

Stereoselective Synthesis of Functionalized Pyrrolidines by Ruthenium Porphyrin-Catalyzed Decomposition of α -Diazo Esters and Cascade Azomethine Ylide Formation/1,3-Dipolar Cycloaddition Reactions

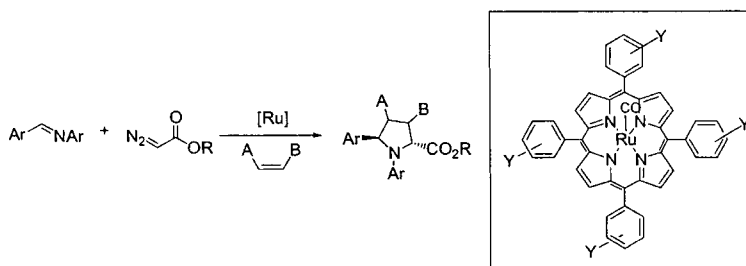
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ABSTRACT



Ruthenium porphyrins catalyze three-component coupling reaction of α -diazo esters with a series of *N*-benzylidene imines and alkenes to form functionalized pyrrolidines in excellent diastereoselectivities. The reaction proceeds via a reactive ruthenium–carbene intermediate and its subsequent reaction with imine to generate azomethine ylide, which reacts with alkenes via 1,3-dipolar cycloaddition.

Dipolar cycloaddition of carbonyl ylides to multiply bonded dipolarophiles continues to be a subject of considerable interest.¹ Notably, the dirhodium carboxylate-catalyzed tandem carbonyl ylide/1,3-dipolar cycloaddition by decomposition of diazocarbonyl compounds has been employed for stereoselective synthesis of oxygen heterocycles.² 1,3-Dipolar cycloaddition of azomethine ylide with olefinic dipolaro-

philes has been proven to be a powerful method for regio- and stereoselective synthesis of functionalized nitrogen heterocycles (e.g., pyrrolidines, alkaloids).^{1b,2} Several routes such as thermal or photolytic ring opening of aziridines,³ desilylation,⁴ dehydrohalogenation of iminium salts,⁵ and

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proton abstraction from imine derivatives of amino acids have been exploited to generate the reactive azomethine ylides *in situ*.⁶ Yet, interaction of metallocarbenoids with imine remains an attractive approach, because of mild reaction conditions and excellent regio- and stereocontrol achieved by elegant catalyst design. Padwa and co-workers⁷ extensively studied the [Rh₂(OAc)₄]-catalyzed intramolecular cyclization of imino-substituted α -diazo carbonyl compounds to form cyclic azomethine ylides, which subsequently underwent 1,3-dipolar cycloaddition with dipolarophiles.² Examples of Cu(I)-catalyzed intermolecular reactions of metallocarbenes with imines to give reactive azomethine ylides are also known in the literature.⁸

Metalloporphyrin-catalyzed carbenoid transformations using diazo compounds are currently receiving attention. We⁹ and others¹⁰ have already reported that ruthenium porphyrins (see Figure 1) are effective catalysts for stereo- and enan-

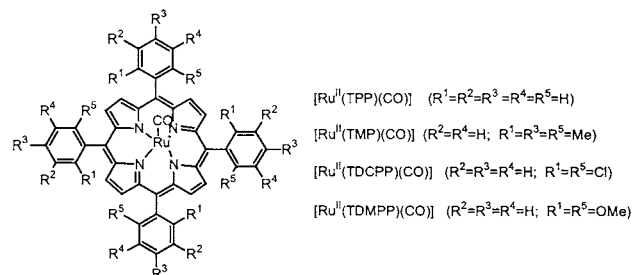


Figure 1. Ruthenium Porphyrins

tiostereoselective cyclopropanation^{9e-f} and C–H insertion reactions^{9b-d} and tandem carbonyl ylide formation/cycloaddition reaction.^{9a} As part of our continuing effort to develop ruthenium–carbene-mediated stereoselective C–C bond formations, we present herein the ruthenium porphyrin-catalyzed tandem azomethine ylide formation/intermolecular cycloaddition reactions to form functionalized pyrrolidines in excellent yields and stereoselectivities.

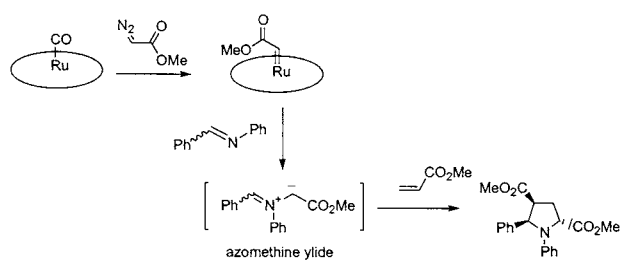


Figure 2. Proposed Mechanism

We began by studying the Ru-catalyzed azomethine ylide formation/cycloaddition involving benzyl diazoacetate (**2a**), *N*-benzylidene imine (**1a**), and acrylate (**3a**). The reaction

of **2a** with **1a** and **3a** (4 equiv) in CH₂Cl₂ in the presence of [Ru^{II}(TMP)(CO)] (0.5 mol %) at room temperature afforded cycloadduct **4a** in 78% isolated yield (Table 1). The structure

Table 1. Effect of Catalyst Loading^a

entry	catalyst loading (mol %)	% yield of 4a
1	1	79
2	0.5	78
3	0.2	74
4	0.1	74

^a Reaction conditions: **1a/2a/3a** = 1:1.1:4 at room temperature.

of **4a** was established by X-ray crystallography. ¹H NMR analysis of the crude reaction mixture detected **4a** as a single diastereomer under our experimental conditions. Different catalyst loadings have been examined under the same conditions. As depicted in Table 1, excellent activity was found even at 0.1 mol % catalyst loading, and cycloadduct **4a** was obtained in 74% yield.

α -Diazo esters **2b,c** also reacted uneventfully with **1a** and **3a** under the Ru-catalyzed conditions to give **4** selectively in ca. 60–75% yields (Table 2). Table 3 shows the effect of

Table 2. Effect of the Ester Substituents^a

entry	R	diazo ester	cycloadduct	% yield
1	Bn	2a	4a	74
2	Et	2b	4b	56
3	Me	2c	4c	76

^a Reaction conditions: [Ru^{II}(TMP)(CO)]/**1a/2/3a** = 0.001:1:1.1:4 in CH₂Cl₂ at room temperature.

solvent on the Ru-catalyzed cycloaddition with **1a**, **2a**, and **3a** as reactants. Apparently, halogenated solvents such as CH₂Cl₂, CHCl₃, and 1,2-dichloroethane are the best solvent systems. Employing toluene and benzene resulted in significant lower yields (ca. 50%) of **4c** under similar reaction conditions.

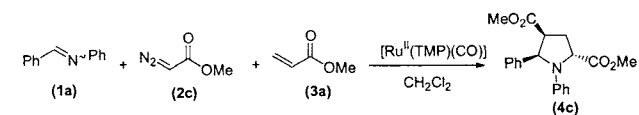
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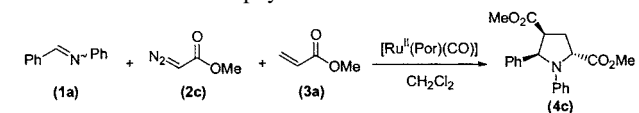
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Table 3. Effect of Solvents^a

entry	solvent	% yield of 4c
1	CH ₂ Cl ₂	68
2	CHCl ₃	72
3	1,2-dichloroethane	73
4	toluene	49
5	benzene	53

^a Reaction conditions: [Ru^{II}(TMP)(CO)]/1a/2c/3a = 0.001:1:1:4 at room temperature.

The effect of ligand structure on the ruthenium porphyrin-catalyzed cycloaddition reactions has been examined. As depicted in Table 4, up to 91% yield of **4c** was obtained

Table 4. Effect of Porphyrin Structure^a

entry	catalyst	% yield of 4c
1	[Ru ^{II} (TMP)(CO)]	78
2	[Ru ^{II} (TPP)(CO)]	79
3	[Ru ^{II} (TDCPP)(CO)]	91
4	[Ru ^{II} (TDMPP)(CO)]	61

^a Reaction conditions: Ru catalyst/1a/2c/3a = 0.001:2.0:1.0:4 at room temperature.

when [Ru^{II}(TDCPP)(CO)] [H₂TDCPP = *meso*-tetrakis(2,6-dichlorophenyl)porphyrin] was employed (entry 3). However, with [Ru^{II}(TDMPP)(CO)] [H₂TDMPP = *meso*-tetrakis(2,6-dimethoxyphenyl) porphyrin], the cycloaddition furnished a lower product yield of 61% (entry 4).

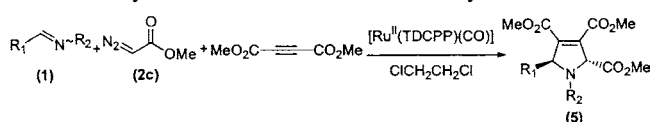
With [Ru^{II}(TDCPP)(CO)] (0.1 mol %) as catalyst, we found that using 1.5 and 4 equiv of acrylate **3** gave similar results for the azomethine ylide cycloaddition, and cycloadd-

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duct **4c** was isolated in 80% yield. For the analogous reactions using other ruthenium porphyrin catalysts, however, 4 equiv of **3a** would be needed to achieve similar yields of the cycloadducts.

To define the scope and generality of the tandem azomethine ylide cycloaddition, we extended our studies by including more benzylidene imines. Using methyl diazoacetate as carbenoid source, dimethyl acetylene-dicarboxylate as a dipolarophile, and [Ru^{II}(TDCPP)(CO)] as catalyst, all the imines employed in this study were found to give the desired cycloadducts in good to excellent yields as shown in Table 5.

Table 5. Cycloaddition with Various *N*-Benzylidene Imines **1**

entry	R ₁	R ₂	cycloadduct	% yield
1	Ph	Ph	5a	90
2	Ph	<i>p</i> -CH ₃ OC ₆ H ₄	5b	84
3	Ph	<i>p</i> -ClC ₆ H ₄	5c	85
4	<i>p</i> -NO ₂ C ₆ H ₄	Ph	5d	59
5	<i>p</i> -ClC ₆ H ₄	Ph	5e	92
6	<i>p</i> -CH ₃ OC ₆ H ₄	Ph	5f	87
7	<i>p</i> -MeC ₆ H ₄	Ph	5g	98
8	<i>m</i> -CH ₃ OC ₆ H ₄	Ph	5h	90
9	Ph	<i>m</i> -ClC ₆ H ₄	5i	69
10	Ph	<i>o</i> -ClC ₆ H ₄	5j	nil

As shown in Table 5, imine **1d** (R₁ = *p*-NO₂-C₆H₄, R₂ = Ph) bearing an electron-withdrawing NO₂ group gave cycloadduct **5d** with the lowest yield (59%). However, **5g** was obtained in almost quantitative yield (98%) for the reaction with imine **1g** (R₁ = *p*-CH₃-C₆H₄, R₂ = Ph) containing an electron-donating substituent.

A less pronounced influence was observed when varying the substituent R₂ (see Table 5, entries 1–3). The yield of the cycloaddition is dependent on the steric factors of the imine. For example, the reaction of **1i** (R₁ = Ph, R₂ = *m*-Cl-C₆H₄) gave **5i** in lower yield of 69%, compared to 85% yield obtained when **1c** (R₁ = Ph, R₂ = *p*-Cl-C₆H₄) was the substrate. Notably, with **1j** (R₁ = Ph, R₂ = *o*-Cl-C₆H₄) as substrate, no cycloadduct was isolated. We attribute this finding to the steric bulkiness of **1j** and **1i**, and the Ru-catalyzed cycloaddition would proceed via a highly organized transition state involving three reaction components.

In this work, we have studied the Ru-catalyzed azomethine ylide cycloaddition with various dipolarophiles. We first examined the reactions with a series of monosubstituted alkenes **3a–c** as dipolarophiles. Reactions of **1b** (1.1 equiv), **2c** (1 equiv), and the alkenes (1.5 equiv) in CH₂Cl₂ in the presence of [Ru^{II}(TDCPP)(CO)] (0.1 mol %) afforded cycloadducts **4d**, **4e**, and **4f** in 63, 57, and 61%, respectively (Table 6, entries 1–3).

Similarly disubstituted alkenes **3d,f** such as α -methyl acrylate, cinnamophenone, and *N*-phenylmaleimide also

Table 6. Cycloaddition with Various Dipolarophiles^a

entry	dipolarophile	product	%yield
1 ^b			63
2 ^b			57
3 ^b			61
4 ^c			45
5 ^c			51
6 ^c			52

^a Reaction conditions: Ru catalyst/**1a**/**2c**/**3** = 0.001:2.0:1.0:4. ^b Reaction was undertaken at room temperature. ^c Reaction was undertaken at 50°C.

reacted with **1b** and **2c** under the Ru-catalyzed conditions to afford the cycloadducts **4g–i** in ca. 50% yield. The moderate yields observed for the reactions with disubstituted

alkenes as dipolarophiles could be ascribed to the increased steric bulkiness of the alkenes. When dimethyl acetylenedicarboxylate was used as dipolarophile, the reaction with **1b** and **2c** proceeded effectively to give the expected cycloadduct in 84% yield.

Previous studies showed that ruthenium(II) porphyrins reacted with diazo compounds to give ruthenium–carbene complexes.^{9c–f} We postulate that the cycloaddition is mediated by an azomethine ylide intermediate, which is generated by the reaction of ruthenium–carbene complexes with imine. The azomethine ylide (which can be a free or metal-bound species) undergoes 1,3-dipolar cycloaddition with alkenes to give the functionalized prolines as products.

In conclusion, ruthenium porphyrin complexes are excellent catalysts for the azomethine ylide-mediated cycloaddition reaction involving *N*-benzylidene imine, diazo esters, and alkenes to form functionalized pyrrolidines with remarkable stereoselectivity. Such a one-pot, three-component coupling system provides a convenient entry to functionalized nitrogen heterocycles that are of interest in organic synthesis.

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Supporting Information Available: Detailed descriptions of experimental procedures, characterization data, and detailed description of the X-ray crystallographic determination of **4d** and **5a**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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