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Stereoselective Synthesis of Multifunctionalized 1,2,4-Triazolidines by a Ruthenium Porphyrin-Catalyzed Three-Component Coupling Reaction

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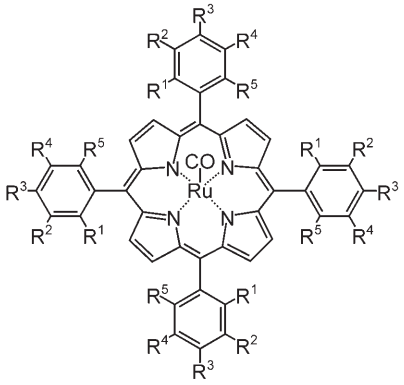
Abstract: Multifunctionalized 1,2,4-triazolidines have been synthesized by a ruthenium porphyrin-catalyzed three-component coupling reaction. In a one-pot reaction, ruthenium porphyrins catalyzed the *in situ* generation of azomethine ylides from α-diazo esters and imines. Stereoselective 1,3-dipolar cycloaddition reactions of the azomethine ylides with dialkyl azodicarboxylates gave the corresponding 1,2,4-triazolidines in good yields (up to 85%). Using chiral 8-phenylmenthanol α-diazo ester as the carbenoid source, chiral 1,2,4-triazolidines have been obtained with good diastereoselectivity (up to 84% *de*). Some of the 1,2,4-triazolidines exhibited good cytotoxicity against human nasopharyngeal carcinoma (SUNE1) (IC_{50} = 10.4 μM) and human cervical carcinoma (Hela) (IC_{50} = 10.7 μM) cell lines.

Keywords: cytotoxicity; 1,3-dipolar cycloadditions; human carcinoma; ruthenium porphyrins; 1,2,4-triazolidines

Multifunctionalized heterocycles are important synthetic building blocks for organic synthesis and key structural moieties of many bioactive natural products and therapeutic drug molecules. Dipolar cycloadditions of carbonyl ylides to multiply bonded dipolarophiles have emerged as an efficient approach for heterocycle synthesis.[1] In particular, the 1,3-dipolar cycloaddition of azomethine ylides with olefinic dipolarophiles has been proven to be a powerful method for the regio- and stereoselective synthesis of functionalized nitrogen heterocycles such as pyrrolidines.[1a,2] However, the analogous cycloaddition reactions using nitrogen-based dipolarophiles to afford multi-nitrogen substituted heterocycles such as 1,2,4-triazolidines remain sparse. A number of routes including thermal or photolytic ring opening of aziridines[3] have been exploited to generate the reactive azomethine ylides *in situ* for cycloaddition with dialkyl azodicarboxylates to afford 1,2,4-triazolidines.[4]

Over the years, we[5] and others[6] have demonstrated that ruthenium porphyrins are effective catalysts for highly stereo- and enantioselective carbenoid transfer reactions. We have also shown that ruthenium porphyrins are effective at catalyzing a three-component coupling reaction between α-diazo esters, imines, and olefinic dipolarophiles in a one-pot reaction for the synthesis of multifunctionalized pyrrolidines[7] and chiral pyrrolines from chiral α-diazo esters.[8]

Here we report the first stereoselective synthesis of 1,2,4-triazolidines based on the aforementioned ruthenium porphyrin-catalyzed three-component coupling process (Figure 1 and Figure 2). In the present work, ruthenium porphyrins catalyze the decomposition of α-diazo esters to give metallocarbenoids that react with imines to afford azomethine ylides. Subsequently, these azomethine ylides undergo 1,3-dipolar cycloaddition reactions with dialkyl azodicarboxylates to afford 1,2,4-triazolidines in good yields. Using chiral 8-phenylmenthanol α-diazo ester as the carbenoid source, the first asymmetric synthesis of chiral 1,2,4-triazolidines with good diastereoselectivity (up to 84%) has been achieved.[9] Interestingly, some of the 1,2,4-triazolidines exhibited good cytotoxicity against human nasopharyngeal carcinoma (SUNE1) (IC_{50} = 10.4 μM) and human cervical carcinoma (Hela) (IC_{50} = 10.7 μM) cell lines.



[Ru(2,6-Cl_2TPP)(CO)] ($R^2 = R^3 = R^4 = H$; $R^1 = R^5 = Cl$)

[Ru(TPP)(CO)] ($R^1 = R^2 = R^3 = R^4 = R^5 = H$)

[Ru(TMP)(CO)] ($R^2 = R^4 = H$; $R^1 = R^3 = R^5 = Me$)

[Ru[4-(OMe)TPP](CO)] ($R^1 = R^2 = R^4 = R^5 = H$; $R^3 = OMe$)

Figure 1. General structures of ruthenium porphyrin catalysts.

At the outset, we examined the cycloaddition of imine **1a**, diethyl azodicarboxylate (**2a**) and ethyl α-diazoacetate (**3a**) using [Ru(2,6-Cl_2TPP)(CO)] as a catalyst. Slow addition of **3a** in toluene to a mixture of **1a**, **2a**, and [Ru(2,6-Cl_2TPP)(CO)] (0.5 mol%) in toluene at 45 °C *via* a syringe pump afforded cycloadduct **4a** in 82% isolated yield (Table 1, entry 1). On the basis of a ^{1}H NMR analysis of the crude reaction mixture, a single diastereomer was obtained under the experimental conditions. Other ruthenium porphyrin catalysts have also been used in the cycloaddition reactions of **1a**, **2a**, and **3a**. As shown in Table 1, [Ru(2,6-Cl_2TPP)CO] gave the highest yield in the cycloaddition reaction. With [Ru(TPP)(CO)], [Ru(TMP)(CO)] or [Ru(4-(OMe)TPP)(CO)] as a catalyst, isolated yields of 70–75% were obtained (entries 2–4).

To define the scope of the three-component coupling reaction, we extended our studies by including different imines **1** and dialkyl azodicarboxylates **2** using α-diazo ester **3a** as the carbenoid source and [Ru(2,6-Cl_2TPP)CO] as a catalyst. As shown in Table 2, comparable yields (78–85%) were obtained

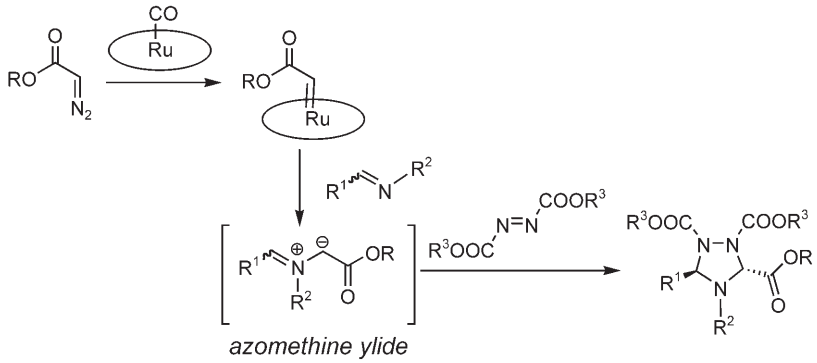
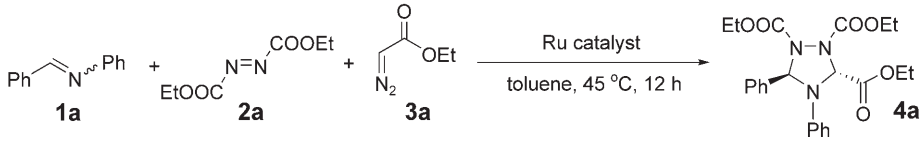


Figure 2. Proposed reaction mechanism

Table 1. Catalyst screening of 1,3-dipolar cycloaddition.[a]

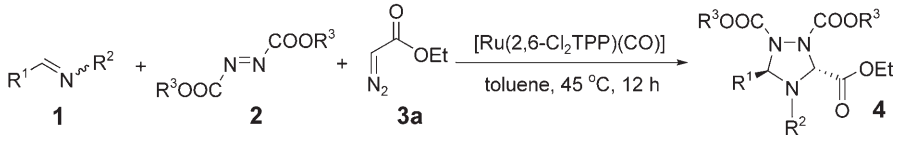


Entry	Catalyst	Yield [%][b]
1	[Ru(2,6-Cl_2TPP)(CO)]	82
2	[Ru(TPP)(CO)]	70
3	[Ru(TMP)(CO)]	72
4	[Ru(4-(OMe)TPP)(CO)]	75

[a] To imine **1a** (1.0 mmol), diethyl azodicarboxylate **2a** (1.2 mmol) and [Ru(Por)(CO)] (Por = porphyrin dianion) catalyst (0.5 mol%) in toluene (3 mL) was added α-diazo ester **3a** (1.2 mmol) in toluene (3 mL) over 10 h *via* a syringe pump at 45 °C. After addition, the resulting solution was stirred for an additional 2 h.

[b] Yield of isolated product.

Table 2. Ruthenium porphyrin-catalyzed 1,3-dipolar cycloaddition.[a]



Entry	Imine (**1**)	R^1	R^2	**2** (R^3)	Product[b]	Yield [%][c]
1	**1a**	Ph	Ph	**2a** (Et)	**4a**	82
2	**1b**	*p*-$MeOC_6H_4$	Ph	**2a** (Et)	**4b**	85
3	**1c**	*m*-$MeOC_6H_4$	Ph	**2a** (Et)	**4c**	78
4	**1d**	*p*-MeC_6H_4	Ph	**2a** (Et)	**4d**	85
5	**1e**	*p*-ClC_6H_4	Ph	**2a** (Et)	**4e**	80
6	**1f**	*p*-$NO_2C_6H_4$	Ph	**2a** (Et)	**4f**	62
7	**1g**	Ph	*p*-ClC_6H_4	**2a** (Et)	**4g**	86
8	**1h**	2-furyl	*m*-$MeOC_6H_4$	**2a** (Et)	**4h**	72
9	**1b**	*p*-$MeOC_6H_4$	Ph	**2b** (*i*-Pr)	**4i**	82
10	**1b**	*p*-$MeOC_6H_4$	Ph	**2c** (*t*-Bu)	**4j**	76
11	**1i**	*p*-$MeOC_6H_4$	*t*-Bu	**2a** (Et)	-	-[d]

[a] Imine **1** (1.0 mmol), **2** (1.2 mmol), **3a** (1.2 mmol), [Ru(2,6-Cl_2TPP)(CO)] (0.5 mol%) and toluene (6 mL).
[b] **3a** was added dropwise *via* a syringe pump for 10 h.
[c] Yield of isolated product.
[d] No reaction was observed.

for imines **1a–d** bearing electron-donating substituents (R^1 = Ph, *p*-$MeOC_6H_4$, *m*-$MeOC_6H_4$, and *p*-MeC_6H_4) and from imines **1e**, **f** with electron-withdrawing substituents (R^1 = *p*-ClC_6H_4 and *p*-$NO_2C_6H_4$) (62–80% yield). Similar product yields (80% *vs.* 86%) were obtained for **1e** (R^1 = *p*-ClC_6H_4, R^2 = Ph) and **1g** (R^1 = Ph, R^2 = *p*-ClC_6H_4). The furyl-substituted cycloadduct was obtained in 72% yield by the coupling reaction with imine **1h** (R^1 = 2-furan, R^2 = *m*-$MeOC_6H_4$). Reactions of diisopropyl azodicarboxylate (**2b**) and di-*tert*-butyl azodicarboxylate (**2c**) with imine **1b** afforded cycloadducts **4i** and **4j** in 82% and 76% yields, respectively (Table 2, entries 9 and 10). The molecular structure of **4i** was established by X-ray crystallography (Figure 3). No reaction was observed for imine **1i** (R^1 = *p*-$MeOC_6H_4$, R^2 = *t*-Bu) (entry 11).

Using chiral 8-phenylmenthanol α-diazo ester **3b** as the carbenoid source, diethyl azodicarboxylate (**2a**) as dipolarophile and [Ru(2,6-Cl_2TPP)(CO)] as catalyst with a series of *N*-benzylidine imines **1**, chiral 1,2,4-triazolidines were obtained in diastereoselectivity up to 84% (Table 3). A diastereoselectivity of 57% was obtained for the cycloaddition of imine **1a** (R^1 = Ph, R^2 = Ph) (entry 1). Cycloaddition of imine **1b** (R^1 = *p*-$MeOC_6H_4$, R^2 = Ph) gave the corresponding cycloadduct **5b** with high diastereoselectivity (84%) (entry 2). Notwithstanding this, less than 10% yield was observed for imine **1c**, probably due to the steric bulkiness of the *m*-OMe substituent (entry 3). We noted that high diastereoselectivity (70–84%) was obtained for imines **1d** (R^1 = *p*-MeC_6H_4, R^2 = Ph) and **1e** (R^1 = *p*-ClC_6H_4, R^2 = Ph) (entries 4 and 5). Imine **1f** (R^1 = *p*-$NO_2C_6H_4$, R^2 = Ph) gave less than 10% yield

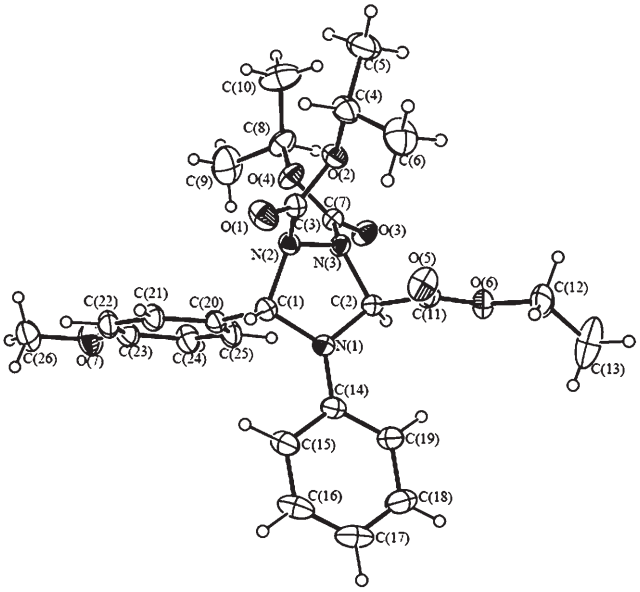
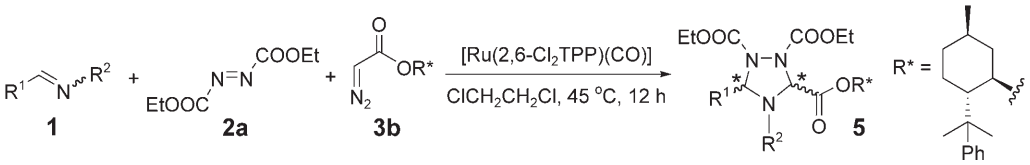


Figure 3. ORTEP plot of **4i**.

(entry 6). Lower diastereoselectivity (32–55%) was obtained for imines **1g** and **1j–l** with R^2 as substituted phenyl groups (R^2 = *p*-ClC_6H_4, *p*-$MeOC_6H_4$, *p*-BrC_6H_4, and *m*-ClC_6H_4) (entries 7–10). Using diisopropyl azodicarboxylate (**2b**) instead of **2a**, 21% *de* was observed (entry 11).

The *trans* configuration of the two substituents (i.e., aryl ring and ethyl ester group) of **4i** was established by X-ray crystallography (Figure 3) and determined by 2D ^{1}H NMR spectroscopy (^{1}H-^{1}H COESY and ^{1}H-^{1}H NOESY) (see Supporting Information). No

Table 3. Ruthenium porphyrin-catalyzed asymmetric 1,3-dipolar cycloaddition.[a]



Entry	Imine	R^1	R^2	Product[b]	Yield [%][c]	*de* [%][d]
1	**1a**	Ph	Ph	**5a**	57	57
2	**1b**	*p*-$MeOC_6H_4$	Ph	**5b**	55	84
3	**1c**	*m*-$MeOC_6H_4$	Ph	**-**	<10	-
4	**1d**	*p*-MeC_6H_4	Ph	**5c**	64	70
5	**1e**	*p*-ClC_6H_4	Ph	**5d**	48	84
6	**1f**	*p*-$NO_2C_6H_4$	Ph	**-**	<10	-
7	**1g**	Ph	*p*-ClC_6H_4	**5e**	43	42
8	**1j**	Ph	*p*-$MeOC_6H_4$	**5f**	54	32
9	**1k**	Ph	*p*-BrC_6H_4	**5g**	42	35
10	**1l**	Ph	*m*-ClC_6H_4	**5h**	28	55
11[e]	**1a**	Ph	Ph	**5i**	50	21

[a] Imine **1** (1.2 mmol), **2a** (2.0 mmol), **3b** (1.0 mmol), [Ru(2,6-Cl_2TPP)(CO)] (1 mol%) and $ClCH_2CH_2Cl$ (10 mL).
[b] **3b** was added dropwise *via* a syringe pump for 10 h.
[c] Yield of isolated product.
[d] Determined by ^1H NMR analysis of crude reaction mixtures.
[e] Imine **2b** was used instead of **2a**.

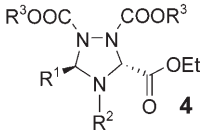
NOE cross-peak was found between the two protons on the 1,2,4-triazolidine ring. For compound **5c**, the *trans* configuration was confirmed by ^1H-^1H NOESY as no NOE cross-peak was found between the two protons on the 1,2,4-triazolidine ring. To determine the absolute configuration of the two stereogenic carbon centers on the 1,2,4-triazolidine ring, we have tried to separate diastereomers of compounds **5** for X-ray crystallographic analysis. However, the diastereomers could not be separated and no crystalline solid of **5** could be obtained even after using different solvent systems and crystal-growing techniques. Asterisk symbols (*) are used to indicate the *trans* stereogenic carbon centers on the 1,2,4-triazolidine ring of **5** with unknown absolute configuration (see Table 3 and Supporting Information).

Multicomponent coupling reactions have greatly facilitated drug discovery processes in both academic and industrial laboratories by providing structurally diverse compound libraries for high-throughput biological screenings in a time- and cost-effective manner.[10] In this work, we found that some of the 1,2,4-triazolidines exhibited good cytotoxicity and selectivity against a number of human carcinoma cell lines.

The *in vitro* cytotoxicity of **4a–j** against human nasopharyngeal carcinoma (SUNE1) and human cervical carcinoma (Hela) cell lines were examined by using the MTT assay (Table 4). It is interesting to note that the cytotoxicities of **4a–j** against SUNE1 cell line vary significantly with the substituents R^1, R^2 and R^3. As illustrated, **4a** (R^1=Ph, R^2=Ph, R^3=Et) exhibited good cytotoxicity of (IC_{50}=14.6 μM) (entry 1). Compounds **4b** (R^1=*p*-$MeOC_6H_4$) and **4c** (R^1=*m*-$MeOC_6H_4$) were relatively non-cytotoxic ($IC_{50}>100$ μM) while **4d** (R^1=*p*-MeC_6H_4), **4e** (R^1=*p*-ClC_6H_4) and **4f** (R^1=*p*-$NO_2C_6H_4$) were cytotoxic (IC_{50}=10.4–48.1 μM). Both *p*-Cl substituted compounds **4e** (R^1=*p*-ClC_6H_4) and **4g** (R^2=*p*-ClC_6H_4) exhibited similar cytotoxicity (IC_{50}=*ca.* 10.4 μM) regardless of the position of the *p*-Cl substituent in R^1 or R^2 (entries 5 *vs.* 7). For **4h** (R^1=2-furyl, R^2=*m*-$MeOC_6H_4$), its IC_{50} value was >100 μM. Note that substituent R^3 also exerted a strong effect on the cytotoxicity. With the same R^1 substituent (R^1=*p*-$MeOC_6H_4$), no cytotoxicity was found for **4b** (R^3=Et) and **4i** (R^3=*i*-Pr). Yet, **4j** bearing a more bulky *tert*-butyl group (R^3=*t*-Bu) is cytotoxic (IC_{50}=16.0 μM). Compounds **4a**, **4d**, **4e** and **4g** are cytotoxic (IC_{50}= 10.7–32.4 μM) against Hela cell line but no cytotoxicity was observed for **4b**, **4c**, **4f** and **4h–j**.

It is interesting to note that compounds **4** displayed good cytotoxicity (IC_{50}=10.4–48.1 μM) against SUNE1 and Hela cell lines. However, this class of compounds has low cytotoxicity ($IC_{50}>100$ μM) against human breast carcinoma (MCF-7) and human hepatocellular carcinoma (HepG2) cell lines. Combinatorial syntheses and cytotoxicity studies of more 1,2,4-triazolidines are in progress to understand the structure-activity relationship and hence to design new derivatives of higher potency.

Table 4. Cytotoxicity of **4**.[a]



4

Entry	Compound	R^1	R^2	R^3	SUNE1 [μM][b]	Hela [μM][b]
1	**4a**	Ph	Ph	Et	14.6	32.4
2	**4b**	*p*-$MeOC_6H_4$	Ph	Et	*n*	*n*
3	**4c**	*m*-$MeOC_6H_4$	Ph	Et	*n*	*n*
4	**4d**	*p*-MeC_6H_4	Ph	Et	21.8	15.9
5	**4e**	*p*-ClC_6H_4	Ph	Et	10.4	13.9
6	**4f**	*p*-$NO_2C_6H_4$	Ph	Et	48.1	*n*
7	**4g**	Ph	*p*-ClC_6H_4	Et	10.5	10.7
8	**4h**	2-furyl	*m*-$MeOC_6H_4$	Et	*n*	*n*
9	**4i**	*p*-$MeOC_6H_4$	Ph	*i*-Pr	*n*	*n*
10	**4j**	*p*-$MeOC_6H_4$	Ph	*t*-Bu	16.0	*n*

[a] All compounds are non-cytotoxic ($IC_{50} > 100$ μM) against MCF-7 and HepG2 cell lines.
[b] *n*: $IC_{50} > 100$ μM.

In conclusion, we have found that ruthenium porphyrins are effective catalysts for stereoselective synthesis of multifunctionalized 1,2,4-triazolidines with high stereoselectivity *via* a three-component coupling reaction involving *N*-benzylidene imines, dialkyl azodicarboxylates and α-diazo esters. In addition, some of 1,2,4-triazolidines displayed good cytotoxicity against human nasopharyngeal carcinoma (SUNE1) ($IC_{50} = 10.4$ μM) and human cervical carcinoma (Hela) ($IC_{50} = 10.7$ μM) cell lines.

Experimental Section

General Remarks

Reagents were obtained commercially and used without further purification unless indicated otherwise. All solvents used were dried using standard, published methods and distilled before use. NMR spectra were recorded on Bruker a AMX-300/400 spectrometer for ^{1}H NMR and at 75/100 MHz for ^{13}C NMR in $CDCl_3$. The chemical shifts are expressed in ppm and coupling constants are given in Hz. Data for ^{1}H NMR are recorded as follows: chemical shift (ppm), multiplicity (s, singlet; d, doublet; t, triplet; m, multiplet), coupling constant (Hz), integration. Data for ^{13}C NMR are reported in terms of chemical shift (δ, ppm).

General Procedure for Ruthenium Porphyrin-Catalyzed Three-Component Coupling Reactions

To a solution of imine **1** (1.0 mmol), dialkyl azodicarboxylate **2** (1.2 mmol) and [Ru(II)(Por)(CO)] (Por = porphyrin dianion) catalyst (0.5×10^{-2} mmol) in toluene (3 mL) was added α-diazo ester **3** (1.2 mmol) in toluene (3 mL) over 10 h *via* a syringe pump at 45 °C. After addition, the resulting solution was stirred for an additional 2 h. The mixture was concentrated and purified by flash column chromatography using a mixture of ethyl acetate/petroleum ether (15:1 to 10:1) as eluent to give the desired cycloadduct.

Acknowledgements

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