ORGANIC LETTERS

2005
Vol. 7, No. 24
5349−5352

Asymmetric Synthesis of Multifunctionalized Pyrrolines by a Ruthenium Porphyrin-Catalyzed Three-Component Coupling Reaction

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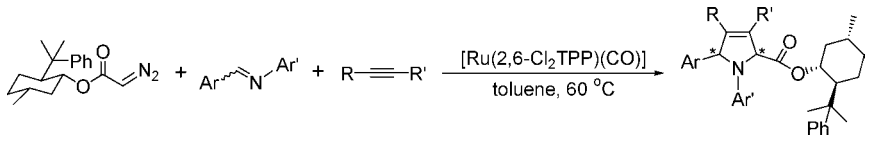
Received April 14, 2005

ABSTRACT



Chiral multifunctionalized pyrrolines have been synthesized by a ruthenium porphyrin catalyzed three-component coupling reaction. In a one-pot reaction, ruthenium porphyrins catalyzed in situ generation of chiral azomethine ylides from chiral diazo esters and imines. Asymmetric 1,3-dipolar cycloaddition reactions of the chiral azomethine ylides with dipolarophiles afforded the corresponding pyrrolines in good yields and high diastereoselectivity (up to 92% de).

Chiral multifunctionalized pyrrolidines are versatile synthetic building blocks for organic synthesis and important structural elements of many therapeutic drug molecules. Generally, such nitrogen-containing heterocycles are synthesized by asymmetric 1,3-dipolar cycloadditions[1] that employ chiral azomethine ylides,[2] chiral olefinic dipolarophiles,[3] or chiral metal catalysts.[4] The cycloadditions of chiral azomethine ylides generated in situ from *N*-metalation of imines,[2a] the desilylation of imines,[2b,e,f] the deprotonation of iminium salts,[2c,g,h,j] and the thermolysis of aziridines[2d,i] have been particularly well studied. However, these synthetic strategies do not readily afford a sufficient variety of structurally diverse pyrrolidines for high-throughput biological screening in a time- and cost-effective manner. Application of multi-component coupling approaches[5] to this area could facilitate future drug discovery efforts in both academic and industrial laboratories.

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(1) For reviews on asymmetric 1,3-dipolar cycloaddition reactions, see: (a) *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*; Padwa, A., Pearson, W. H., Eds.; Wiley: Huboken, NJ, 2003. (b) Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863. (c) Karlsson, S.; Högberg, H. E. *Org. Prep. Proced. Int.* **2001**, *33*, 105. (d) Nájera, C.; Sansano, J. M. *Curr. Org. Chem.* **2003**, *7*, 1105.

(2) For examples, see: (a) Dogan, Ö.; Öner, I.; Ülkü, D.; Arici, C.; *Tetrahedron: Asymmetry* **2002**, *13*, 2099. (b) Karlsson, S.; Högberg, H.-E. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1076. (c) Chinchilla, R.; Falvello, L. R.; Galindo, N.; Nájera, C. *Eur. J. Org. Chem.* **2001**, 3133. (d) Garner, P.; Dogan, Ö.; Youngs, W. J.; Kennedy, V. O.; Protasiewicz, J.; Zaniewski, R. *Tetrahedron* **2001**, *57*, 71. (e) Karlsson, S.; Högberg, H.-E. *Tetrahedron: Asymmetry* **2001**, *12*, 1975. (f) Karlsson, S.; Högberg, H.-E. *Tetrahedron: Asymmetry* **2001**, *12*, 1977. (g) Enders, D.; Meyer, I.; Runsink, J.; Raabe, G. *Tetrahedron* **1998**, *54*, 10733. (h) Grigg, R. *Tetrahedron: Asymmetry* **1995**, *6*, 2475. (i) Garner, P.; Dogan, O. *J. Org. Chem.* **1994**, *59*, 4. (j) Deprez, P.; Royer, J.; Husson, H.-P. *Tetrahedron: Asymmetry* **1991**, *2*, 1189.

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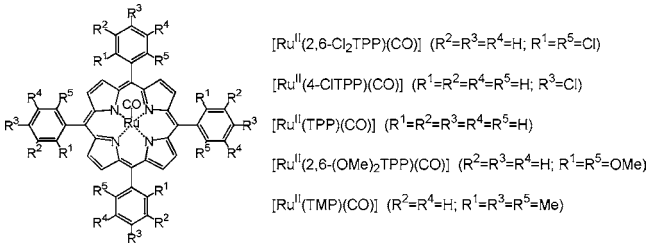
10.1021/ol050819n CCC: $30.25
Published on Web 10/29/2005

Over the years, we[6] and others[7] 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[8] for pyrrolidine synthesis.[9−10]



Herein is described the first asymmetric synthesis of chiral pyrrolines based on the aforementioned ruthenium porphyrin catalyzed three-component coupling process (Figure 1). In this work, we show that ruthenium porphyrins catalyze the decomposition of chiral 8-phenylmenthol α-diazo esters to give metallocarbenoids that react with imines to afford chiral azomethine ylides. Subsequently, these chiral azomethine ylides undergo 1,3-dipolar cycloaddition reactions with dipolarophiles to afford chiral pyrrolines in good yields and high diastereoselectivities (up to 92% de). In addition, we provide experimental evidence for the proposed mechanism of the three-component coupling reaction.

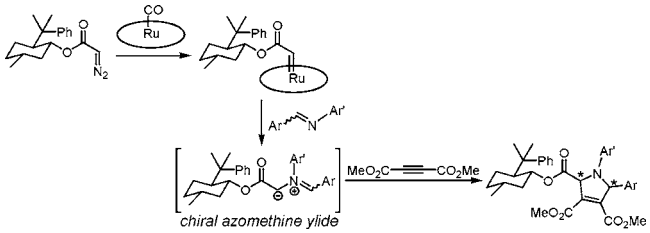
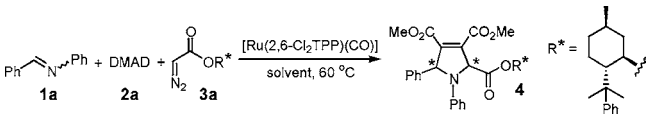


Figure 1. Proposed mechanism.

At the outset, we examined the cycloaddition of chiral 8-phenylmenthanol α-diazo ester **3a** with imine **1a** and dimethyl acetylenedicarboxylate (DMAD) **2a** using [Ru(2,6-Cl$_2$TPP)(CO)] as catalyst. Slow addition of **3a** in CH_2Cl_2 to a mixture of **1a**, **2a**, and [Ru(2,6-Cl$_2$TPP)(CO)] (0.1 mol %) in CH_2Cl_2 at 40 °C via a syringe pump afforded cycloadduct **4** in 70% isolated yield. On the basis of ^{1}H NMR analysis of the crude reaction mixture, two diastereomers were judged to be present in a ratio of 2.1:1 (i.e., 36% de) (Table 1, entry 1).

Table 1. Effect of Solvent[a]



entry	solvent	yield[b] (%)	de[c] (%)
1	CH_2Cl_2	70	36
2	$ClCH_2CH_2Cl$	27	33
3	$CHCl_3$	no reaction	–
4	toluene	70	79
5	benzene	27	50
6	ethylbenzene	40	66
7	xylene	54	67
8	chlorobenzene	49	71
9	THF	no reaction	–

[a] Ru catalyst/**1a**/**2a**/**3a** = 0.001:1.2:2:1. [b] Isolated yield. [c] Determined by ^{1}H NMR analysis of the crude products.

We next examined the effect of different solvents on the Ru-catalyzed cycloaddition reaction of **1a**, **2a**, and **3a**. As shown in Table 1, remarkable solvent effects were observed on the diastereoselectivity of cycloaddition. Significant improvements in diastereoselectivity (50−79% de) could be achieved using aromatic solvents (toluene, benzene, ethylbenzene, xylene, and chlorobenzene), when compared with halogenated solvents (CH_2Cl_2 and $ClCH_2CH_2Cl$) (33−36% de). Notably, up to 79% de and 70% yield of **4** could be attained by using toluene as the reaction solvent, and this

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(10) For examples on three-component 1,3-dipolar cycloaddition reactions, see: (a) Fokas, D.; Ryan, W. J.; Casebier, D. S.; Coffen, D. L. *Tetrahedron Lett.* **1998**, *39*, 2235. (b) Hamper, B. C.; Dukesherer, D. R.; South, M. S. *Tetrahedron Lett.* **1996**, *37*, 3671. (c) Murphy, M. M.; Schullek, J. R.; Gordon, E. M.; Gallop, M. A. *J. Am. Chem. Soc.* **1995**, *117*, 7029.

was employed for the subsequent studies. No reaction was observed when the reactions were performed in $CHCl_3$ or THF.

The effect of ligand structure on the ruthenium porphyrin catalyzed cycloaddition reactions of **1a**, **2a**, and **3a** was also examined (Table 2). [Ru(2,6-Cl_2TPP)CO] was found to exhibit the best diastereoselectivity (79%) and good yield (70%) in the cycloaddition reaction. With [Ru(4-ClTPP)(CO)] or [Ru(TPP)(CO)] as catalyst, comparable yields (71−73%) and diastereoselectivities (71−72%) were obtained. While [Ru(2,6-$(OMe)_2$TPP)(CO)] and [Ru(TMP)(CO)] displayed poor catalytic activity, only a trace amount of cycloaddition product was detected.

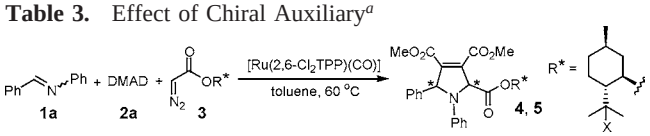
Table 2. Effect of Porphyrin Structure[a]

entry	catalyst	yield[b] (%)	de[c] (%)
1	[Ru(2,6-Cl_2TPP)(CO)]	70	79
2	[Ru(4-ClTPP)(CO)]	73	72
3	[Ru(TPP)(CO)]	71	71
4	[Ru(2,6-$(OMe)_2$TPP)(CO)]	trace	–
5	[Ru(TMP)(CO)]	trace	–

[a] Ru catalyst/**1a**/**2a**/**3a** = 0.001:1.2:2:1. [b] Isolated yield. [c] Determined by ^{1}H NMR analysis of the crude products.

When the 8-phenyl ring of chiral α-diazo ester **3a** was replaced by a hydrogen atom, a significant decrease in diastereoselectivity (from 79% to 33%) resulted (Table 3).

Table 3. Effect of Chiral Auxiliary[a]



entry	α-diazo ester	X	cycloadduct	yield[b] (%)	de[c] (%)
1	**3a**	Ph	**4**	70	79
2	**3b**	H	**5**	90	33

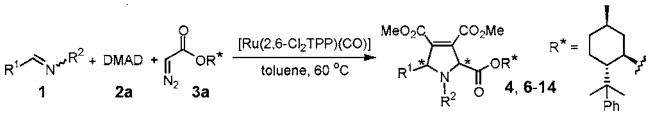
[a] Ru catalyst/**1a**/**2a**/**3** = 0.001:1.2:2:1. [b] Isolated yield. [c] Determined by ^{1}H NMR analysis of the crude products.

The bulky 8-phenyl ring was therefore crucial to achieving high diastereoselectivity in the cycloaddition reaction.

To define the scope of the Ru-catalyzed cycloaddition process, we extended our studies to a range of *N*-benzylidine imines with different substituents on the two aromatic rings (i.e., R^1 and R^2). Using chiral α-diazo ester **3a** as the carbenoid source, DMAD (**2a**) as dipolarophile, and [Ru(2,6-Cl_2TPP)(CO)] as catalyst, with a series of *N*-benzylidine imines **1a**−**k**, the chiral pyrrolines were obtained in good yields and high diastereoselectivity (Table 4).

We note that higher yields (58−70%) were obtained for imines **1a**−**d** bearing electron-donating substituents (R^1 = Ph, *m*-MeOPh, *p*-MeOPh, and *p*-MePh) when compared imines **1e**,**f** with electron-withdrawing substituents (R^1 = *p*-ClPh and *p*-NO_2Ph) (39−45% yield). Nevertheless, high diastereoselectivities (70−85%) were achieved for all the imines **1a**−**f**. Notably, up to 85% diastereoselectivity was attained for imine **1f** with a *p*-NO_2 substituent (entry 6).

Table 4. Cycloaddition with Various *N*-Benzylidene Imines[a]



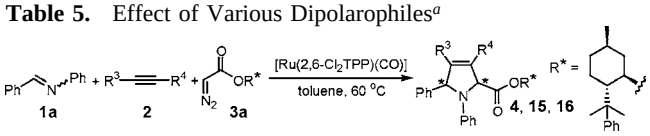
entry	imine	R^1	R^2	cycloadduct	yield[b] (%)	de[c] (%)
1	**1a**	Ph	Ph	**4**	70	79
2	**1b**	*m*-MeOPh	Ph	**6**	58	70
3	**1c**	*p*-MeOPh	Ph	**7**	68	77
4	**1d**	*p*-MePh	Ph	**8**	67	74
5	**1e**	*p*-ClPh	Ph	**9**	45	73
6	**1f**	*p*-NO_2Ph	Ph	**10**	39	85
7	**1g**	Ph	*p*-MeOPh	**11**	61	74
8	**1h**	Ph	*p*-BrPh	**12**	30	60
9	**1i**	Ph	*p*-ClPh	**13**	47	70
10	**1j**	Ph	*m*-ClPh	**14**	32	72
11	**1k**	Ph	*o*-ClPh		no reaction	

[a] Ru catalyst/**1**/**2a**/**3a** = 0.001:1.2:2:1. [b] Isolated yield. [c] Determined by ^{1}H NMR analysis of the crude products.

Similarly, a higher yield (61%) was obtained for imine **1g** bearing an electron-donating substituent (R^2 = *p*-MeOPh) while 30−47% yields were obtained for imines **1h**−**j** bearing electron-withdrawing substituents (R^2 = *p*-BrPh, *p*-ClPh, and *m*-ClPh). Interestingly, imines **1i** (with *p*-Cl) and **1j** with (*m*-Cl) substituents on the phenyl ring gave the corresponding cycloaddition products **13** and **14** with high diastereoselectivities (70 and 72%, respectively). Notwithstanding this, no reaction was observed for the *o*-Cl-substituted imine **1k**, probably due to the steric bulkiness of the *o*-Cl substituent.

With [Ru(2,6-Cl_2TPP)CO] as catalyst, the cycloadditions of **3a** with dipolarophiles of different steric bulkiness and electronic properties were also examined (Table 5). Remarkably, up to 92% de was achieved for the bulky dipolarophile **2c** (R^3 = R^4 = CO_2-*i*-Pr) while only 67% de was attained for **2b** (R^3 = R^4 = CO_2Et). This result suggests that high diastereoselectivity can be achieved via modification of the steric bulk of the dipolarophiles. For the less electron-deficient dipolarophile **2d**,**e**, no reactions were observed.

Table 5. Effect of Various Dipolarophiles[a]

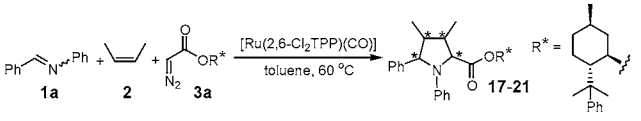


entry	dipolarophile	R^3	R^4	cycloadduct	yield[b] (%)	de[c] (%)
1	**2a**	CO_2Me	CO_2Me	**4**	70	79
2	**2b**	CO_2Et	CO_2Et	**15**	59	67
3	**2c**	CO_2-*i*-Pr	CO_2-*i*-Pr	**16**	50	92
4	**2d**	H	CO_2Me		no reaction	
5	**2e**	Me	CO_2Me		no reaction	

[a] Ru catalyst/**1a**/**2**/**3a** = 0.001:1.2:2:1. [b] Isolated yield. [c] Determined by ^{1}H NMR analysis of the crude products.

Cycloaddition reactions with different olefinic dipolarophiles were conducted (Table 6). High diastereoselectivity

Table 6. Cycloaddition with Olefinic Dipolarophiles[a]



entry	olefinic dipolarophile		cycloadduct	yield (%)[c]	de (%)[d]
1	**2f**	R = Me	**17**	74	78
2	**2g**	R = Ph	**18**	76	71
3	**2h**	R = CH_2Ph	**19**	64	71
4[b]	**2i**	R = CO_2Me	**20**	47	35
5[b]	**2j**	R = CN	**21**	30	nd

[a] Ru catalyst/**1a**/**2**/**3a** = 0.001:1.2:1:1.1, at 60 °C. [b] Ru catalyst/**1a**/**2**/**3a** = 0.001:1.2:1:4, at 90 °C. [c] Isolated yield. [d] Determined by ^{1}H NMR analysis of the crude products.

(up to 78%) and good yields (64−76%) were obtained for cyclic imides **2f**−**h** while less satisfactory results were found for terminal alkenes **2i**,**j**. However, attempts to use chalcone, methyl crotonate, and *trans*-4-phenyl-3-buten-2-one failed to give the corresponding cycloadducts under the same reaction conditions. Instead, an unexpected 8-phenylmenthol phenylamino ester **22** (45−56% yield) was obtained (see the Supporting Information). Probably, the ester arose from an N−H insertion of 8-phenylmenthol carbene into aniline, which was generated from the decomposition of imine **1a**. No reactions were observed for maleic anhydride and dimethyl maleate.

It is well-known that azomethine ylides undergo 1,3-dipolar cycloaddition with dipolarophiles to give pyrrolidines. However, there is sparse evidence on the generation of azomethine ylides from metallocarbenes and imines for cycloaddition. Here, we have found that pyrrolidines can be prepared from the one-pot reaction of an isolated ruthenium−carbene complex together with imine and dipolarophile.

An isolated Ru−carbene complex **24** was prepared from the reaction of [Ru(2,6-Cl_2TPP)CO] with diazo ester **23** in 1,2-dichloroethane at 60 °C for 0.5 h under an argon atmosphere (Figure 2). Complex **24** was recrystallized from 1,2-dichloroethane/hexane.

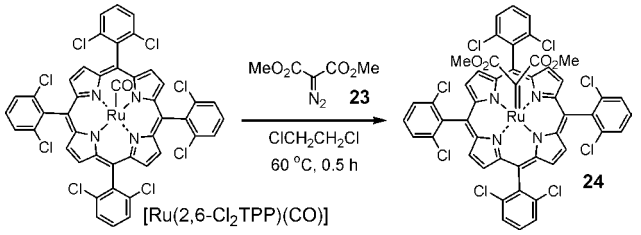


Figure 2. Synthesis of **24**.

On the basis of X-ray crystallographic analysis of **24**, the ruthenium−carbene distance is 1.854(8) Å, which is comparable to the reported examples[11] (see the Supporting Information).

In a one-pot reaction, bicyclic pyrrolidine **25** was obtained in 61% yield by reacting a stoichiometric amount of Ru−carbene complex **24**, imine **1d**, and dipolarophile **2g** in refluxing toluene for 16 h (Figure 3). This experiment offers an experimental evidence that ruthenium-carbene complex can react with imines to generate azomethine ylides for 1,3-dipolar cycloaddition with cyclic imides.

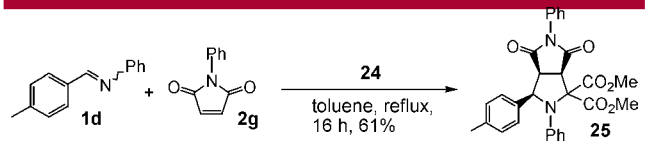


Figure 3. Synthesis of **25**.

In conclusion, we have found that ruthenium porphyrins are effective catalysts for asymmetric synthesis of multi-functionalized pyrrolines with remarkable stereoselectivity via a three-component coupling reaction involving chiral diazo esters, *N*-benzylidene imines, and dipolarophiles.[12]

Acknowledgment. We are thankful for the support of the Areas of Excellence Scheme established under the University Grants Committee of the Hong Kong Special Administrative Region, China (AoE/P-10/01), The University of Hong Kong (University Development Fund), and Hong Kong Research Grants Council (HKU 7099/01P). H.W.X. and G.Y.L. thank the Croucher Foundation of Hong Kong for the postgraduate studentships.

Supporting Information Available: Detailed experimental procedures, characterization data, X-ray crystallographic data of **24**, ^{1}H NMR spectra, and HPLC analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

OL050819N

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(12) Several attempts failed to obtain crystalline solids of the cycloaddition products for absolute configuration determination by X-ray crystallography analysis. Current efforts are directed toward the preparation of other pyrroline analogues for X-ray crystallography analysis.