Donor-Acceptor-Acceptor 1,3-Bisdiazo Compounds: An Exploration of Synthesis and Stepwise Reactivity

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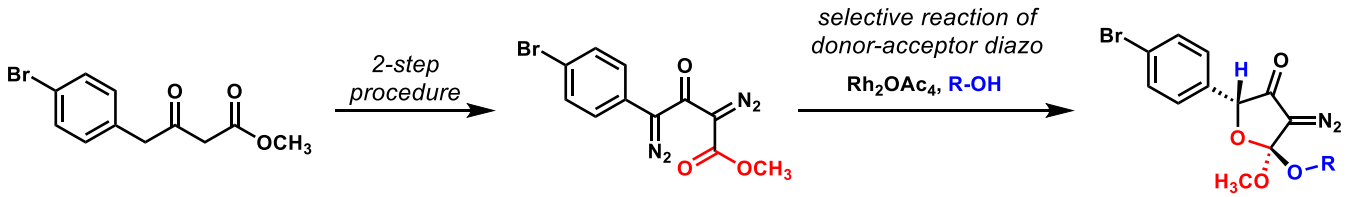
Supporting Information Placeholder



donor-acceptor-acceptor 1,3-bisdiazo

ABSTRACT: Metal carbenoids, derived from the decomposition of diazo compounds, are valued for their capacity to perform a variety of transformations. A unique class of acyclic, bis-diazo compounds, the donor-acceptor-acceptor 1,3-bisdiazo compounds, are described herein. These compounds are available from acyclic β-keto esters and especially reactive at the donor-acceptor diazo unit. These bisdiazo compounds react smoothly with rhodium acetate and alcohols to give monodiazo, cyclic orthoesters, presumably through the capture of a transient oxonium ylide.

Warning: Although the authors did not experience any adverse events on handling the mono- and bisdiazo compounds described herein, they and their relatives are high energy compounds and potentially explosive. They should be handled with care, and behind a blast shield whenever possible.

C-H functionalization is a powerfully enabling technology, which has experienced rapid innovation and growth in recent years.[1–4] These advances allow strong, even electronically unactivated, carbon-hydrogen bonds to be viewed as direct progenitors to diverse functionalities and new carbon-carbon bonds, thus enabling the use of simplified starting materials and more direct transformations requiring minimal functional group manipulations.[5–8] Like many of the strategic C-H functionalization manifolds, the C-H insertion of metal carbenoids derived from organic diazo compounds has had great adoption in synthesis.[9–12] Typical carbenoid precursors can be classified by the electronic environment around the diazo-bearing carbon; the number of electron-withdrawing groups, such as a carbonyl, or electron-donating groups, such as an arene, divide the compound class into acceptor-only, donor-acceptor, and acceptor-acceptor diazo compounds, which produce the analogous carbenoid on decomposition (Figure 1). Although all varieties have been demonstrated to possess utility for synthesis and selectivity, donor-acceptor carbenoids have enjoyed a broader range of reactivity and higher selectivity in *intermolecular* reactions. This phenomenon is attributable to a combination of a more facile nucleophilic "decomposition" step to form the carbenoid, and a slower, and therefore potentially more discerning, electrophilic bond-forming step, both due to influence of the donor group.[10,11,13]

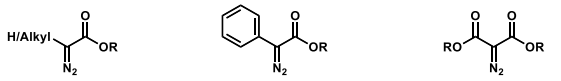


Figure 1. The three classes of carbenoid precursors

In our efforts to conceive bold strategies for synthesis that are reliant on C-H functionalization methods, we were drawn to the structure of silvestrol (**1**, Figure 2). Silvestrol is an anticancer flavagline natural product, which together with its relatives, has been the target of numerous undertakings in synthesis.[14,15] We envisioned that the 8b-3a and 2-3 carbon-carbon bonds (highlighted in red) might be forged through a cascade of dirhodium-catalyzed carbenoid C-H insertions. This rapid construction of the densely-functionalized C-ring would logically be preceded by monocyclic intermediate **2**, bearing an unusual 1,3-bisdiazo functionality about a central ketone. Central to the success of this strategy would be the need for a selective and stepwise pair of diazo decompositions. Formation of the C8b-C3a bond at the B-C ring juncture, derived from the donor-acceptor diazo moiety, would likely need to occur first, so as to capitalize on the high propensity of dirhodium carbenoids to form 5-membered rings.[11]

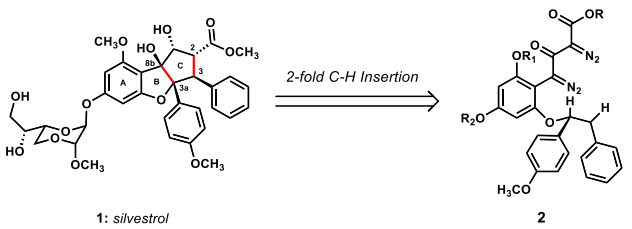


Figure 2. Our envisioned retrosynthesis of the natural product silvestrol.

Unexpected challenges beset our effort to synthesize a model system structurally analogous to **2** and thus undermined our effort to probe the feasibility of the ring annulation concept outlined in Figure 2. However, we remained intrigued by the reactivity that a molecule bearing two electronically differentiated bisdiazo functions would display and especially the possibility that we might achieve predictable and controllable reactions at each diazo locus. Acyclic bisdiazo compounds of the donor-acceptor-acceptor type were undescribed at the outset of this effort; our inquiry into their synthesis and reactivity is the main subject of this report.

As early as 1959, Kirmse had reported the first dialkyl bisdiazo ketone (Figure 3a, **3**).[16–19] These studies were subsequently followed by the first syntheses of the analogues bearing two electron-withdrawing groups on either side (**4**, termed herein acceptor-acceptor-acceptor)[20–22] and two electron-donating groups (**5**, termed herein donor-acceptor-donor).[19,23,24] However, it was not until several decades later that Murata and Tomioka reported the first, and until now only, donor-acceptor-acceptor 1,3-bisdiazo compound **6**.[25–27] Importantly, the cyclic, aromatic nature of the synthetic precursor of **6** meant it was unclear to us whether either the synthesis or behavior of the acyclic analogues we sought (e.g. **7**) would bear any resemblance to those studies. Hence, we set out to determine if it is possible to synthesize and handle acyclic donor-acceptor-acceptor systems of type **7**, establish which is the more reactive diazo moiety, and determine if this type of unique compound is capable of two sequential carbene transformations.

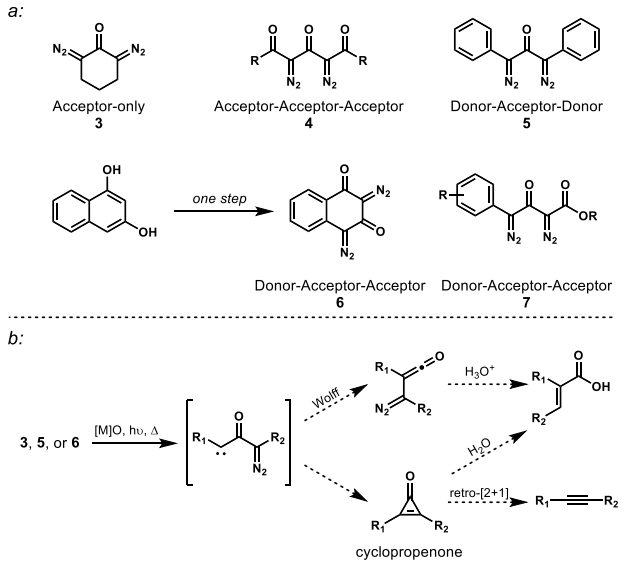
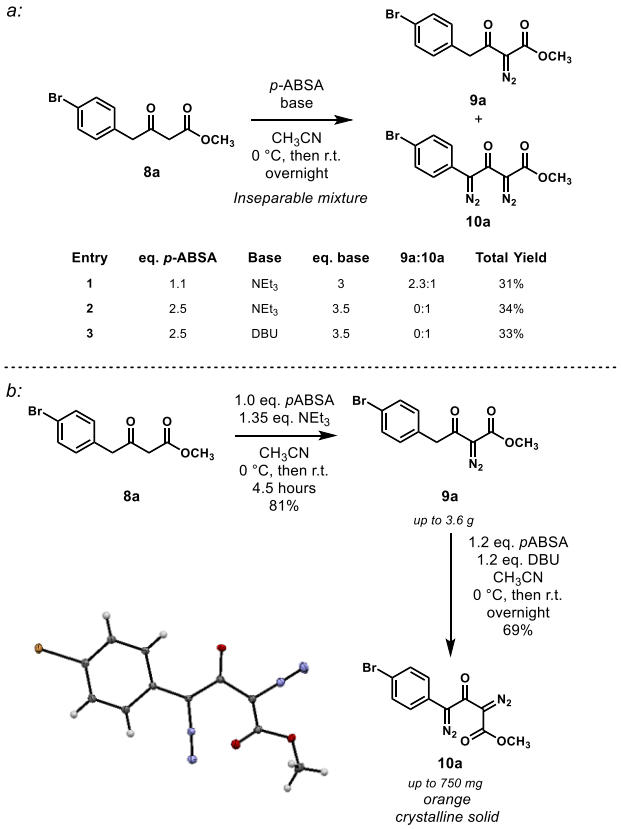


Figure 3. The classes (a) and typical reactivity (b) of 1,3-bisdiazo compounds.

Known reactivity of these early systems is largely limited to their decomposition by metal salts, heat or light, often proceeding through either Wolff rearrangements or cyclopropenone formation (Figure 3b).[16,18,19,24,26] Selective metal-catalyzed bond forming reactions of 1,3-bisdiazo compounds are rare in the literature.[25,28] With respect to order of reaction, it was known that tethered bisdiazo compounds react in a predictable manner, with more rapid decomposition of the donor-acceptor diazo, for the reasons discussed above.[29–31] However, what was known about the order of reactivity in these 1,3-bidiazo settings was largely limited to a wavelength dependent product distribution reported by Murata and Tomioka.[26,27]



Entry	eq. *p*-ABSA	Base	eq. base	9a:10a	Total Yield
1	1.1	NEt_3	3	2.3:1	31%
2	2.5	NEt_3	3.5	0:1	34%
3	2.5	DBU	3.5	0:1	33%

Figure 4. (a) The optimization of the synthesis of **10a**; (b) the optimal, scalable synthesis of **10a** and the crystal structure of **10a**. *p*-ABSA = para-acetamidobenzenesulfonyl azide. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

Our first goal was to develop conditions for the synthesis of these donor-acceptor-acceptor bisdiazo compounds. We began with the reaction of methyl 4-(4-bromophenyl)-acetoacetate (**8a**, Figure 4a), seeking to install each diazo unit in a stepwise manner. To our surprise, conditions typically employed for the installation of an acceptor-acceptor diazo provided an inseparable mixture of the mono- and bisdiazo (**9a** and **10a**) in modest combined yield (Figure 4a, entry 1). Increasing the quantity of transfer agent and base drove the reaction to full conversion, but without significant improvement in yield; moreover, changing the base to DBU, more typically used for the installation of a donor-acceptor diazo, provided similar results. However, we found that limiting the quantity of transfer agent to 1 equiv., as well as decreasing the reaction time, permitted a more efficient synthesis of **9a**. This compound was subsequently converted to bisdiazo **10a** in good yield (Figure 4b). Crystallization of **10a** from ethyl acetate (see supporting in-

formation) yielded crystals suitable for X-ray crystallographic analysis (Figure 4b). A notable feature of the solid-state structure of **10a** is the twisted arrangement, as drawn in Figure 4b, with the two carbon-nitrogen bonds pointing away from each other, rather than parallel, and the ester carbonyl directed toward the donor-acceptor diazo.

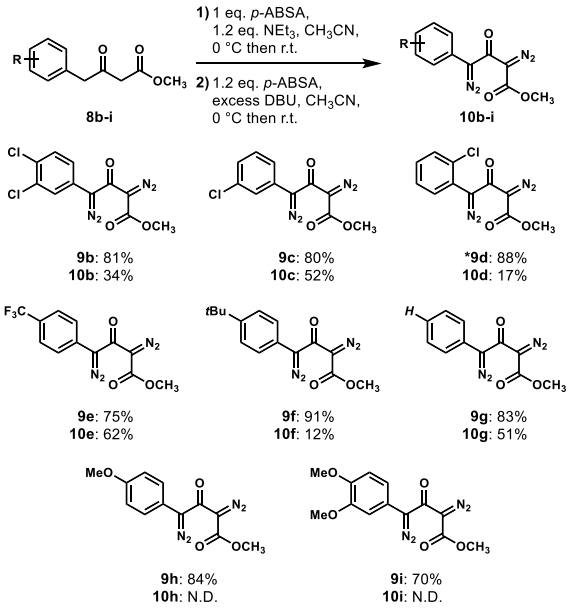


Figure 5. Scope of two step diazo transfer. Yields of **9b-i** from **8b-i** following step 1, yields of **10b-g** are from **9b-g** following step 2. *p*-ABSA = para-acetamidobenzenesulfonyl azide. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene. N.D.= Not Detected. * = 1.2 eq. p-ABSA, 1.2 eq. NEt_3.

We then explored the scope of 4-arylacetoacetate derivatives **8b-i**, which could be transformed into the donor-acceptor-acceptor bisdiazo **10b-i** through this two-step procedure (Figure 5). We found that electron-neural and electron-poor substituents in the 3- and 4-position of the donor arene were tolerated in this process. However, *ortho* substitution, as in the case of **10d**, and electron-rich substituents like *tert*-butyl, methoxy, and dimethoxy (**10f**, **10h**, **10i**) provided low or no yield of bisdiazo.

At this juncture, we turned to a study of the reactivity of these molecules. Could the reactivity of a single diazo be harnessed in such a system to perform one reaction specifically, and then subsequently a second reaction? Our initial instinct was to explore the reactivity of these donor-acceptor-acceptor bisdiazo compounds with cinnamyl alcohol (Figure 6, Equation 1). We assumed that the first carbenoid to form would undergo selective O-H insertion on the alcohol, followed by an intramolecular cyclopropanation of the second carbenoid onto the pendant olefin. **10a** was chosen as a representative bisdiazo compound with which to begin to understand reactivity, due to a high yielding synthesis and high long-term stability at low temperatures, allowing for the accumulation and storage of large quantities. If indeed the donor-acceptor nucleus selectively underwent the first decomposition, this would provide oxabicyclo[4.1.0]heptane **11** as the product from **10a**. In the tethered bisdiazo examples reported by Moody,[29] Muthusamy[30] and Padwa,[31] further heating, often refluxing in benzene, is employed to affect full reaction of the acceptor-acceptor diazo. Therefore, our design was to employ heating after initial dropwise addition, to encourage full conversion of both diazo moieties.

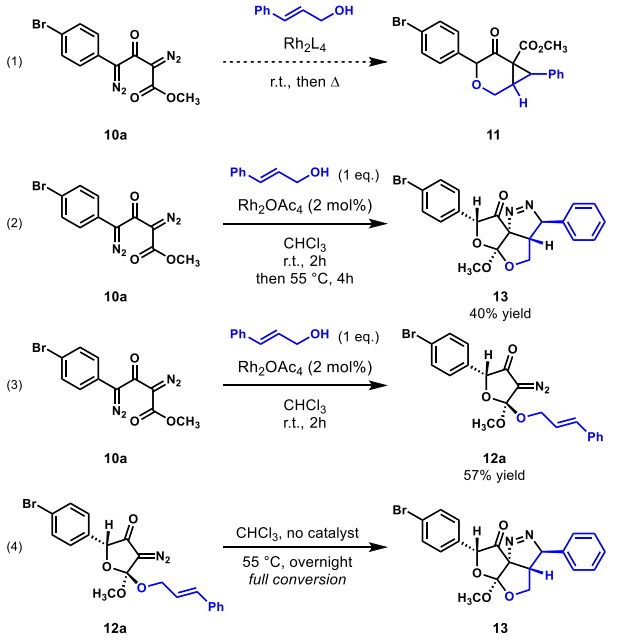


Figure 6. Exploration of the reactivity of donor-acceptor-acceptor bisdiazo **10a**. All yields were determined from NMR integrations compared to tert-butyl acetate as an internal standard and averaged over 3 runs (see Supporting Information).

The slow addition of a solution of **10a** and cinnamyl alcohol to Rh_2OAc_4 in chloroform, followed by heating to 55 °C for four hours, provided a crystalline material in 40% yield, which from the IR analysis indicated that both diazo groups had reacted, and from the proton NMR indicated that both the bisdiazo skeleton and the cinnamyl alcohol had been incorporated into the product. The expected arrangement of aliphatic protons from the cinnamyl alcohol (methylene-methine-methine) were present, but the coupling constants were inconsistent with a cyclopropane, and the carbon NMR indicated the presence of only a single carbonyl. Further, the mass spectral data indicated that two of the original four nitrogens were retained in the structure, which could be further confirmed by ^{15}N NMR. Eventually, X-ray crystallographic analysis revealed that the unexpected product was tricyclic pyrazoline **13** (Figure 6, Equation 2). In order to better understand the origins of **13**, the same conditions were employed, dropwise addition at ambient temperature, but without subsequent heating (Figure 6, Equation 3). Under these conditions, monodiazo orthoester **12a** was the major product in 57% yield. Furthermore, heating of a purified sample of **12a** in chloroform induced diazo-alkene [3+2] dipolar cycloaddition, yielding **13** essentially quantitatively (Figure 6, Equation 4).[32–35] These data suggest that the initial reaction to form orthoester **12a** is rhodium-dependent, but that cycloaddition to form **13** is a purely thermally-driven process.

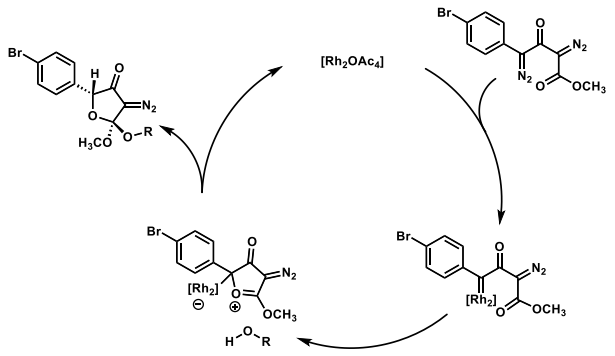


Figure 7. The proposed mechanism for the formation of monodiazo orthoesters ***12*a-d** from **10a**.

We attribute the product of the rhodium-catalyzed reaction of **10a** to rapid formation of an ylide following carbenoid formation (Figure 7). Ylide formation is well known in dirhodium carbenoid chemistry, and the enforced propinquity of the ester carbonyl likely encourages this mode of reactivity.[36–39] Following ylide formation, the alcohol traps the oxocarbenium as the orthoester, and the dirhodium enolate is protonated to restore the catalyst.[40,41] Whether the observed single diastereoisomer is the result of a rapid epimerization and high thermodynamic preference, or a kinetically controlled intramolecular protonation step, is unclear. Conversely, protonation of the dirhodium enolate could occur first, and the resulting oxocarbenium/alkoxide ion pair could collapse in a facially selective manner to afford the single diastereoisomer. With these conditions in hand, we explored a sample of other alcohols. The isolated yield of **12a** well matched the NMR yields observed above, and ethanol, methanol, and benzyl alcohol all underwent the same transformation, providing the isolable monodiazo orthoesters **12b-d** in comparable isolated yields (Figure 8).

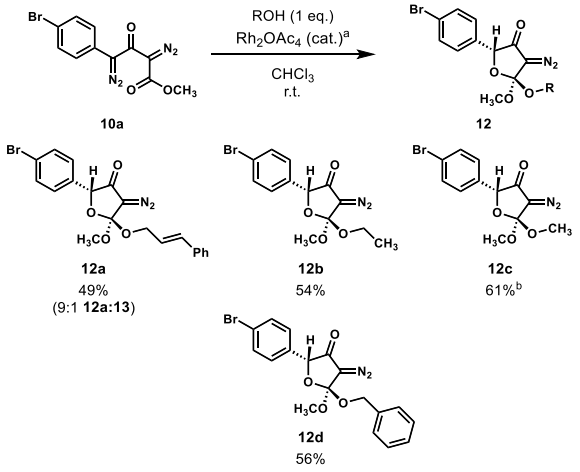


Figure 8. Scope of O-H insertion reaction. All yields are isolated. [a] <1 mol% Rh_2OAc_4. [b] 1.3 mol% Rh_2OAc_4.

Interestingly, in none of these cases were products detected attributable to reaction of the remaining acceptor-only diazo moiety, or from reaction of the acceptor-acceptor diazo unit in **10a**. Additionally, this is likely not due to catalyst deactivation, as subjecting a pure sample of **12b** to Rh_2OAc_4 in chloroform over several hours affords **12b** unchanged following chromatography. Heating a sample of **12b** either to 75 °C in benzene with Rh_2OAc_4 or at room temperature in chloroform with $Rh_2(esp)_2$ results in slow conversion (over several hours) to the same unknown major product. Unfortunately, efforts to isolate and characterize this product were unsuccessful.

Herein, we have demonstrated the synthesis of acyclic 1,3-bisdiazo compounds bearing one donor and one acceptor on either side of the central ketone. These studies confirm that diazo derivatives flanked by one donor and one acceptor group are more prone to rhodium-catalyzed nitrogen extrusion than analogous derivatives flanked by two acceptor groups. The bisdiazo compounds described undergo an intramolecular reaction in which the carbene is trapped by the pendant ester carbonyl to generate an ylide, with one of the diazo functionalities retained. This ylide can be trapped intermolecularly by various alcohols to form orthoesters adjacent to a diazo function, and in the case of cinnamyl alcohol, further reactivity in the form of diazo-alkene [3+2] dipolar cycloaddition is observed. These studies further illustrate the novel transformations that can be discovered as one challenges dirhodium carbene chemistry with more elaborate substrates inspired by potential synthetic applications.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, spectral data, and crystallographic data (PDF)
X-ray data for compound **10a** (CIF)
X-ray data for compound **13** (CIF)

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Author Contributions

The manuscript was written through contributions of all authors. / All authors have given approval to the final version of the manuscript.

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