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Communication

Development of a Scalable and Sublimation-Free Route to MTAD

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ABSTRACT: The cyclic azodicarbonyl 4-methyl-1,2,4-triazoline-3,5-dione (MTAD) is a versatile and powerful reagent used mainly in cycloaddition chemistry. Though known for more than 50 years, its unsafe preparation, as well as purification by sublimation, hampered its widespread applicability on a larger scale. Herein we report a scalable and safe route to MTAD, which avoids the generation of methyl isocyanate. Moreover, we demonstrate that sublimation can be circumvented by the application of judicious oxidation conditions, followed by simple filtration. Overall, up to 25 g of MTAD was prepared in a single batch from commercial starting materials in three steps, with recrystallization serving as the only purification in the sequence. When employed in dearomative methodologies, the MTAD obtained by this protocol displayed synthetic efficiency equivalent to that of MTAD purified by sublimation.

KEYWORDS: *MTAD, 1,2,4-triazoline-3,5-dione, arenophile, dienophile, urazole*

Five-membered cyclic azodicarbonyls (triazolinediones, TADS) encompass an interesting class of materials capable of undergoing a range of transformations, including Diels–Alder cycloadditions,[1] [2+2] cycloadditions,[2] and Alder-ene reactions[3] (Figure 1A). As a result of their high reactivity and widespread reaction utility, these molecules have found application in a vast range of scientific areas, including the tagging of biological compounds,[4] development of functional materials,[5] and organic synthesis.[6]

More recently, our group has been interested in these compounds, specifically 4-methyl-1,2,4-triazoline-3,5-dione (MTAD, **1**), for their use in visible-light-mediated dearomative cycloadditions (Figure 1A).[7] Given the pervasiveness of MTAD in our laboratory, large quantities are required for reaction discovery and natural product total synthesis.[7c,8] To date, our lab has produced well over several kilograms of **1**; however, we noted safety and scalability concerns in our initial route. Herein, we disclose a scalable synthesis of MTAD, which obviates the use of toxic materials and intermediates, requires only a single purification step, and removes the necessity for sublimation to attain a high purity of **1**.

It should be noted that our initial route to MTAD (**1**) was a modification of a known literature procedure (Figure 1B).[1a,9] Beginning with dimethylurea (**2**), nitrosylation yielded *N*-nitroso compound **3**, which underwent purification *via* separatory extraction with dichloromethane. Extreme precaution was taken when handling and storing **3**, as similar compounds are known to be highly carcinogenic.[10] Thermolysis of **3** in boiling water releases methylisocyanate, a volatile and toxic reagent, which is trapped with ethyl carbazate (**4**) *in situ* to yield **5** in quantitative yield.[11] Without purification, subsequent addition of KOH and heating induces cyclization to the corresponding 4-methylurazole (**6**); this was isolated by acidification and evaporation of solvents, extraction with hot ethanol, filtration, and recrystallization in water to obtain high purities of **6**. This sequence suffered from reproducibility issues, specifically in the final recrystallization step. As an auxiliary safety concern, premature addition of KOH before thermolysis of **3** is complete can induce the formation of diazomethane, which could violently decompose. As a result of these limitations, the overall production of urazole **6** *via* this procedure was limited to roughly 10 g in a single pass.

In our work, sublimation served as the bottleneck, as even with the employment of a relatively large sublimation apparatus (see Supporting Information), we were only capable of generating around 5 g of MTAD per 6 h purification. This step also demonstrated a large variability with respect to yield, sometimes by as much as 30%, which was attributed to the heat-induced decomposition of MTAD at the sublimation temperature (50 °C).

The combination of concerns and shortcomings, including the handling of carcinogenic intermediates, formation of toxic gases, irreproducibility of product formation, and purification through sublimation, limited our synthetic use of **1**. Thus, we sought to develop an improved route to **1** that was efficient, safe, and scalable to provide ample amounts for use in our laboratory. We gained inspiration from methodologies that utilized carbonyldiimidazole (CDI) as an isocyanate surrogate, which, in combination with amines, provided cyclization precursors to 4-substituted urazoles (Figure 1C). However, following the conditions described using methylamine,[12] purification by silica gel chromatography would be required to obtain pure **5**. We initially hypothesized that this separation would not be necessary and that **5** could be cleanly cyclized to yield **6** in the presence of imidazole. Isolation would simply

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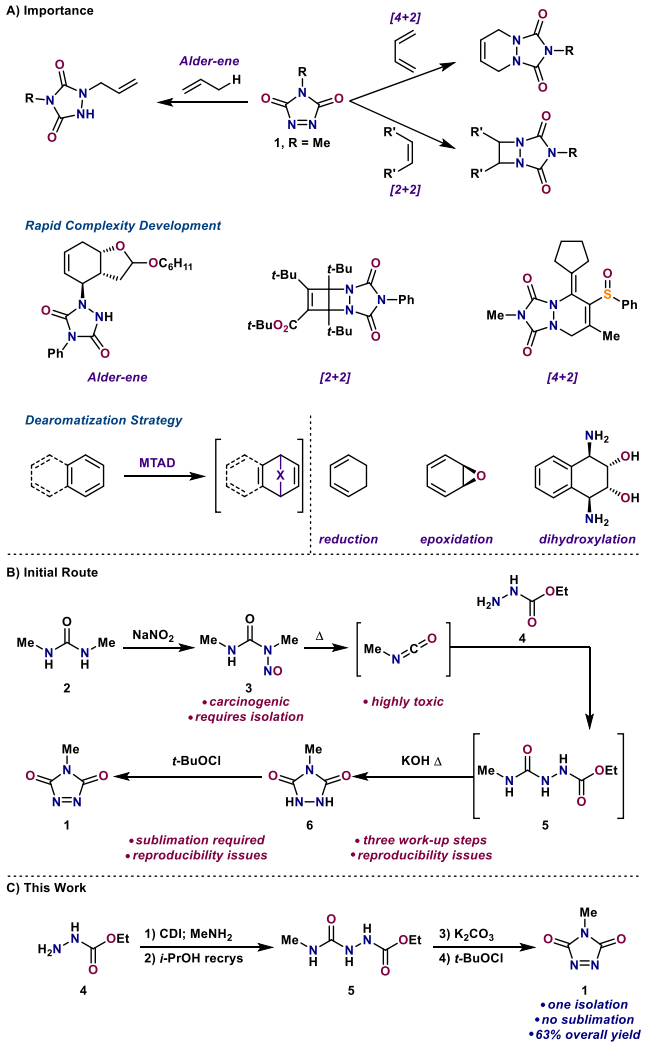
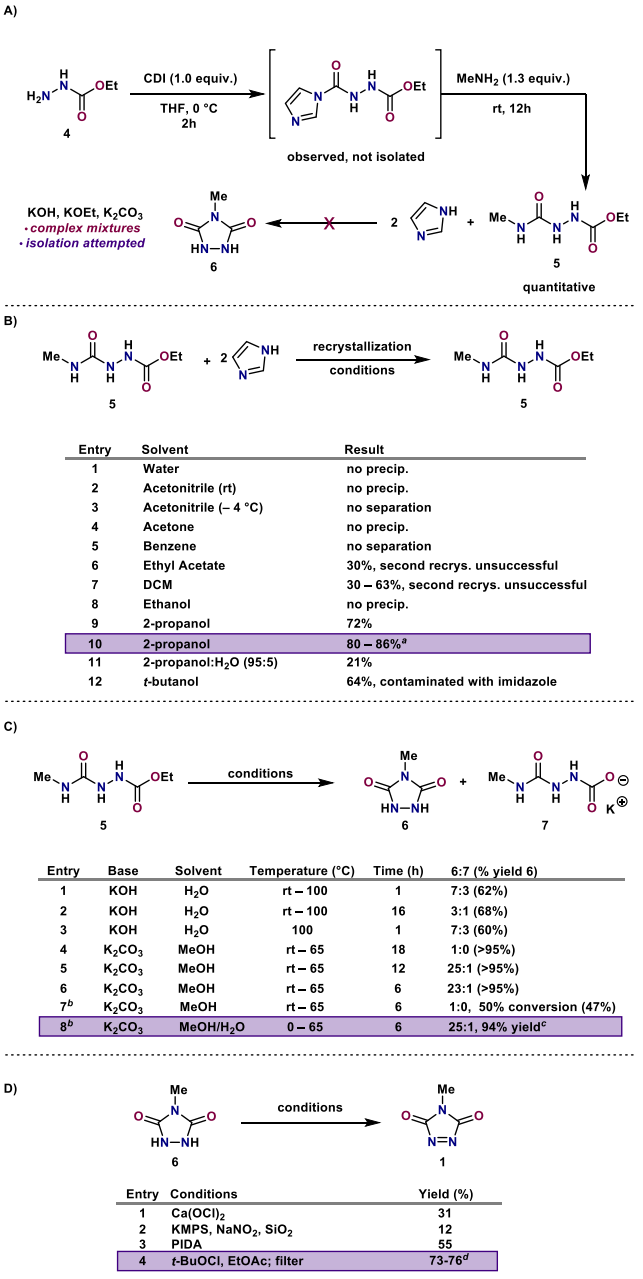


Figure 1. (A) Common methodologies employing MTAD and their applications. (B) First-generation route to synthesize urazole. (C) The work described herein.

involve protonation of imidazole in the presence of **6**, which could be separated through either recrystallization or extraction.

Indeed, we were pleased to find that reaction with ethyl carbazate (**4**) and CDI at 0 °C followed by the addition of aqueous methylamine furnished **5** in a single step and quantitative yield (Figure 2A). We discovered that other viable options such as triphosgene were either highly toxic or gave inferior yields. Unfortunately, attempts to directly cyclize **5** with 2 equiv of imidazole byproduct still present in solution gave unsatisfactory and inconsistent yields; consequently, we aimed to develop an efficient separation of **5** (Figure 2B).[13] Initially, we attempted a series of acid/base extractions with a range of pH levels in an attempt to form the salt of either imidazole or **5** selectively. However, all our efforts led to minimal, if not ineffective, separation or rapid decomposition of **5** at more extreme pH levels. We then reasoned that the solubility profiles of imidazole and **5** might allow for purification *via* recrystallization. Though both compounds either were completely soluble or showed no separation in a variety of solvents, we eventually arrived at ethyl acetate as a viable solvent to separate **5**, albeit in 30% yield. However, attempts to perform a second recrystallization to improve the



Entry	Solvent	Result
1	Water	no precip.
2	Acetonitrile (rt)	no precip.
3	Acetonitrile (– 4 °C)	no separation
4	Acetone	no precip.
5	Benzene	no separation
6	Ethyl Acetate	30%, second recrys. unsuccessful
7	DCM	30 – 63%, second recrys. unsuccessful
8	Ethanol	no precip.
9	2-propanol	72%
10	2-propanol	80 – 86%[a]
11	2-propanol:H_2O (95:5)	21%
12	*t*-butanol	64%, contaminated with imidazole

Entry	Base	Solvent	Temperature (°C)	Time (h)	6:7 (% yield 6)
1	KOH	H_2O	rt – 100	1	7:3 (62%)
2	KOH	H_2O	rt – 100	16	3:1 (68%)
3	KOH	H_2O	100	1	7:3 (60%)
4	K_2CO_3	MeOH	rt – 65	18	1:0 (>95%)
5	K_2CO_3	MeOH	rt – 65	12	25:1 (>95%)
6	K_2CO_3	MeOH	rt – 65	6	23:1 (>95%)
7[b]	K_2CO_3	MeOH	rt – 65	6	1:0, 50% conversion (47%)
8[b]	K_2CO_3	MeOH/H_2O	0 – 65	6	25:1, 94% yield[c]

Entry	Conditions	Yield (%)
1	$Ca(OCl)_2$	31
2	KMPS, $NaNO_2$, SiO_2	12
3	PIDA	55
4	*t*-BuOCl, EtOAc; filter	73-76[d]

Figure 2. (A) Preparation of **5**. (B) Purification and separation of **5** and imidazole. (C) Optimization of cyclization: base (2.0 equiv), solvent (1.0 M), **5** (1.0 mmol). (D) Conditions to oxidize urazole: [a]Two crops were collected. [b]Reaction was performed on 0.09 mol scale. [c]Dimethylmalonic acid was used as internal standard. [d]From **5**.

yields were unsuccessful. Initial use of dichloromethane provided a moderate yield of 63%; however, it was found to vary widely. Finally, we noted that *i*-PrOH maintained high solubility of imidazole even at −20 °C, while **5** proved to be fairly insoluble and provided 86% yield after collecting two crops (<2% imidazole impurity by NMR). Notably, we found that exclusion of water was necessary for high yields during this recrystallization, as 5% of water by volume completely suppressed the crystallization of **5**.

The aforementioned cyclization conditions (KOH and water, reflux) led to a 7:3 mixture of urazole and byproduct **7**, which could be observed by ^{1}H NMR (Figure 2C). Further optimization eventually led to potassium carbonate in

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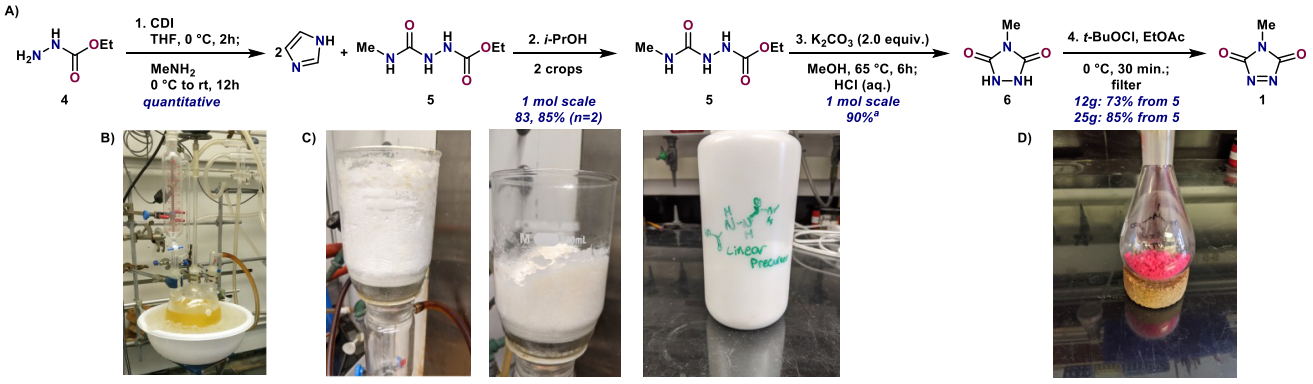

Figure 3. (A) Scale-up conditions: step 1, ethyl carbazate (**4**) (1.0 equiv), carbonyldiimidazole (1.0 equiv), THF (1.0 M), 0 °C; $MeNH_2$ (1.3 equiv, 40% aq), 0 °C to rt, 12 h; step 2, *i*-PrOH, two crops; step 3, **5** (1.0 equiv), K_2CO_3 (2.0 equiv), MeOH (1.0 M), 65 °C, 6 h; HCl (4.0 equiv, 12 M, aq); step 4, urazole (**6**) (1.0 equiv), *t*-BuOCl (1.05 equiv), EtOAc (0.75−1.0 M), 0 °C, 30 min. (B) Reaction vessel to yield **5**. (C) Left, first crop filtration; middle, second crop filtration; right, 137 g of **5**. (D) 20 g of MTAD produced in one step.

methanol, providing urazole in near-quantitative yield, though the yields varied significantly from batch to batch on a large scale. It was eventually found that the low solubility of salts formed seized the stirring on larger scales, ultimately halting the reaction around 50% conversion. This issue was circumvented by the addition of minor amounts of water (10−13 vol %) 2 h into the reaction, which eliminated stirring issues without affecting the overall yield. On the other hand, when water was added at the beginning of the reaction, the yield was reduced by approximately 10%, due to increased formation of **7**.

Once employed, these conditions provided the product in 94% yield, with a 25:1 ratio of **6**:**7**. Following acidification with HCl, solvent removal, and rigorous drying, we were left with an analytically pure mixture of urazole **6** and KCl. Importantly, we postulated that the KCl was a benign byproduct and took the crude mixture forward for the subsequent oxidation step to avoid hot ethanol extraction and recrystallization, previously used for separation.

In an effort to eliminate the need for sublimation, we attempted to follow a number of literature procedures that claim to oxidize 4-methylurazole (**6**) to MTAD (**1**) in near-quantitative yields;[14] however, unfortunately, we found that none of these methods were successful in our hands (Figure 2D). Revisiting our original oxidation conditions using *t*-BuOCl,[15] we postulated that of the compounds present in solution after oxidation (MTAD, KCl, urazole, *t*-BuOH, and HCl), only MTAD, *t*-BuOH, and HCl are soluble in ethyl acetate. As a result, we were pleased to find that oxidation of the urazole/KCl mixture with *t*-BuOCl followed by a simple filtration and solvent removal yielded analytically pure MTAD.

With the route to MTAD optimized, we investigated the scalability of this approach (Figure 3). The initial step was performed on 1 mol scale to provide over 130 g (83%, 87%, *n* = 2) of **5** in a single pass, and we have synthesized nearly 1 kg of this intermediate to date using this methodology. The recrystallization to remove 2 equiv of imidazole was independent of scale, with a constant volume (mL/g) of *i*-PrOH with respect to crude **5** yielding consistent results. Linear cyclization precursor **5** is benchtop stable open to air for at least 2 months and indefinitely stable at 4 °C under an atmosphere of nitrogen. Cyclization of **5** on 1 mol scale provided a urazole/KCl mixture which can be oxidized as needed.

Next, we compared the synthetic utility of the filtered MTAD, prepared as described herein, with the freshly sublimed batch by employing them in the enantioselective carboamination of benzene, previously developed in our group (Figure 4). We synthesized 12 g of MTAD in a single batch

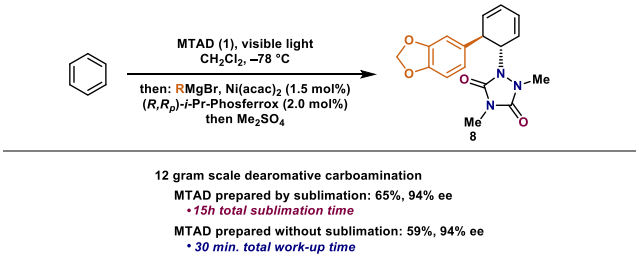

Figure 4. Comparison of MTAD purification procedures relative to a known reaction. Conditions: benzene (10 equiv), **1** (1.0 equiv), CH_2Cl_2, visible light, −78 °C; then $[Ni(acac)_2]$ (1.5 mol%), (R,Rp)-*i*-Pr-Phosferrox (2.0 mol%), 3,4-methylene dioxyphenylmagnesium bromide (2.5 equiv), CH_2Cl_2 THF, −78 to 25 °C; then Me_2SO_4, K_2CO_3.

without sublimation (73% from **5**) and used it in a Ni-catalyzed enantioselective *trans*-1,2-carboamination. We found only a minor decrease in the overall yield (59% *vs* 65%) and no erosion in enantioselectivity when compared to the reaction using sublimed MTAD.

MTAD (**1**) is a molecule of high synthetic importance, and derivatives thereof have seen widespread utility in various fields. Many previous syntheses, including our first route, have relied on the formation of methyl isocyanate, multiple tedious purification steps, or final sublimation to yield pure material. We demonstrated that CDI and methylamine can be used to bypass the generation of methyl isocyanate, where recrystallization from *i*-PrOH is the only purification in this sequence. Cyclization with K_2CO_3 and subsequent HCl neutralization provides excellent yields of urazole, which can be stored as a mixture with KCl until oxidation. The requirement for sublimation can be bypassed through a simple filtration and drying under the reduced pressure to remove the unwanted salts and volatile byproducts. With regard to scalability, we were able to prepare urazole on a 1 mol scale. We isolated 25 g of MTAD in a single pass, which previously would have required several sublimations, and demonstrated that the dearomatization provides results similar to those obtained with

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freshly sublimed MTAD. This method provides rapid access to MTAD and could also find potential applications toward the preparation of other diverse members in the urazole and triazolinedione family.

EXPERIMENTAL PROCEDURES

General Considerations. Tetrahydrofuran (THF), methanol, and *i*-PrOH were purchased from Fisher and used without further purification. Ethyl carbazate was purchased from Alfa Aesar. Carbonyldiimidazole (CDI) was purchased from Oakwood. Methylamine (40% aq) was purchased from Sigma-Aldrich. K_2CO_3 (anhydrous) was purchased from Fisher. *t*-BuOCl was prepared according to the known literature procedure.[15] All other reagents were purchased from commercial suppliers and used without further purification.

^{1}H and ^{13}C NMR spectra were recorded on Varian Unity 500 (500 MHz, ^{1}H; 126 MHz, ^{13}C) MHz or Bruker 500 (500 MHz, ^{1}H; 126 MHz, ^{13}C) spectrometers. Spectra are referenced to residual chloroform (δ = 7.26 ppm, 1H; 77.16 ppm, ^{13}C) or residual methanol (δ = 3.31 ppm, ^{1}H; 49.0 ppm, ^{13}C). Chemical shifts are reported in parts per million (ppm). Multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). Coupling constants *J* are reported in hertz (Hz). Mass spectrometry (MS) was performed by the University of Illinois Mass Spectrometry Laboratory. Electron impact (EI^+) spectra were performed at 70 eV using methane as the carrier gas, with time-of-flight (TOF) mass analyzer. Chemical ionization (CI^+) spectra were performed with methane reagent gas, with either a double focusing sector field (DFSF) or time-of-flight (TOF) mass analyzer. Electrospray ionization (ESI^+) spectra were performed using a time-of-flight (TOF) mass analyzer. Data are reported in the form of *m*/*z* (intensity relative to the base peak = 100). Infrared (IR) spectra were measured neat on a Perkin-Elmer spectrum BX FT-IR spectrometer. Peaks are reported in cm^{-1} with indicated relative intensities: s (strong, 0−33% T); m (medium, 34−66% T), w (weak, 67−100% T), and br (broad). Melting points were measured on a Buchi B-540 meting point apparatus and are uncorrected. Optical rotations were recorded on a Jasco P-2000 polarimeter at 589 nm and are reported in units of 10^{-1} (deg cm^2 g^{-1}). HPLC was performed on a Shimadzu Prominence HPLC system with an SPDM20A UV/vis photodiode array detector (220 nm).

Preparation of Ethyl 2-(Methylcarbamoyl)hydrazine-1-carboxylate (5). To a three-neck, 2 L round-bottom flask, equipped with a mechanical stirrer and thermometer, were added THF (1.0 L, 1.0 M) and ethyl carbazate (104.1 g, 1.0 mol, 1.0 equiv), and the mixture was cooled in an ice bath under an atmosphere of nitrogen. CDI (162.2 g, 1.0 mol, 1.0 equiv) was added slowly over 15 min, regulating the internal temperature to remain below 15 °C, and allowed to stir at 0 °C for 2 h. Thereafter, methylamine (40 wt% in H_2O, 113 mL, 1.3 mol, 1.3 equiv) was added in a single portion, and the flask was removed from the ice bath and allowed to warm up to room temperature. Full conversion was noted after 4 h (TLC); however, the solution can be stirred overnight with no noticeable loss in yield. After completion, the solvent was removed under reduced pressure (bath temperature: 40 °C, pressure: 20−45 mbar) until a thick oil formed. The remaining solvent was removed under vacuum (<1 mbar) with stirring (bath temperature: 35 °C, time: 16 h) until the oil solidified. At this point, the purity of the crude material was analyzed by ^{1}H NMR (D_2O), yielding near quantitative conversion to the product along with 2.0 equiv of imidazole. The residue solid was recrystallized from *i*-PrOH (3.8 L, reflux) and left overnight at room temperature. The solution was filtered through a glass frit, and the filter cake was dried on the frit for 2 h with suction, then washed with cold *i*-PrOH (2 × 300 mL). The mother liquid and filtrates were combined and reduced to an overall volume of 1.0 L and placed in a freezer (−20 °C) to recrystallize overnight. The resulting mixture was filtered, washed with *i*-PrOH (2 × 100 mL), and dried under vacuum. Both crops were combined to yield 137.2 g (85%) of **5**. General note: If imidazole is present in a quantity greater than 5% by ^{1}H NMR, another wash with *i*-PrOH is required for adequate reproducibility in the next step.

^{1}H NMR: (500 MHz, D_2O) δ 4.15 (q, *J* = 7.1 Hz, 1H), 2.69 (s, 2H), 1.23 (t, *J* = 7.1 Hz, 1H).

^{13}C NMR: (126 MHz, D_2O, CD_3OD) δ 162.1, 159.8, 63.8, 26.9, 14.7.

IR: 3312 (m, br), 3213 (m,br), 2992 (m, br), 1720 (m), 1706 (m), 1660 (s), 1543 (m), 1278 (s), 1223 (s), 660 (m).

m.p.: 140−144 °C.

HRMS: (ESI-TOF, *m*/*z*) calcd for $C_5H_{12}N_3O_3^{\bullet+}$ $[M+H]^{\bullet+}$, 162.0873 found: 162.0879.

The analytical data were in accordance with previously reported values.[9]

Preparation of 4-Methyl-1,2,4-triazolidine-3,5-dione (6). To a 2 L round-bottom flask were added **5** (161.6 g, 1 mol, 1.0 equiv) and methanol (1.0 L, 1.0 M), and the mixture was stirred and cooled in an ice bath for approximately 30 min. Potassium carbonate (276.4 g, 2 mol, 2.0 equiv) was added in a single portion, and the flask was equipped with a reflux condenser and heated to 65 °C under an atmosphere of nitrogen. After 2 h, stirring halted due to formation of solids, which was resolved by the addition of H_2O (100 mL) with heating continued for an additional 12 h. The reaction mixture was then cooled to 0 °C before dropwise acidification with concentrated HCl (400 mL, 12 M aq., 4.0 mol, 4.0 equiv) to a pH of 1. [***Caution!*** *This step is highly exothermic and generates large quantities of* CO_2.] The solvent was first removed under reduced pressure (bath temperature, 40 °C; pressure, 150 mbar), and the bath temperature and pressure were adjusted to 80 °C and 20 mbar, until most of the water was removed, and the mixture could be scraped into a free-flowing solid. The solid **6**/KCl mixture was then placed under vacuum (<1 mbar) overnight and then placed in a vacuum desiccator for 2 days before further use. The solid (25 wt% of **6**), was stored until oxidation to **1** was needed. The yield of this transformation was determined to be 90% by ^{1}H NMR using dimethyl malonic acid as an internal standard in D_2O.

^{1}H NMR: (500 MHz, D_2O) δ 3.06.

^{13}C NMR: (126 MHz, D_2O, CH_3OH) δ 156.6, 25.1.

IR: 3312 (m, br), 3007 (s, br), 2762 (m, br), 1671 (s), 1491 (s), 1269 (m), 983 (w), 606 (s).

m.p.: 233−235 °C.

HRMS: (ESI-TOF, *m*/*z*) calcd for $C_3H_5N_3O_2Na^+$ $[M+Na]^+$, 138.0279 found: 138.0274.

Preparation of 4-Methyl-3*H*-1,2,4-triazole-3,5(4*H*)-dione (1) from 5. To a 500 mL round-bottom flask charged with **5** (25 g, 155 mmol, 1.0 equiv) and methanol (155 mL, 1.0 M) was added potassium carbonate (42.9 g, 310 mmol, 2.0 equiv) in a single portion. The round-bottom flask was placed into an oil bath, equipped with a reflux condenser, and heated to 65 °C under an atmosphere of nitrogen. After 2 h, stirring

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halted due to formation of solids, which was restored by the addition of H_2O (20 mL) with heating continued for an additional 12 h. The reaction was then removed from the oil bath and cooled to 0 °C before dropwise acidification with concentrated HCl (52 mL, 620 mmol, 4.0 equiv) to a pH of 1. The solvent was removed under reduced pressure (bath temperature, 40 °C; pressure, 150 mbar). The bath temperature and pressure were adjusted to 80 °C and 20 mbar, until most of the water was removed, and the mixture could be scraped into a free-flowing solid. The solid **6**/KCl mixture was then placed in a vacuum desiccator for 2 days before use.

For the oxidation step, the above-obtained **6**/KCl mixture was suspended in EtOAc (206 mL, 0.75 M), and the solution was cooled to 0 °C for 30 min. From this point forward, all reactions and manipulations were performed in the absence of light. Then *t*-BuOCl[15] (17.7 g, 163 mmol, 1.05 equiv) was added dropwise, and a gentle stream of nitrogen was blown through the headspace of the reaction (needle vent) to remove HCl. The ice bath was removed, and the solution was allowed to stir for 1 h. Afterward, the solution was directly filtered through a fritted funnel and washed with EtOAc (100 mL). The solvent was removed under reduced pressure at 35 °C and furnished a bright pink solid, which was placed under the vacuum (<1 mbar) for 10 min. The MTAD (**1**, 12.8 g, 113 mmol, 73%) was obtained and stored in a vial protected from light and condensation (see SI) in the freezer (−4 °C).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 3.24 (s, 3H).

^{13}C NMR: (126 MHz, $CDCl_3$) δ 159.3, 26.9.

IR: 3038 (w,br), 1770 (m), 1713 (s), 1439 (m), 1379 (m), 1271 (m), 949 (m), 738 (s).

m.p.: 99−101 °C.

The analytical data were in accordance with previously reported values.[16]

Preparation of 4-Methyl-3*H*-1,2,4-triazole-3,5(4*H*)-dione (1) from Isolated 6/KCl Mixture. The yield of the previous reaction to form **6** was determined by IS-^{1}H NMR. A quantity of the crude mixture which contained 25 g of **6** (217 mmol, 1.0 equiv), was added to a 500 mL round-bottom flask. EtOAc (217 mL, 1.0 M) was added, and the solution was cooled in an ice bath for 30 min. At this point all manipulations were performed in the absence of light and under a blanket of nitrogen. Neat *t*-BuOCl[15] (24.8 g, 228 mmol, 1.05 equiv) was added dropwise, and a gentle stream of nitrogen was blown through the headspace of the reaction (needle vent) to remove HCl. The ice bath was removed, and the solution was allowed to stir for 1 h. The compound was then filtered through a glass frit and washed with EtOAc (200 mL), the solvent was removed under reduced pressure, and the product was placed under the vacuum (<1 mbar) for approximately 20 min to ensure removal of all solvents. [Note: Prolonged exposure of **1** to high vacuum could gradually results in product loss via sublimation.] The MTAD (**1**, 20.8 g, 184 mmol, 85%) was obtained and stored in three 20 mL vials protected from light and condensation (see SI) in the freezer (−20 °C) until use.

Preparation of 1-((1*S*,6*R*)-6-(Benzo[*d*][1,3]dioxol-5-yl)cyclohexa-2,4-dien-1-yl)-2,4-dimethyl-1,2,4-triazolidine-3,5-dione (7). In an oven-dried 1 L media bottle, MTAD (**1**, 12.00 g, 106 mmol, 1.0 equiv) was dissolved in anhydrous CH_2Cl_2 (531 mL) under nitrogen atmosphere and cooled to −78 °C. Benzene (94.6 mL, 1.06 mol, 10 equiv) was slowly added, and the solution was stirred for 5 min. The pink solution was irradiated with LED lights at −78 °C until complete loss of color. Upon decolorization, the LED lights were turned off, and a solution of [Ni(acac)$_2$] (408.9 mg, 1.59 mmol, 1.5 mol%) and (R_pR_p)-*i*-Pr-Phosferrox (1.02 g, 2.12 mmol, 2.0 mol%) in CH_2Cl_2 (64 mL) (pre-stirred at 20 °C for 45 min then cooled to −78 °C) was added, followed by dropwise addition of 3,4-methylenedioxyphenylmagnesium bromide (88.4 mL, 3.0 M in THF, 265 mmol, 2.5 equiv) at the rate to keep the internal temperature below −65 °C. After addition, the cold bath temperature was warmed to −45 °C and allowed to slowly warm to 0 °C over 3 h. Reaction vessel was removed from the cold bath, and after stirring at room temperature for 15 min, Me_2SO_4 (50.3 mL, 530 mmol, 5.0 equiv) and K_2CO_3 (36.0 g, 265 mmol, 2.5 equiv) were added sequentially, and the resulting mixture was stirred at 35 °C for 8 h. The mixture was cooled to 0 °C and 5% aq NH_4OH (300 mL) was added, the phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 400 mL). The combined organic extracts were washed with water (2 × 400 mL) and brine (400 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, hexanes:EtOAc = 5:1 → 3:1) to give the desired compound as a colorless solid [20.6 g, 62.9 mmol, 59%, 97:3 er].

Enantiomeric ratio was determined with HPLC analysis using a Diacel Chiracel OJ-3 column, 50% *i*-PrOH in hexanes, 0.8 mL/min t_R(minor) = 9.8 min, t_R(major) = 14.5 min.

R_f: 0.36 (SiO_2, hexanes:EtOAc = 1:1).

$[\alpha]_D^{24}$: +275.9 (c = 0.78 in $CHCl_3$).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 6.75 (d, J = 1.8 Hz, 1H), 6.68 (d, J = 8.0 Hz, 1H), 6.64 (dd, J = 8.0, 1.8 Hz, 1H), 6.15−6.10 (m, 1H), 6.08−6.03 (m, 1H), 5.92 (d, J = 1.5 Hz, 1H), 5.91 (d, J = 1.5 Hz, 1H), 5.83 (ddt, J = 9.3, 3.1, 1.0 Hz, 1H), 5.68 (ddq, J = 9.7, 3.1, 1.0 Hz, 1H), 5.12 (dt, J = 13.6, 2.9 Hz, 1H), 3.89 (dt, J = 13.6, 3.1 Hz, 1H), 3.18 (s, 3H), 2.89 (s, 3H).

^{13}C NMR: (126 MHz, $CDCl_3$) δ 156.1, 155.1, 147.9, 147.0, 135.4, 130.9, 126.6, 125.5, 123.4, 121.5, 108.7, 108.2, 101.2, 61.0, 44.7, 35.1, 25.5.

IR: (ATR, neat, cm^{-1}) 2895 (m), 2250 (w), 1767 (w), 1700 (s), 1481 (m), 1035 (m), 912 (w), 725 (m).

m.p.: 121−122 °C.

HRMS: (ESI-TOF, m/z) calcd For $C_{17}H_{17}N_3O_4Na$ [M+Na]$^+$ calc.: 350.1117; found: 350.1115.

The analytical data were in accordance with previously reported values.[8a]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.oprd.0c00470.

Procedure for storage of MTAD (**1**) and analytical data; ^{1}H and ^{13}C NMR spectra of compounds **1**, **5**, **6**, and **7** (PDF)

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Notes

The authors declare no competing financial interest.

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