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Ruthenium Porphyrin Catalyzed Three-Component Reaction of Diazo Compounds, Nitrosoarenes, and Alkynes: An Efficient Approach to Multifunctionalized Aziridines

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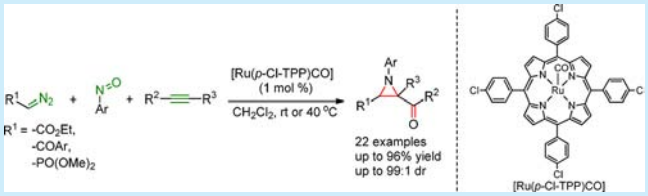
Supporting Information

ABSTRACT: A ruthenium porphyrin catalyzed three-component reaction of diazo compounds, nitrosoarenes, and alkynes gives multifunctionalized aziridines in good to high yields and with moderate to high diastereoselectivity.



Aziridines are versatile building blocks widely used in the synthesis of nitrogen-containing compounds and are present in many biologically active natural products and pharmaceuticals.[1] Among the various functionalized aziridines, aziridine 2-carboxylates undergo highly regio- and stereoselective ring-opening reactions and hence are good precursors of α- and β-amino acids.[2] Aziridine 2-phosphonates are isosteric analogues of aziridine 2-carboxylates having similar reactivity and selectivity and can be used as starting materials for the synthesis of diversely substituted amino phosphonic acids; the latter are surrogates for amino acids that exhibit a broad range of biological activities including anticancer, antibacterial, and antiviral activity, as well as herbicidal and insecticidal properties.[3] The syntheses of aziridine 2-carboxylates and aziridine 2-phosphonates mainly rely on cyclization of 1,2-aminoalcohols[4] and 1,2-azidoalcohols,[5] Darzens-type reaction,[6] addition of nitrene to alkenes,[7] and addition of carbene to imines.[8] While these methods are effective for the synthesis of simple aziridines, advanced starting materials or multistep syntheses are ususally required for the construction of complex aziridines via these literature methods. In view of the broad applications of functionalized aziridine 2-carboxylates and aziridine 2-phosphonates in organic synthesis, there has been continuing interest to develop efficient and straightforward methods for the rapid synthesis of these functionalized aziridine compounds.

Multicomponent reactions are appealing in the context of expeditious construction of complex molecules from simple or readily accessible building blocks.[9] In multicomponent reactions, several bonds can be formed in a single operation without the need of isolation of reaction intermediate(s). This feature enables multicomponent reactions to be used for rapid assembly of structurally diverse compounds for high-throughput biological screening in drug discovery research. In continuation of our interest in multicomponent reactions mediated/catalyzed by metal carbene intermediate,[10] herein is described an efficient ruthenium porphyrin catalyzed three-component reaction of diazo compounds, nitrosoarenes, and alkynes, which can be used for the synthesis of functionalized aziridine 2-carboxylates and aziridine 2-phosphonates. This ruthenium porphyrin catalyzed three-component reaction features the formation of two C−N bonds, one C−C bond, and one C═O bond in a one-pot manner.

Recently, we reported a ruthenium porphyrin catalyzed tandem nitrone formation/1,3-dipolar cycloaddition of α-diazocarbonyl compounds, nitrosoarenes, and alkenes to stereoselectively form isoxazolidines, in which nitrones are generated *in situ* by the reaction of ruthenium-carbene and nitroso compounds followed by subsequent 1,3-dipolar cycloaddition with alkenes.[10b] In this work, when an alkyne such as 3-methyl butynol **3a** was used as dipolarophile, the reaction did not give the corresponding 1,3-dipolar cycloadduct but afforded 3-acylaziridine-2-carboxylate **4a** in 87% yield with a *cis*:*trans* ratio of 67:33 (Scheme 1). The structure of *cis*-**4a** was inferred by the X-ray crystal structure of its analogue *cis*-**4n** and NOE experiment (see Supporting Information). This finding prompted us to apply this three-component reaction in the synthesis of highly functionalized aziridines.

At the outset, we examined the catalytic activity of a panel of transition metal complexes toward the three-component reaction of ethyl diazoacetate (EDA) **1a**, nitrosobenzene **2a**, and 3-methyl butynol **3a**. Compared to [Ru(TTP)CO] (H_2TTP = *meso*-tetrakis(4-tolyl)porphyrin), the other catalysts, [Co(TTP)], [Fe(TTP)Cl], [Ru(*p*-cymene)Cl_2]$_2$, [Ru(salen)-CO] (salen = *N*,*N*′-bis(3-bromosalicylidene)-1,2-cyclohexanediamino), [$Rh_2(O_2CCH_3)_4$], [Rh_2(esp)$_2$] (esp = α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid), and [Cu(OTf)$_2$]

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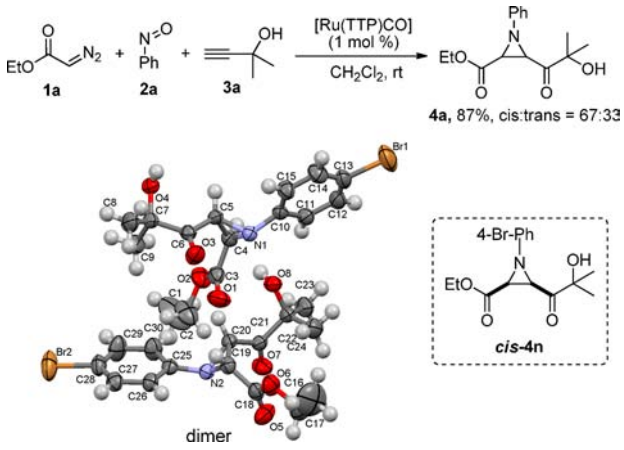
Scheme 1. Three-Component Reaction of EDA 1a, Nitrosobenzene 2a, and Alkyne 3a for the Synthesis of Aziridine 4a



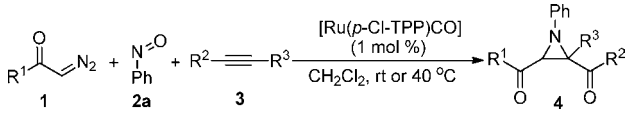
were less efficient, giving **4a** in 18−42% yields with diastereoselectivity values similar to that obtained by [Ru(TTP)CO] (see Supporting Information). With [Ru(TTP)CO] as catalyst, CH_2Cl_2 was found to be the best solvent for the catalysis. Examination of the effect of porphyrin ligand revealed that [Ru(*p*-Cl-TPP)CO] (H_2*p*-Cl-TPP = *meso*-tetrakis(4-chlorophenyl)porphyrin) was the most efficient catalyst, affording **4a** in 95% yield and with *cis*:*trans* ratio of 67:33 (see Supporting Information).

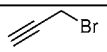
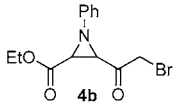
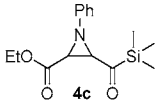
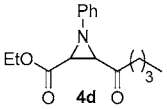
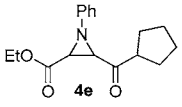
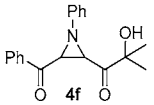
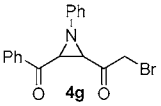
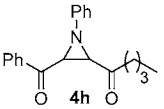
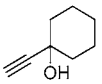
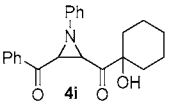
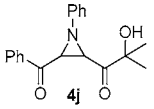
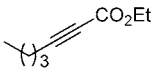
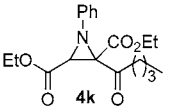
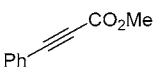
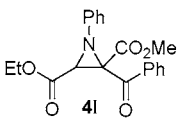
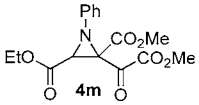
With the optimized reaction conditions, the substrate scope of the [Ru(*p*-Cl-TPP)CO]-catalyzed three-component reaction was examined. As depicted in Table 1, a variety of alkynes including propargyl alcohols, propargyl halides, trimethylsilyl acetylene, acyclic and cyclic aliphatic acetylenes, and alkoxycarbonylacetylenes were observed to undergo the three-component reaction to give aziridines in good to high yields and with moderate to excellent diastereoselectivties. For example, the reaction of EDA, nitrosobenzene and propargyl bromide led to aziridine **4b** in 93% yield with a *cis*:*trans* ratio of 67:33. Compound **4b** has a α-bromoacetyl moiety, which is an useful functional group commonly used in organic synthesis[11] (entry 1). Similarly, trimethylsilyl acetylene reacted with EDA and nitrosobenzene in the presence of [Ru(*p*-Cl-TPP)CO] giving aziridinyl acylsilane **4c** in 91% yield, the latter is an useful precursor for Brook rearrangement reaction[12] (entry 2). Compared to EDA, the reactions of aryldiazoketones, terminal alkynes, and nitrosobenzene are more stereoselective, giving corresponding aziridines **4f**−**4j** in good to high dr values (*trans*:*cis* = 86:14−90:10, 51−91% yields, entries 5−9). Interestingly, *trans*-aziridines were obtained as the major isomers contrasting to the similar reactions with EDA that resulted in products with *cis* selectivity.

Compared to terminal alkynes, internal aliphatic alkynes failed to give aziridination products. However, electron-deficient internal alkynes such as bis(methoxycarbonyl)-acetylene,[13] ethyl 2-heptynoate, and methyl phenylpropiolate were reactive giving corresponding aziridines **4k**−**4m** in good to high yields (77−96%) and excellent diastereoselectivities (dr >95:5, entries 10−12). The *cis* stereochemistry of **4k**−**4m** was assigned on the basis of NOE experiments.

Next we turned to synthesize functionalized aziridine 2-phosphonates by using α-diazophosphonate as carbene source. As depicted in Table 2, the reactions of α-diazophosphonate,

Table 1. Three-Component Reaction of α-Diazocarbonyl Compounds, Nitrosobenzene, and Alkynes[a]



entry	R^1	alkyne	product	% yield[b] *dr*[c]
1[d]	EtO		 **4b**	93 67:33[f]
2[e]	EtO		 **4c**	91 70:30[f]
3[d]	EtO		 **4d**	96 68:32[f]
4[d]	EtO		 **4e**	95 68:32[f]
5[e]	Ph		 **4f**	85 90:10[g]
6[d]	Ph		 **4g**	73 86:14[g]
7[d]	Ph		 **4h**	51 86:14[g]
8[d]	Ph		 **4i**	91 86:14[g]
9[d]	Ar[h]		 **4j**	70 90:10[g]
10[d]	EtO		 **4k**	77 >95:5[f]
11[d]	EtO		 **4l**	96 >99:1[f]
12[e]	EtO	DMAD[i]	 **4m**	87 >95:5[f]

[a] **1**:**2a**:**3**:[Ru(*p*-Cl-TPP)CO] = 1:2:2:0.01. [b] Isolated yield. [c] Determined by ^{1}H NMR of reaction mixture. [d] Reaction temperature = 40 °C. [e] Reaction temperature = room temperature. [f] dr = *cis*:*trans*. [g] dr = *trans*:*cis*. [h] Ar = 4-NO_2-Ph. [i] DMAD = dimethyl acetylenedicarboxylate

various terminal alkynes, and nitrosoarenes in the presence of 1 mol % [Ru(*p*-Cl-TPP)CO] gave corresponding 3-acylaziridine-2-phosphonates in good to high yields (up to 98%). In contrast

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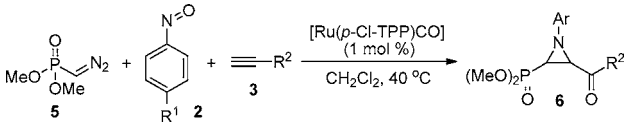
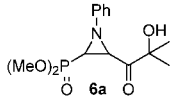
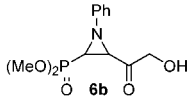
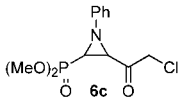
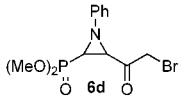
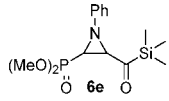
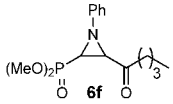
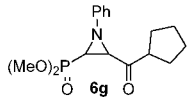
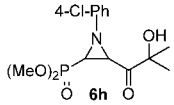
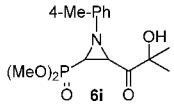
Table 2. Three-Component Reaction of α-Diazophosphonates, Nitrosoarenes, and Alkynes[a]



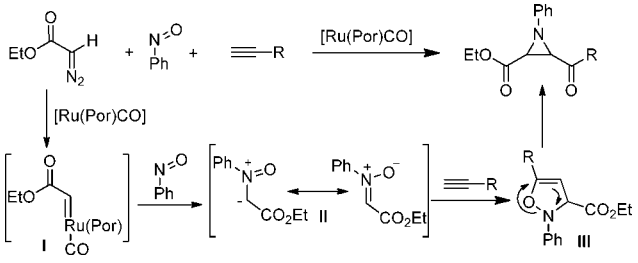
entry	R^1	alkyne	product	% yield [b] *dr* [c]
1	H		 **6a**	98 91:9
2	H		 **6b**	95 90:10
7	H		 **6c**	87 92:8
3	H		 **6d**	85 91:9
4	H		 **6e**	45 >99:1
5	H		 **6f**	77 >99:1
6	H		 **6g**	78 >99:1
8	Cl		 **6h**	85 90:10
9	Me		 **6i**	94 90:10

[a] **5**:**2**:**3**:[Ru(*p*-Cl-TPP)CO] = 1:2:2:0.01. [b] Isolated yield. [c] Determined by ^{1}H NMR, dr = *trans*:*cis*.

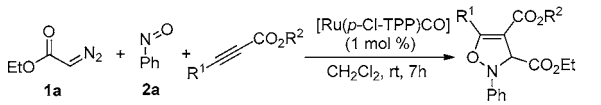
to the moderate diastereoselectivity observed in the reaction of EDA, nitrosobenzene, and terminal alkynes, the use of α-diazophosphonate as carbene source led to aziridines in excellent diastereoselectivity values (*trans*:*cis* = 90:10−99:1); in a number of cases, only one isomer was observed (entries 4−6). The high stereoselectivity might be attributed to the bulky phosphonate group. The internal alkynes were found to be not as effective as terminal alkynes giving corresponding aziridine 2-phosphonates in low yields.

A tentative reaction mechanism is depicted in Scheme 2. Ruthenium porphyrin decomposes the diazo compound to generate ruthenium−carbene complex **I**, which is trapped by nitrosoarene to form nitrone intermediate **II**.[10b] This *in situ* generated nitrone undergoes 1,3-dipolar cycloaddition with alkynes to give isoxazolines **III**; the latter undergo rapid rearrangement to give aziridines.[14] Control reaction of EDA, nitrosobenzene, and ethyl 2-heptynoate or methyl phenylpropiolate at room temperature for 7 h gave isoxazolines **7** and **8** in 35% and 69% yields, respectively (Scheme 3). These two

Scheme 2. Proposed Mechansim of the Three-Component Reaction



Scheme 3. Control Reaction of EDA, Nitrosobenzene, and Ethyl 2-Heptynoate or Methyl Phenylpropiolate



7, R^1 = ^{n}Bu, R^2 = Et, 35%
8, R^1 = Ph, R^2 = Me, 69%

compounds were observed to convert to corresponding aziridines at 40 °C, thereby lending support to the intermediacy of isoxazoline **III** in the three-component reaction.

In summary, an efficient three-component reaction that can be used for the rapid synthesis of diverse multifunctionalized aziridines from simple starting materials has been developed. With [Ru(*p*-Cl-TPP)CO] as catalyst, the one-pot reaction of diazoesters or diazophophonates, nitrosoarenes, and various alkynes gave a series of functionalized aziridine-2-carboxylates and aziridine-2-phophonates in good to high yields and with moderate to excellent diastereoselectivities. The reaction is stereoselective and tolerant to various functionalities and can be operated under mild conditions. It also features highly efficient formation of four new bonds in a single operation.

■ ASSOCIATED CONTENT

Supporting Information

General procedures and characterization data (including selected ^{1}H and ^{13}C NMR spectra) for compound **4a**−**4n**, **6a**−**6i**, **7**, and **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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