Hz, 0.2H, rot.2), 3.63 (m, 0.8H, rot.1), 1.55 – 1.33 (m, 18H); <sup>13</sup>C NMR (75 MHz, CD<sub>3</sub>CN) δ 156.1 (2C, rot.1), 155.0 (2C, rot.2), 137.9, 129.4 (2C), 128.9 (4C), 128.3 (1C, rot.1), 127.8 (1C, rot.2), 125.0 (1C, rot.1), 124.8 (1C, rot.2), 82.0 (2C, rot.2), 80.9 (2C, rot.1), 67.1, 61.0 (1C, rot.2), 59.7 (1C, rot.1), 44.5 (1C, rot.2), 42.4 (1C, rot.1), 28.4 (3C), 28.3 (3C); IR (neat) ν (cm<sup>-1</sup>): 3338, 2978, 2933, 1705, 1499, 1456, 1408, 1367, 1325, 1222, 1162, 1075, 1044, 982, 873, 852, 751, 697; HRMS (ESI+, *m/z*): [M+Na]<sup>+</sup> calculated for C<sub>22</sub>H<sub>31</sub>N<sub>3</sub>O<sub>6</sub>Na<sup>+</sup>: 456.2107, found 456.2111.

#### 4.1.12 Di-tert-butyl 3-(((benzyloxy)carbonyl)amino)-4-methyl-3,6-dihydropyridazine-1,2-dicarboxylate (**3k**)

Prepared according to the typical procedure described above. Reaction on 21.7 mg (0.10 mmol) of dienecarbamate to afford 44.1 mg of a colorless oil, 99% yield. <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>CN) δ 7.51 – 7.19 (m, 5H), 6.28 (d, *J* = 8.8 Hz, 1H), 5.87 (d, *J* = 5.4 Hz, 1H), 5.61 (s, 1H), 5.22 – 4.97 (m, 2H), 4.23 (d, *J* = 18.2 Hz, 1H), 3.58 (d, *J* = 17.6 Hz, 1H), 1.72 (s, 3H), 1.48 – 1.40 (m, 10H), 1.36 (s, 8H); <sup>13</sup>C NMR (75 MHz, CD<sub>3</sub>CN) δ 156.7, 129.5, 129.0, 128.9, 128.7, 122.5, 122.3, 122.0, 67.4, 67.2, 63.2, 44.7, 42.6, 28.5 (2 C), 28.4 (3 C), 28.3, 24.4, 19.6, 19.5, 17.9 (rot. 1), 17.8 (rot. 2); IR (neat) ν (cm<sup>-1</sup>): 3345, 2979, 1709, 1500,

1455, 1394, 1368, 1323, 1224, 1165, 1026, 859, 698; HRMS (ESI<sup>+</sup>, m/z): [M+Na]<sup>+</sup> calculated for C<sub>23</sub>H<sub>33</sub>N<sub>3</sub>O<sub>6</sub>Na<sup>+</sup>: 470.2262, found 470.2263.

#### 4.1.13 Di-tert-butyl 3-(((benzyloxy)carbonyl)amino)-5-methyl-3,6-dihydropyridazine-1,2-dicarboxylate (**3l**)

Prepared according to the typical procedure described above. Reaction on 21.7 mg (0.10 mmol) of dienecarbamate to afford 41.3 mg of a colorless oil, 92% yield. <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>CN) δ 7.52–7.22 (m, 5H), 6.19 (d, *J* = 8.4 Hz, 1H), 6.00 (s, 1H), 5.52 (s, 1H), 5.07 (q, *J* = 12.5 Hz, 2H), 4.15 (d, *J* = 17.4 Hz, 1H), 3.55 (d, *J* = 17.4 Hz, 1H), 1.70 (s, 3H), 1.52–1.40 (m, 10H), 1.36 (s, 8H); <sup>13</sup>C NMR (75 MHz, CD<sub>3</sub>CN) δ 156.1, 138.0 (rot. 1), 136.7 (rot. 2), 129.5 (2 C), 129.0 (2 C), 119.4, 119.0, 80.9, 67.1, 59.6, 47.9, 45.8, 28.5 (2 C), 28.4 (4 C), 24.4, 19.8, 17.9, 17.8 (rot. 1), 15.0 (rot. 2); IR (neat) ν (cm<sup>-1</sup>): 3338, 2978, 2933, 1705, 1499, 1406, 1393, 1367, 1330, 1224, 1147, 1062, 859, 753, 698; HRMS (ESI<sup>+</sup>, m/z): [M+Na]<sup>+</sup> calculated for C<sub>23</sub>H<sub>33</sub>N<sub>3</sub>O<sub>6</sub>Na<sup>+</sup>: 470.2262, found 470.2263.

#### 4.1.14 Di-tert-butyl 3-((tert-butoxycarbonyl)amino)-6-methyl-3,6-dihydropyridazine-1,2-dicarboxylate (**3m**)

Prepared according to the typical procedure described above. Reaction on 18.3 mg (0.10 mmol) of dienecarbamate to afford 35.6 mg of a colorless oil, 86% yield. <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>CN) δ 5.98 (s, 1H), 5.78 (dd, *J* = 9.1, 4.1 Hz, 2H), 5.69 (d, *J* = 9.8 Hz, 1H), 4.15 (d, *J* = 6.0 Hz, 1H), 1.52 (d, *J* = 6.2 Hz, 3H), 1.43 (s, 27H); <sup>13</sup>C NMR (75 MHz, CD<sub>3</sub>CN) δ 155.54, 135.41, 127.73, 124.64, 124.45, 79.92, 60.86, 59.94, 52.36, 51.82, 28.62 (6 C), 28.37 (3 C), 20.88; IR (neat) ν (cm<sup>-1</sup>): 2978, 2933, 1711, 1486, 1392, 1366, 1311, 1257, 1156, 1047, 851, 798; HRMS (ESI<sup>+</sup>, m/z): [M+Na]<sup>+</sup> calculated for C<sub>20</sub>H<sub>35</sub>N<sub>3</sub>O<sub>6</sub>Na<sup>+</sup>: 436.2418, found 436.2422.

#### 4.1.15 Di-tert-butyl 3-(((allyloxy)carbonyl)amino)-6-methyl-3,6-dihydropyridazine-1,2-dicarboxylate (**3n**)

Prepared according to the typical procedure described above. Reaction on 16.7 mg (0.10 mmol) of dienecarbamate to afford 36.2 mg of a colorless oil, 91% yield. <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>CN) δ 6.14 (d, *J* = 8.6 Hz, 1H), 6.08–5.86 (m, 2H), 5.80 (ddd, *J* = 9.8, 4.3, 1.5 Hz, 1H), 5.71 (d, *J* = 10.2 Hz, 1H), 5.32 (d, *J* = 17.1 Hz, 1H), 5.19 (d, *J* = 10.5 Hz, 1H), 4.54 (d, *J* = 5.2 Hz, 2H), 4.23–4.07 (m, 1H), 1.54 (d, *J* = 6.6 Hz, 3H), 1.48–1.33 (m, 18H); <sup>13</sup>C NMR (75 MHz, CD<sub>3</sub>CN) δ 156.2, 135.9, 134.3 (rot. 1), 133.6 (rot. 2), 127.3, 124.3 (rot. 1), 124.1 (rot. 2), 117.7 (rot. 1), 117.6 (rot. 2), 66.0, 60.2, 60.2 (rot. 1), 60.1 (rot. 2), 52.5, 51.9 (rot. 1), 50.5 (rot. 2), 28.6 (2 C), 28.4 (4 C), 20.6 (rot. 1), 20.5 (rot. 2), 17.7; IR (neat) ν (cm<sup>-1</sup>): 3339, 2978, 2931, 1714, 1497, 1392, 1367, 1311, 1258, 1156, 1095, 1045, 800; HRMS (ESI<sup>+</sup>, m/z): [M+Na]<sup>+</sup> calculated for C<sub>19</sub>H<sub>31</sub>N<sub>3</sub>O<sub>6</sub>Na<sup>+</sup>: 420.2105, found 420.2101.

#### 4.1.16 Tert-butyl (8-methyl-1,3-dioxo-2-phenyl-2,3,5,8-tetrahydro-1H-[1,2,4]triazolo[1,2-a]pyridazin-5-yl)carbamate (**3o**)

Prepared according to the typical procedure described above. Reaction on 18.3 mg (0.10 mmol) of dienecarbamate to afford 21.7 mg of a white powder, 61% yield. Mp: 178 °C; <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>CN) δ 7.58–7.36 (m, 5H), 6.06–5.97 (m, 2H), 5.96–5.88 (m, 1H), 5.82 (dq, *J* = 10.2, 2.0 Hz, 1H), 4.40 (dq, *J* = 6.8, 2.4 Hz, 1H), 1.59 (d, *J* = 6.6 Hz, 3H), 1.42 (s, 9H); <sup>13</sup>C NMR (75 MHz, CD<sub>3</sub>CN) δ 155.2, 154.3, 152.3, 132.6, 131.4, 130.0 (2C), 129.2, 127.2 (2C), 123.2, 80.5, 59.4, 52.7, 28.4 (3C), 19.1; IR (neat) ν (cm<sup>-1</sup>): 3318, 2978, 2935, 1781, 1717, 1600, 1503, 1415, 1367, 1245, 1162, 1045, 1023, 872, 767, 690; HRMS (ESI<sup>+</sup>, m/z): [M+H]<sup>+</sup> calculated for C<sub>18</sub>H<sub>23</sub>N<sub>4</sub>O<sub>4</sub>: 359.1719, found 359.1728.

#### 4.1.17 Allyl (8-methyl-1,3-dioxo-2-phenyl-2,3,5,8-tetrahydro-1H-[1,2,4]triazolo[1,2-a]pyridazin-5-yl)carbamate (**3p**)

Prepared according to the typical procedure described above. Reaction on 16.7 mg (0.10 mmol) of dienecarbamate to afford 29.6 mg of a colorless oil, 86% yield. <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>CN) δ 7.61–7.32 (m, 5H), 6.37 (s, 1H), 6.13–6.02 (m, 1H), 6.00–5.89 (m, 2H), 5.89–5.79 (m, 1H), 5.30 (ddd, *J* = 17.3, 2.9, 1.6 Hz, 1H), 5.18 (ddd, *J* = 10.5, 2.9, 1.4 Hz, 1H), 4.54 (d, *J* = 5.3 Hz, 2H), 4.47–4.35 (m, 1H), 1.60 (d, *J* = 6.7 Hz, 3H); <sup>13</sup>C NMR (75 MHz, CD<sub>3</sub>CN) δ 154.4, 152.4, 134.1, 132.6, 131.8, 130.0 (2 C), 129.3, 127.3, 122.9, 117.7, 66.3, 62.8, 59.6, 52.9, 21.1, 19.2; IR (neat) ν (cm<sup>-1</sup>): 3310, 2935, 1781, 1716, 1522, 1503, 1415, 1291, 1222, 1145, 1038, 768, 690; HRMS (ESI<sup>+</sup>, m/z): [M+Na]<sup>+</sup> calculated for C<sub>17</sub>H<sub>18</sub>N<sub>4</sub>O<sub>4</sub>Na<sup>+</sup>: 365.1220, found 365.1222.

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## Supplementary data

Experimental details, characterization of new compounds, selected NMR and HPLC spectra. This material can be found at <http://dx.doi.org/10.1016/j.tet>.

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### Catalyst-free cycloaddition of 1,3-diene-1-carbamates with azodicarboxylates: a rapid click reaction

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