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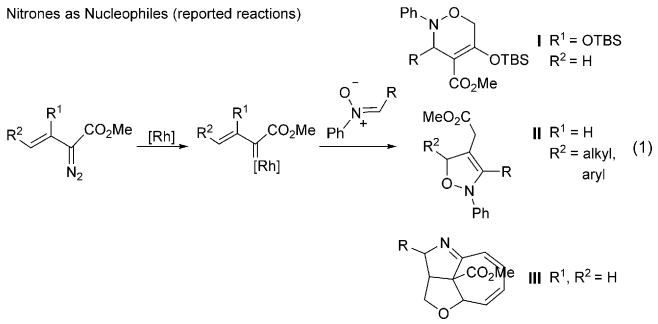
Gold-Catalyzed Cycloaddition Reactions of Ethyl Diazoacetate, Nitrosoarenes, and Vinyldiazo Carbonyl Compounds: Synthesis of Isoxazolidine and Benzo[*b*]azepine Derivatives**

*Vinayak Vishnu Pagar and Rai-Shung Liu**

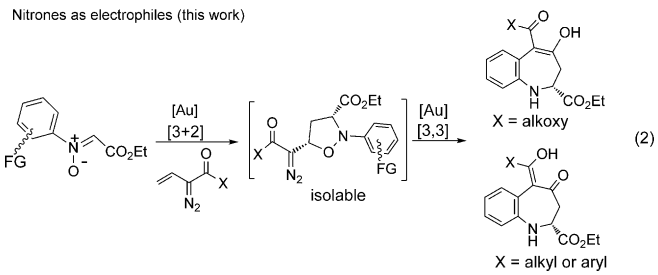
Abstract: *Gold-catalyzed cycloadditions of ethyl diazoacetate, nitrosoarenes, and vinyldiazo carbonyl species to yield isoxazolidine derivatives stereoselectively are described. Treatment of these isoxazolidine products with the same catalyst results in a novel 1,2-H shift/[3,3] rearrangement to give benzo[b]azepine compounds. The mechanism of this skeletal rearrangement is elucidated with deuterium-labeling experiments.*

Alkenyldiazo reagents are versatile three-carbon building blocks to access carbo- or heterocyclic frameworks through metal-catalyzed cycloadditions.[1] The major use involves an initial formation of electrophilic metal carbene intermediates through a diazo decomposition, thus enabling stereo- or regioselective [3C + *n*] cycloadditions (*n* = 2–4) with small nucleophilic molecules including imines, nitrones, azomethine imines, pyridines, and pyrroles to afford diverse cycloadducts.[2–4] Alternatively, alkenyldiazo species can serve as weak nucleophiles to react with electrophilic aldehydes, acetals, and enones to form additional products containing diazo functionalities.[5] Little attention has been focused on this method for catalytic cycloadditions because many late-transition-metal complexes readily decompose the diazo functionality.[5b]

Rhodium-catalyzed cycloadditions of alkenyldiazo esters with nitrones have been extensively investigated by the groups of Doyle and Davies.[6,7] The reaction chemoselectivities depend strongly on the substituents of the alkenyldiazo esters. These cycloadditions proceed exclusively through an initial formation of rhodium carbenes which react subsequently with nitrone nucleophiles to complete [3+3] or [3+2] cycloadditions to afford compounds **I** and **II** [Eq. (1); TBS = *tert*-butyldimethylsilyl].[6] For vinyldiazo acetate ($R^1 = R^2 =$ H), the rhodium-catalyzed reactions with the same nitrones proceed by notable cascade reactions including initial [3+2] cycloadditions, cyclopropanations, and structural rearrangements to yield the tricyclic products **III**.[7] In this work, we report [3+2] cycloaddition reactions of vinyldiazo esters with electron-deficient nitrones to evade the diazo decomposition. Particularly notable is the subsequent formation of their metal carbenes to enable a 1,2-H shift/[3,3] rearrangement to yield benzo[*b*]azepine derivatives [Eq. (2); FG = functional group].



(1)



(2)

Table 1 represents the optimization of the reactions between ethyl diazoacetate[8] (**1a**) and nitrosobenzene (**2a**) with the vinyldiazo ester **3a** using various acidic catalysts. In a typical reaction, a 1,2-dichloroethane (DCE) solution of **1a** (1.5 equiv), **2a** (1.3 equiv), and **3a** (1 equiv) was added slowly to a DCE solution of the catalyst at 0 °C for 10 minutes. The mixture was stirred at 25 °C for 5–7 hours to complete the consumption of **3a**. We first examined the reaction with 5 mol % [IPrAuCl]/$AgNTf_2$ (IPr = 1,3-bis(diisopropylphenyl)imidazol-2-ylidene), **1a**, **2a**, and **3a** in DCE for 5 hours, thus providing ethyl 5-(1-diazo-2-ethoxy-2-oxoethyl)-2-phenylisoxazolidine-3-carboxylate (**4a**) as a single diastereomer in 65 % yield (entry 1). The *cis*-configuration of **4a** was elucidated with the ^{1}H NOE effect. The alteration to a silver salt as in [IPrAuCl]/$AgSbF_6$ increased the yield of **4a** to 85 % (entry 2). Other gold catalysts including [P(*t*Bu)$_2$(*o*-biphenyl)AuCl]/$AgSbF_6$ and [PPh_3AuCl]/$AgSbF_6$ appear to be less efficient, thus giving **4a** in 68 and 45 % yields, respectively (entries 3 and 4). Copper catalysts such as [IPrCuCl] and $Cu(OTf)_2$ (5 mol %) were less effective, thus giving **4a** in 60 and 30 % yields

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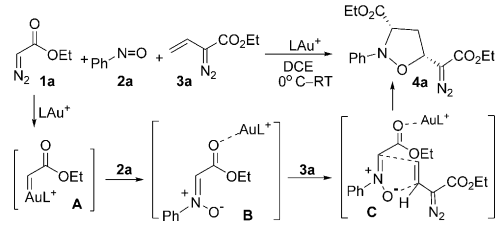
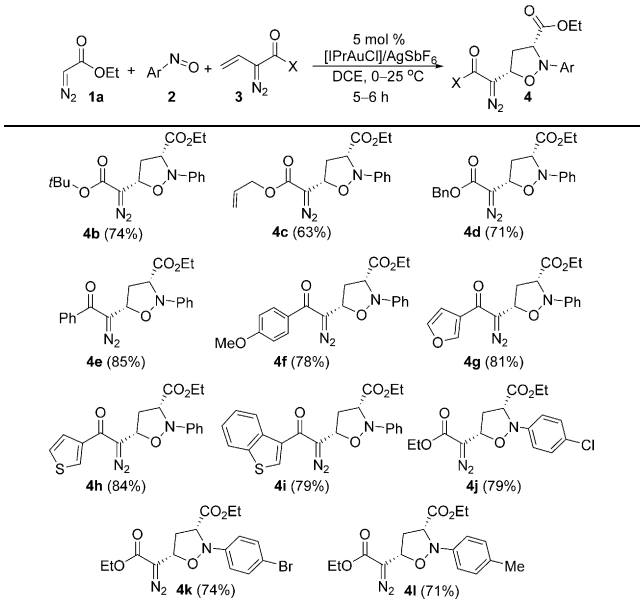
Table 1: Conditions for three-component cycloadditions.[a]



Entry	Catalyst[b] (mol%)	*t* [h]	**4a** Yield [%][a]
1	[IPrAuCl]/$AgNTf_2$ (5)	5	65
2	[IPrAuCl]/$AgSbF_6$ (5)	5	85
3	[LAuCl]/$AgSbF_6$ (5)	5	68
4	[PPh_3AuCl]/$AgSbF_6$ (5)	5	45
5	[IPrCuCl] (5)	6	60
6	$Cu(OTf)_2$ (5)	7	30
7	$[Rh_2(OAc)_4]$ (1)	3	complex mixture
8	$AgSbF_6$ (5)	5	45

[a] Reaction conditions: **3a** (0.23 M, 1 equiv), **1a** (1.5 equiv), **2a** (1.3 equiv). [a] Yield of compound isolated after purification from a silica column. IPr = 1,3-bis(diisopropylphenyl)imidazol-2-ylidene, L = P(*t*Bu)$_2$-(*o*-biphenyl), Tf = trifluoromethanesulfonyl.

Table 2: Reaction scope for the [3+2] cycloaddition.[a]



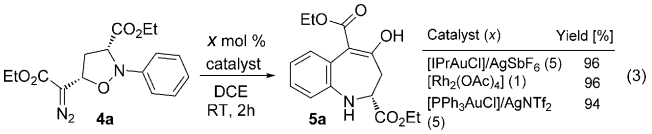
[a] Reaction conditions: **3** (0.23 M, 1 equiv), **1a** (1.5 equiv), **2** (1.3 equiv). Product yields are given for compounds isolated after purification from a silica column.

(entries 5 and 6). Commonly used $[Rh_2(OAc)_4]$ (1.0 mol%) led to a complete consumption of the diazo species **1a** and **3a**, but a complex mixture resulted (entry 7). In control experiments (entry 8), $AgSbF_6$ alone gave **4a** in a diminished yield 45%.

As shown in Table 1, the gold catalyst decomposes **1a** selectively to form the gold carbene **A**, whereas **3a** remains intact. A subsequent reaction of **A** with **2a** yields the highly electrophilic nitrone intermediate **B**[9] which is too reactive to isolate because of its rapid hydrolysis. [IPrAuCl]/$AgSbF_6$ coordinates this nitrone species to facilitate its concerted [3+2] cycloaddition with **3a** in an *exo*-cycloaddition to control the *cis*-configuration, as depicted in **C**. The success of this [3+2] cycloaddition relies on both a selective diazo decomposition between two diazo esters.

Table 2 shows the substrate scope of these formal [3+2] cycloadditions using various alkenyldiazo carbonyl compounds and nitrosoarenes. In a standard operation, these three reactants were dissolved in DCE before treatment with [IPrAuCl]/$AgSbF_6$ (5 mol%) in DCE (0–23 °C) for 5–6 hours, thus leading to a complete consumption of the vinyldiazo compounds **3**. A work-up of the reaction mixture delivered the isoxazolidine derivatives **4** as a single diastereomeric product. This cycloaddition tolerates the vinyldiazo species **3** bearing various esters (X = O*t*Bu, Oallyl, OBn), thus giving the desired compounds **4b–d** in 63-74% yields. The same reaction worked well with the alkenyldiazo ketones **3e** and **3f**, thus giving the expected products **4e** (85%) and **4f** (78%), respectively. We also tested the reactions on the heteroaryl-derived vinyldiazo ketones **3g–i** (X = 3-furanyl, 3-thienyl, 3-benzothienyl) which delivered the desired cycloadducts **4g–i** in excellent yields (79–84%). To expand the reaction scope, we also prepared various nitrosoarenes bearing both electron-deficient and electron-rich substituents including 4-chloro, 4-bromo, and 4-methyl groups, thus providing the desired products **4j–l** in 71–79% yield. We attempted to perform the reaction of 2- or 3-methylvinyldiazo esters with **1a** and **2a**, and they gave a complex mixture of products.

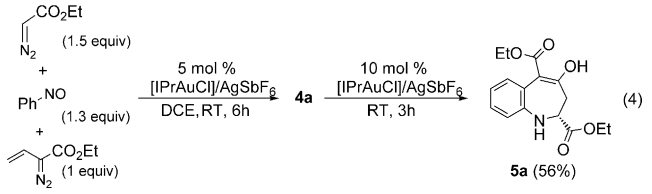
Diazo decomposition of the representative isoxazolidine **4a** with [IPrAuCl]/$AgSbF_6$ (5 mol%) in DCE (25 °C, 2 h) is particularly interesting because the reaction occurs with a [3,3] shift to afford the seven-membered benzoazepine **5a** with a yield up to 96% [Eq. (3)]. The same chemoselectivity



Catalyst (*x*)	Yield [%]
[IPrAuCl]/$AgSbF_6$ (5)	96
$[Rh_2(OAc)_4]$ (1)	96
[PPh_3AuCl]/$AgNTf_2$ (5)	94

(3)

was attained with $[Rh_2(OAc)_4]$ (1 mol%) and [PPh_3AuCl]/$AgNTf_2$ (5 mol%) to afford the benzoazepine **5a** in 94–96% yields. The molecular structure of **5a** was determined with X-ray diffraction to show a γ-hydroxy unsaturated ester.[10] We performed also a one-pot reaction for the synthesis of this azepine by treatment of the reaction mixture containing **4a** with [IPrAuCl]/$AgSbF_6$ (10 mol%) in DCE (25 °C, 3 h). The desired **5a** was obtained in an overall 56% yield [Eq. (4)],

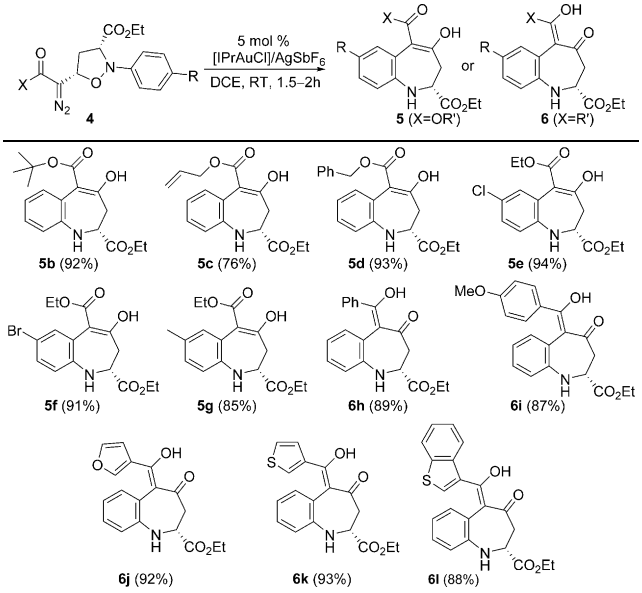


(4)

and this one-pot reaction appears to be less efficient than that (ca. 82%) of the two-step sequence in Equation (3). We propose that species other than **4** in the reaction mixture tend to decrease the acidity of the gold catalyst, thus rendering the one-pot reaction less efficient.

Table 3 shows the generalization of this benzoazepine synthesis using the same isoxazolidines **4b–l** listed in Table 2. In a typical operation, initially the isoxazolidines **4** were

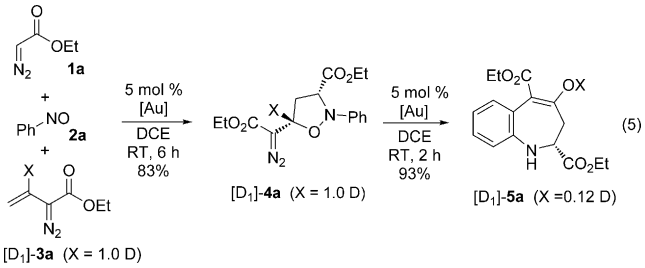
Table 3: Scope of synthesis of benzoazepines.[a]

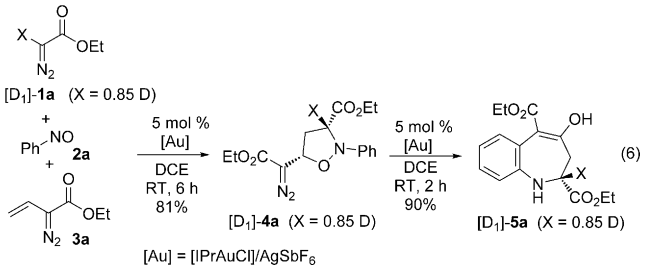


[a] Reaction conditions: **4** (0.10 M, 1.0 equiv). Product yields are given for product isolated after purification from a silica column.

treated with [IPrAuCl]/$AgSbF_6$ (5 mol%) in DCE (25°C) for 1.5–2.0 hours to attain complete conversion, thus giving the benzoazepine derivatives **5b–g** and **6h–l** exclusively. These products have two distinct γ-oxo-β-en-α-ol forms depending on the types of esters and ketones. The reactions with **4b–d**, bearing various esters (X = O*t*Bu, Oallyl, OBn), deliver the desired products **5b–d** with satisfactory yields (76–93%). The reactions also worked well with the isoxazolidine species **4** bearing various 4-phenyl substituents (R = Cl, Br and Me), thus yielding the desired products **5e–g** in 85–94%. The generality of this diazo decomposition was manifested in its application to diazo ketone derivatives (X = phenyl, 4-methoxyphenyl, 3-furanyl, 3-thienyl, 3-benzothienyl), thus giving the expected benzoazepine **6h–l** in 87-93% yields. X-ray diffraction of **6h** was performed to determine its molecular structure.[10]

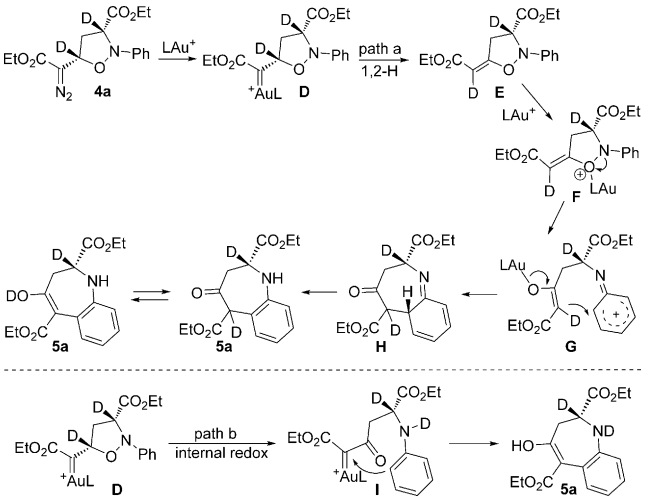
Equations (5) and (6) show deuterium-labeling experiments which were run to elucidate the reaction mechanism. We prepared the deuterated compound [D_1]-**3a** in which C2 is fully deuterated. The corresponding product [D_1]-**4a** was fully deuterated as depicted. Treatment of [D_1]-**4a** with [IPrAuCl]/$AgSbF_6$ provided the seven-membered benzoazepine [D_1]-**5a** which had 12% deuterium content at its hydroxy group and no deuterium at the NH group. We also prepared the ethyl diazoacetate [D_1]-**1a** with the diazo C1 85% deuterated, and





the same reaction with **2a** and **3a** gave the isoxazolidine [D_1]-**4a** having an 85% deuterium content at the carbon atom α to the ester [Eq. (6)]. A subsequent gold-catalyzed transformation of species [D_1]-**4a** provided the benzoazepine [D_1]-**5a** containing the same deuterium content at the carbon.

In Scheme 1, we propose a plausible mechanism involving an initial diazo decomposition of **4a** to form the gold carbene intermediate **D**. Two paths, a or b, are for the formation of **5a** from **D.** In path a, **D** undergoes a 1,2-hydrogen shift[11] to form the isoxazolidine species **E**. The gold catalyst likely coordinates with the isoxazolidine oxygen atom to open the ring to form the gold-enolate-containing anilinium species **G**. A subsequent intramolecular cyclization[12] of this species is expected to give **5a**[13] This pathway can fully rationalize our deuterium-labeling results in Equations (5) and (6) in which the resulting **5a** has a large deuterium content at the carbon atom α to the ester and a small deuterium content at OH position. Although path b is appealing because only one postulated intermediate (**I**) is generated from an internal



Scheme 1. Proposed mechanism.

redox reaction of **D**, this mechanism is expected to give **5a** with some deuterium content at the NH proton position, and is inconsistent with our result in Equation (5).

In summary, we have developed gold-catalyzed three-component reactions involving readily available ethyl diazoacetate, nitrosoarenes, and vinyldiazo carbonyl species to provide easy access to diazo-containing isoxazolidine derivatives with high stereoselectivity. This reaction sequence involves nitrones as electrophiles which are subsequently attacked by vinyldiazo esters. These resulting isoxazolidine derivatives are notably catalyzed with the same gold catalysts to yield seven-membered benzoazepine species (**5**) through a novel 1,2-H shift/[3,3] rearrangement.

Keywords: cycloaddition · diazo compounds · gold · heterocycles · synthetic methods

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[10] Crystallographic data of compounds **5a** and **6h** are provided in the Supporting Information. CCDC 1035677 (**5a**) and 1035678 (**6h**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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