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Unprecedented Intramolecular [4 + 2]-Cycloaddition between a 1,3-Diene and a Diazo Ester

Huang Qiu,[†,‡,§] Harathi D. Srinivas,[†] Peter Y. Zavalij,[‡] and Michael P. Doyle*[,†]

[†]Department of Chemistry, The University of Texas at San Antonio, San Antonio, Texas 78249, United States
[‡]Department of Chemistry and Biochemistry, University of Maryland, College Park, Maryland 20742, United States
[§]Shanghai Engineering Research Center of Molecular Therapeutics and New Drug Development, School of Chemistry and Molecular Engineering, East China Normal University, Shanghai 200062, China

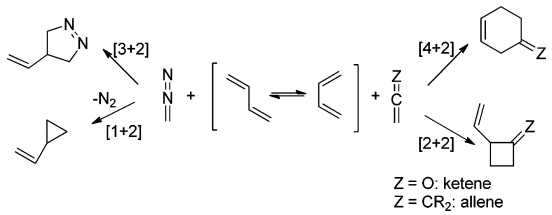
Supporting Information

ABSTRACT: Diazo compounds that are well-known to undergo [3 + 2]-cycloaddition provide the first examples of the previously unknown [4 + 2]-cycloaddition with dienes that occur thermally under mild conditions and in high yields. Reactions are initiated from reactants prepared from propargyl aryldiazoacetates that undergo gold(I)-catalyzed rearrangement to activated 1,3-dienyl aryldiazoacetates. These reactions proceed to mixtures of both [4 + 2]-cycloaddition and the 1,3-dienyl aryldiazoacetate after long reaction times. At short reaction times, however, both *E*- and *Z*-1,3-dienyl aryldiazoacetates are formed and, after isolation, thermal reactions with the *E*-isomers form the products from [4 + 2]-cycloaddition with $\Delta H^{\ddagger}_{298}$ = 15.6 kcal/mol and $\Delta S^{\ddagger}_{298}$ = −27.3 cal/(mol·°C). The *Z*-isomer is inert to [4 + 2]-cycloaddition under these conditions. The Hammett relationships from aryl-substituted diazo esters (ρ = +0.89) and aryl-substituted dienes (ρ = −1.65) are consistent with the dipolar nature of this transformation.

In the long history of Diels−Alder reactions there has not been a reported example of [4 + 2]-cycloaddition between a diene and a diazo compound.[1] Their isoelectronic allene and ketene counterparts, however, do undergo these reactions and have received considerable attention. Concerted thermal [4 + 2]-cycloaddition reactions of dienes with highly polarized allenes have been extensively investigated,[2] but favorable competing stepwise [2 + 2]-cycloaddition reactions diminish their synthetic importance. Transition-metal-catalyzed allene−diene cycloaddition reactions, although recent in their discovery,[3] have circumvented this competition and become a mainstay of new process developments.[4] Ketenes readily undergo [2 + 2]-cycloaddition[5] and, recently, [4 + 2]-cycloaddition reactions, but for the latter only with highly activated diene equivalents[6] or with the aid of suitable catalysts.[7] In contrast, diazo compounds commonly react with one double bond of dienes by dipolar cycloaddition[8] or, following dinitrogen extrusion, by cyclopropanation[9] (Scheme 1), but not by [4 + 2]-cycloaddition.

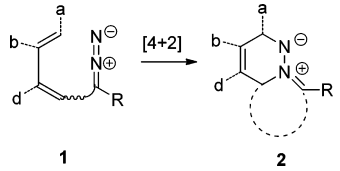
That [4 + 2]-cycloaddition reactions occur with allenes and ketenes, but not with diazo compounds, suggested to us that the facility with which diazo compounds undergo dipolar cycloaddition prevents [4 + 2]-cycloaddition and that, if dipolar cycloaddition could be electronically and/or sterically inhibited,

Scheme 1. Reactions of Dienes with Diazo Compounds, Allenes and Ketenes



perhaps [4 + 2]-cycloaddition should be observed. Inhibition of dipolar cycloaddition with deactivation of the C−C double bond toward dipolar cycloaddition would require constraints in the alignment of the diazo functional group with either one of the double bonds of the diene. To design such a system we were encouraged by a recent report by Brewer et al. of a polar intramolecular [4 + 2]-cycloaddition of aryl-1-aza-2-azoniaallene salts that produced protonated azomethine imines.[10] One such structural design appropriate for intramolecular [4 + 2]-cycloaddition between a diene and a diazocarbonyl compound (Scheme 2) would produce a dipolar azomethine species (**2**) that

Scheme 2. Proposed Intramolecular [4 + 2]-Cycloaddition of Dienes with Diazo Compounds



could serve as a suitable stabilized product. Add to this design activation of the diene with electron-donating substituents, as well as further stabilization of the dipolar azomethine product, and this cycloaddition reaction appears feasible. However, additional constraints that include the linkage between the diene and the diazo units, as well as the geometry of attachment to the diene, remain unresolved.

For this investigation we chose to synthesize diene-linked aryldiazoacetates **1** (Scheme 3). This structure contains the

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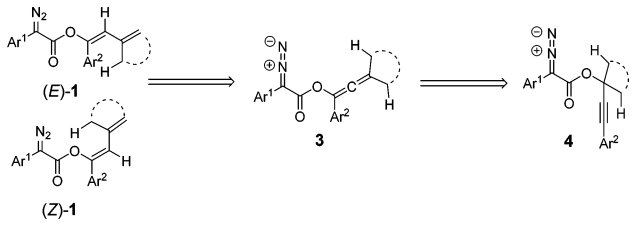
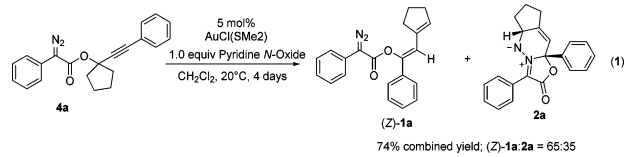
Scheme 3. Synthesis of Diene-Linked Aryldiazoacetates



elements of activation and stabilization that we believe to be requirements for diene−diazo [4 + 2]-cyclization.[11] Gold-catalyzed 1,3-acyloxy migration of propargylic carboxylates is known to form allene intermediates (**3**) suitable for diene formation, and the generation of dienes from propargylic esters through a gold(I)-catalyzed 1,3-migratory cascade involving allene intermediates has been established.[12]

Treatment of propargyl phenyldiazoacetates **4** with a broad selection of neutral gold catalysts under various conditions of temperatures and solvents gave either no reaction or complex product mixtures (Supporting Information (SI), Table S1) that suggested the formation of diene **1**, although not in high yield. Due to the possibility that proton transfer might be limiting this process, a variety of bases were used as additives but without improvement in the yield of **1** (see SI, Table S2). However, reactions using a pyridine-*N*-oxide in stoichiometric amounts resulted in the formation of (*Z*)-**1** and a product anticipated from diene-diazo [4 + 2]-cycloaddition (**2**) in a combined yield of up to 74% (eq 1). Uses of pyridine-*N*-oxides as bases rather than



oxygen transfer agents have been reported.[13] $AuCl(Me_2S)$ and 4-chloropyridine-*N*-oxide were optimal for the reaction performed in toluene at 20 °C (SI, Table S3). Structures for both the diene (*Z*)-**1e** and cycloaddition product **2f** were confirmed by X-ray diffraction (Figure 1). Both the cascade reaction

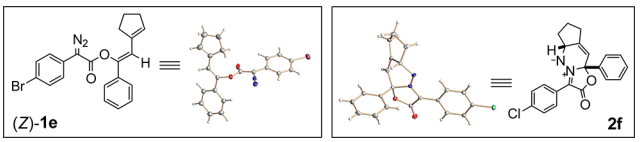


Figure 1. X-ray structures of diene (*Z*)-**1e** and cycloaddition product **2f**. CCDC 1422281 contains supplementary crystallographic data for (*Z*)-**1e**, and CCDC 1423163 contains supplementary crystallographic data for **2f**.

anticipated from initial dinitrogen extrusion by the catalyst at the diazo carbon[14] and product(s) from dipolar cycloaddition between the diazo compound and diene were not observed, and the absence of the cascade reaction product indicated a high preference of the gold catalyst for reaction at the carbon−carbon triple bond rather than with the phenyldiazoacetate. Homologous products were formed using the cyclohexyl analogue of **4a**, but not with the dimethyl analogue, and replacing the phenyl group of the alkyne with TMS prevented the gold-catalyzed reaction presumably due to steric restrictions.

The influence of aryl substituents, including ethers, halides, nitro, trifluoromethyl, alkyl, and aryl, of both the diazoacetate and the propargyl functional groups was examined to further understand the formation of diene-linked aryldiazoacetates and the diene−diazo [4 + 2]-cycloaddition process (SI, Table S4). The variation in the ratio of products (*Z*)-**1**:**2** was low (26:74 to 50:50) despite high levels of conversion (70−94% yields), although strongly electron-withdrawing substituents on the aryl group visibly slowed the reaction rate. That the ratio of products was minimally influenced by substituents and, in separate experiments, by temperature or solvent, suggested that the two products were formed from a common intermediate, which in the case of the apparent cycloaddition product **2** could be (*E*)-**1**.

To determine if both (*E*)-**1** and (*Z*)-**1** were formed initially after which (*E*)-**1** underwent cycloaddition to **2**, we examined the gold-catalyzed reaction at shorter reaction times. If (*E*)-**1** was the precursor to **2**, this diene should be observed as an initially formed product. Fortunately, during 6−12 h of reaction time at room temperature with relatively low conversion of **4**, both (*E*)-**1** and (*Z*)-**1** were obtained at apparent equivalent rates. Isolation of (*E*)-**1a** by column chromatography at room temperature provided sufficient material to examine if this diene could undergo uncatalyzed formation of **2a** or if cycloaddition required the intervention of a catalyst. In the absence of catalyst, isolated (*E*)-**1a** underwent quantitative conversion to cycloaddition product **2a** in toluene at room temperature for 4 days. Furthermore, compound (*E*)-**1a** was dissolved in $CDCl_3$ and the progress of the reaction was monitored by ^1H NMR spectroscopy. The reaction was first-order in (*E*)-**1a** with k_{obs} = 9.6 × 10^{-5} s^{-1} at 41 °C in $CDCl_3$ (Figure 2); the addition of the gold

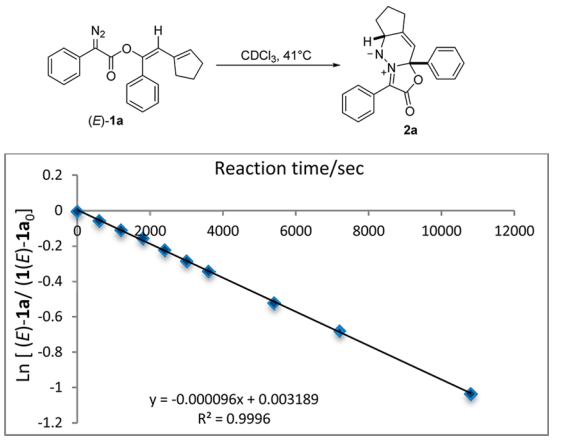


Figure 2. Linear relationship between reaction time and ln [(*E*)-**1a**/(*E*)-$\mathbf{1a}_0$]. Reaction performed in $CDCl_3$ at 41 °C.

catalyst in amounts similar to those used for reactions with propargyl aryldiazoacetates **4** did not influence the rate of conversion of (*E*)-**1a** to **2a**, confirming that the cycloaddition reaction was uncatalyzed. The variation of rate constant over temperatures ranging from 20 to 49 °C provided E_{act} = 16.2 kcal/mol, $\Delta H^{\ddagger}_{298}$ = 15.6 kcal/mol, and $\Delta S^{\ddagger}_{298}$ = −27.3 cal/(mol·°C). Multiple determinations of reaction rates after separations of (*E*)-**1a** from different reaction mixtures were made to ensure that there was consistency in results. Cycloaddition occurred with rate constants that were independent of the batch source of (*E*)-**1a**.

Surprisingly, the geometrical isomer of (*Z*)-**1a** did not undergo [4 + 2]-cycloaddition. Stable at room temperature in the absence of catalyst for more than 7 days in toluene, (*Z*)-**1a** underwent

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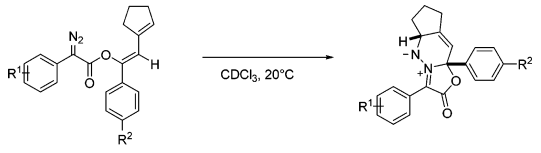
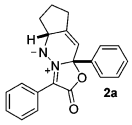
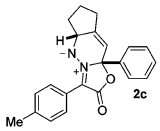
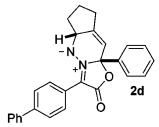
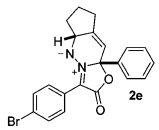
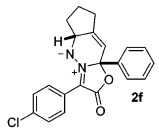
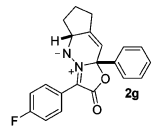
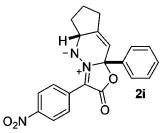
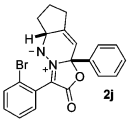
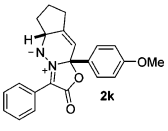
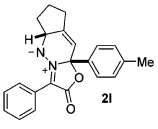
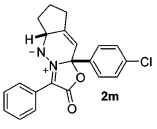
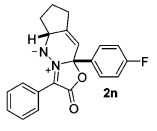
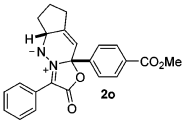
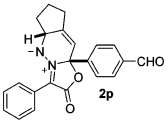
Table 1. Product and Kinetic Studies of Intramolecular [4 + 2]-Cycloaddition



(*E*)-**1** **2**

Entry[a]	2	time[b] (days)	yield of **2** from (*E*)-**1**[c] (directly from **4**)	rate constant[d] (s^{-1})	(*Z*)-**1**:**2**[e]
1	 **2a**	4	90[f] (48)	1.50×10^{-5}	40:60
2	 **2c**	4	92[f] (54)	1.47×10^{-5}	42:58
3	 **2d**	4	93[f] (53)	2.57×10^{-5}	42:58
4	 **2e**	4	90[f] (50)	3.41×10^{-5}	44:56
5	 **2f**	4	88[f] (52)	3.04×10^{-5}	41:59
6	 **2g**	4	91[f] (50)	2.38×10^{-5}	40:60
7	 **2i**	2	85[f] (56)	9.82×10^{-5}	26:74
8	 **2j**	21	87 (55)	0.33×10^{-5}	27:73
9	 **2k**	4	92[f] (42)	3.71×10^{-5}	50:50
10	 **2l**	4	90[f] (45)	3.04×10^{-5}	48:52
11	 **2m**	7	88[f] (45)	0.72×10^{-5}	47:53
12	 **2n**	7	88[f] (45)	0.86×10^{-5}	45:55
13	 **2o**	15	89 (45)	0.45×10^{-5}	45:55
14	 **2p**	21	87 (41)	0.30×10^{-5}	47:53

[a]Reactions were performed at 20 ± 0.5 °C on a 0.05 mmol scale: under a nitrogen atmosphere. The solution of (*E*)-**1** in 0.5 mL of $CDCl_3$ was monitored by ^1H NMR spectroscopy over a period of time until over 80% of (*E*)-**1** was converted into the cycloaddition product **2**. [b]The reaction time was determined from the disappearance of (*E*)-**1** by ^1H NMR spectroscopy. [c]Isolated yields from the conversions of (*E*)-**1** to **2**. [d]Determined by ^1H NMR. [e]Ratio of isolated products from $AuCl(Me_2S)$ catalyzed reaction of **1**; the yields of **1** + **2** ranged from 70% to 94% with the average yield being 84%. [f]The solution of (*E*)-**1** and (*Z*)-**1** in 0.5 mL of $CDCl_3$ was monitored by ^1H NMR spectroscopy; conversion of (*E*)-**1** to **2** occurred without any noticeable conversion of (*Z*)-**1**.

complete decomposition resulting in complex mixtures at 60 °C in $CDCl_3$ for 24 h that did not include evidence for **2a** or similar cycloaddition products. In contrast, (*E*)-**1a** underwent what is a facile [4 + 2]-cycloaddition reaction that occurred without evidence for formation of a dipolar cycloaddition product.

The design of (*E*)-**1** with its strategically placed phenyl groups allows the examination of the influence substituents on the rates for cycloaddition for both the dienophile and the diene in the same compound. To perform these determinations we isolated (*E*)-**1** from a representative series of gold-catalyzed reactions of **4**, determined the yields for their conversion to [4 + 2]-cycloaddition product, and measured the rates for their conversion to **2** at constant temperature. As shown in Table 1, the intramolecular [4 + 2]-cycloaddition reaction of (*E*)-**1** gave **2** in high yields with complete diastereocontrol. Reaction rates were dependent on the compounds (*E*)-**1** with arylacetic acid derived substituents Ar^1 and arylacetylene-derived aryl substituents Ar^2. A *p*-tolylacetic acid derived substituent slightly decreased the reaction rate (Table 1, entry 2); other arylacetic acid derived substituents, such as *p*-Ph, *p*-Br, *p*-Cl, and *p*-F, increased the reaction rate (entries 3−6). Moreover, the aryldiazoacetate with the strongly electron-withdrawing *p*-NO_2

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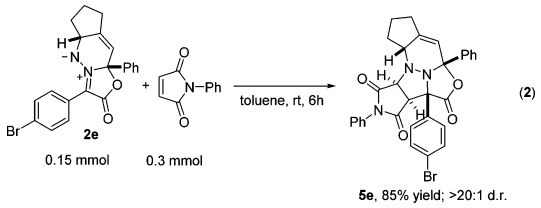
group gave the highest reaction rate (entry 7). In contract, an electron-withdrawing group on the benzene ring of the phenylacetylene-derived substituents decreased the reaction rate (entries 11−14), whereas electron-donating groups increased the reaction rate (entries 9 and 10). Hammett plots of the intermolecular [4 + 2]-cycloaddition reaction of (*E*)-**1** showed good correlations between σ values and $\log(k_X/k_H)$ with ρ-values of +0.89 (R^2 = 0.96) for the para-substituted aryldiazo esters and −1.65 (R^2 = 0.95) for the para-substituted aryldienes (SI, Figures 6 and 7). The diazo functional group exhibits electrophilic character in these reactions while the diene is its nucleophilic partner. In addition, the *o*-bromophenylacetic acid derived substituent underwent reaction much slower than did the *p*-bromophenylacetic acid derived compound, suggesting a possible steric inhibition (Table 1, entry 8).

The [4 + 2]-cycloaddition products formed from (*E*)-**1** are stable dipolar species, and their suitability toward dipolar cycloaddition with reactive alkenes and alkynes was examined. Treatment of **2e** with *N*-phenylmaleimide at room temperature for 6 h gave the nitrogen-fused pentacyclic compound **5e** in 85% yield with complete diastereocontrol (eq 2). The structure of **5e** was confirmed by X-ray diffraction.



(2)

In summary, aryl-substituted 1-(1,3-dienyl) aryldiazoacetates were formed selectively and in moderate to high yields by Au(I)-catalyzed rearrangement of propargyl phenyldiazoacetates performed in the presence of a pyridine-*N*-oxide. Complete selectivity for Au(I) activation of the alkyne rather than metallocarbene formation from the diazoacetate occurred, and both aryl-substituted 1-(1,3-dienyl) aryldiazoacetates and the products from intramolecular [4 + 2]-cycloaddition of the diazo N═N bond to the diene were formed. Aryl-substituted (*E*)-1-(1,3-dienyl) aryldiazoacetates underwent intramolecular [4 + 2]-diene−diazo cycloaddition under mild conditions without catalysis by the Au(I) reagent used in its formation and without evidence of a competing dipolar cycloaddition. Cycloaddition was first-order in the substrate, and both the activation parameters and the Hammett relationships for the conversion of (*E*)-**1** to **2** are consistent with those for other intramolecular Diels−Alder reactions.[15]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b12877.

Experimental procedures and full characterization of propargyl phenyldiazoacetates and their diene and [4 + 2]-cycloaddition products, X-ray and spectral determinations, and kinetic analyses (PDF)
Crystallographic data for (*Z*)-**1e** (CIF)
Crystallographic data for **2f** (CIF)
Crystallographic data for **5e** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*michael.doyle@utsa.edu

Notes

The authors declare no competing financial interest.

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