ORGANIC LETTERS

2004
Vol. 6, No. 10
1621−1623

Highly Selective Intra- and Intermolecular Coupling Reactions of Diazo Compounds to Form *cis*-Alkenes Using a Ruthenium Porphyrin Catalyst

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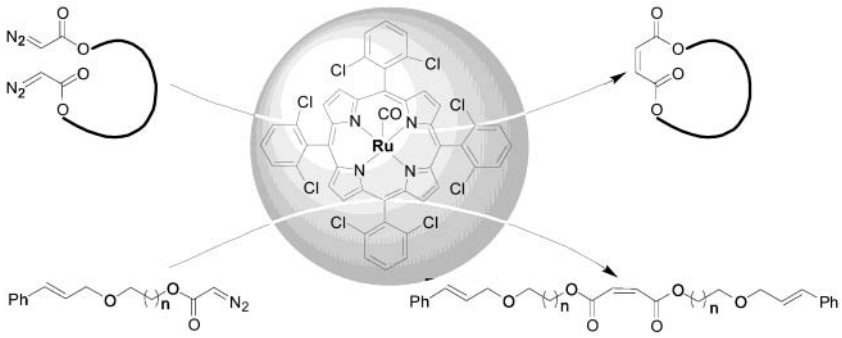
Received March 1, 2004

ABSTRACT



[Ru(2,6-Cl$_2$TPP)(CO)] catalyzed intramolecular coupling reactions of bisdiazoacetates and intermolecular coupling reactions of monodiazoacetates to afford the coupling products in up to 76% and 93% yields, respectively. Only the cis isomers were obtained from the reactions. Employing such a ruthenium-catalyzed coupling reaction of a diazo compound as a key step allowed the synthesis of Patulolide B in 67% yield with a ratio of >40:1 against its trans isomer.

It is well-documented that metal complexes can catalyze coupling reactions of diazo compounds to form alkenes (probably through carbenoid intermediates);[1] however, studies on using such a process to synthesize alkenes with good yields and high cis selectivity are sparse[1h,i,k,*o*−q,s] and less attention has been paid to the intramolecular coupling reactions.[1f,g,k,p,q] Recently, we demonstrated the efficiency of ruthenium porphyrins in catalyzing carbenoid transfer to alkenes, imines, and carbonyl compounds with high selectivity and isolated or characterized some reactive ruthenium carbene species.[2−4] We now report here the highly cis-selective intra- and intermolecular coupling reactions of diazo compounds catalyzed by a ruthenium porphyrin as a viable synthetic methodology for organic synthesis.

The catalyst is [Ru(2,6-Cl$_2$TPP)(CO)] [**1**, H$_2$(2,6-Cl$_2$TPP) = *meso*-tetra(2,6-dichlorophenyl)porphyrin],[5] which was previously shown to be an excellent catalyst for three-component coupling reaction of α-diazo esters with *N*-benzylidene imines and alkenes to form functionalized pyrrolidines.[3] The bisdiazoacetates **4a**−**f** were prepared by conventional reactions (see Supporting Information). Surprisingly, the thermodynamically unstable cis isomer **5a** was obtained as the single macrocylic product in the presence of 2 mol % catalyst **1**. With 1 mol % catalyst, the isolated yield was 60%. In view of the major competing process being

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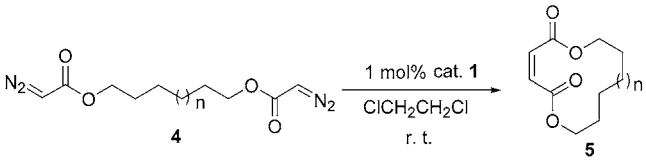
10.1021/ol049626a CCC: $27.50
Published on Web 04/15/2004

intermolecular oligomerization, we employed a doubly diluted solution (0.05 mol/L) for the reaction, and a 68% product yield was obtained. Upon extending the carbon number *n* of the bisdiazoacetates, the macrocyclic 12−18-membered ring products were formed in comparable yields (Table 1).

Table 1. Intramolecular Coupling of Diazo Compounds **4a**−**f**



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entry	*n*	product	yield (%)
1	1	**5a**	68
2	2	**5b**	61
3	3	**5c**	65
4	4	**5d**	72
5	5	**5e**	66
6	7	**5f**	63

The most interesting finding is the excellent cis/trans selectivity: no trans isomer was isolated from the reactions. To confirm the configuration of the product, the structure of compound **5e** was established by X-ray crystal analysis and is depicted in Figure 1.

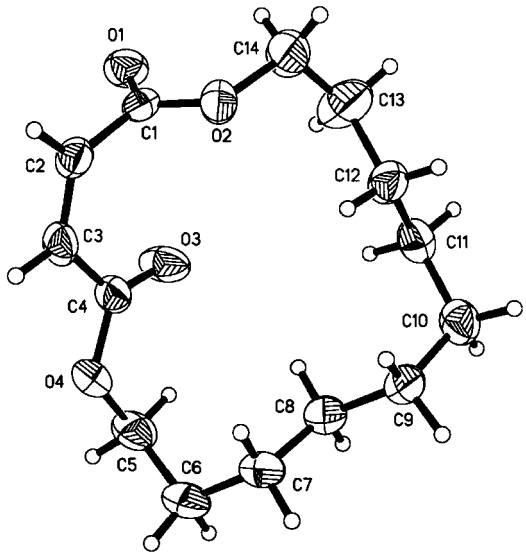
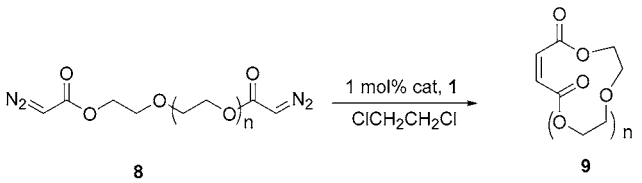


Figure 1. Perspective view of **5e**.

Intramolecular coupling of the bisdiazoacetates **8a**−**d** prepared from glycols (see Supporting Information) gave the cis products **9a**−**d** in up to 76% yield (Table 2). With **8d** as substrate, a 23-membered ring **9d** was obtained in 69% yield (entry 4 in Table 2).

Intermolecular coupling reactions of monodiazoacetates **13a**−**h** were also examined. In the presence of 0.1 mol % catalyst **1**, the coupling reaction of **13a** afforded the cis product **14a** in 81% yield (entry 1 in Table 3); neither the trans isomer nor the intramolecular cyclopropanation product was detected. In the cases of **13b**−**h**, their coupling products **14b**−**h** were isolated as the cis isomer in higher yields (Table 3). For example, when **13b** was used as a substrate, up to 93% yield of **14b** was achieved (entry 2 in Table 3).

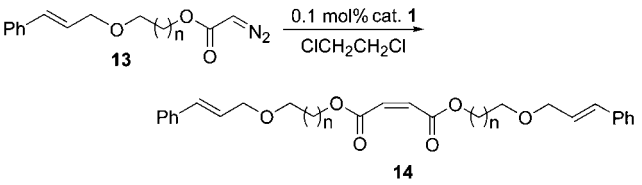
Table 2. Intramolecular Coupling of Diazo Compounds **8a**−**d**



8 9

entry	*n*	product	yield (%)
1	1	**9a**	76
2	2	**9b**	71
3	3	**9c**	65
4	5	**9d**	69

Table 3. Intermolecular Coupling of Diazo Compounds **13a**−**h**



13 14

entry	*n*	product	yield (%)	TON
1	1	**14a**	81	810
2	3	**14b**	93	930
3	4	**14c**	83	830
4	5	**14d**	89	890
5	6	**14e**	87	870
6	7	**14f**	85	850
7	8	**14g**	88	880
8	9	**14h**	82	820

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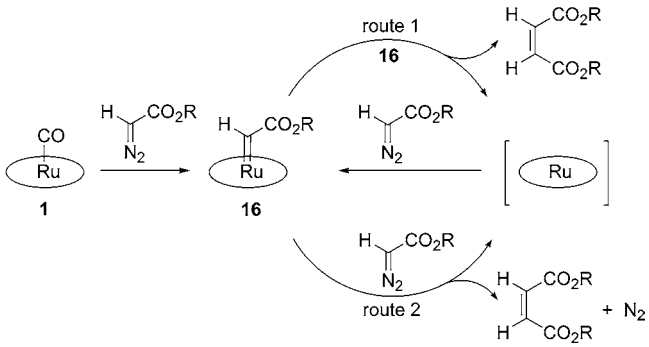
There are two possible pathways for the intermolecular coupling reaction of monodiazoacetates N_2CHCO_2R (**15**) catalyzed by complex **1**: the first is bimolecular reaction of the ruthenium carbene intermediate [Ru(2,6-Cl_2TPP)-($CHCO_2R$)] (**16**) (route 1 in Scheme 1), and the second is

Scheme 1



reaction of the ruthenium carbene intermediate **16** with the diazo compound (route 2 in Scheme 1). Analogous pathways can be proposed for the intramolecular coupling reaction of bisdiazoacetates catalyzed by **1**.

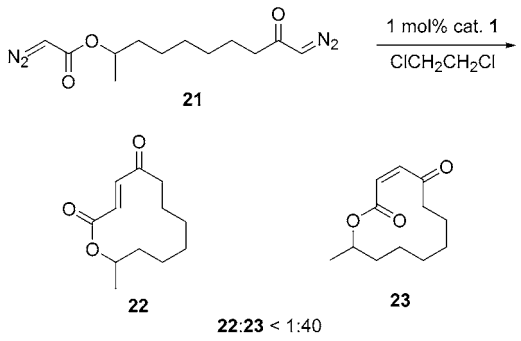
To provide mechanistic insight, we reacted ruthenium porphyrin **1** with slightly excess methyl diazoacetate under an argon atmosphere at −78 °C. When the resulting solution was followed by ^{1}H NMR spectroscopy, five peaks that did not originate from the reactants were observed. The peaks at δ = 6.24 and 3.77 ppm can be attributed to the coupling product, and the three peaks at δ = 13.28 (1H), 8.38 (8H), and 2.24 ppm (3H) are assignable to the intermediate **16** (R = Me). When the solution was left standing at room temperature for 10 h, the ruthenium carbene species **16** was still detected, although some decomposition had occurred. Further addition of methyl diazoacetate to the solution at this stage increased the amount of the coupling product. Therefore, we propose that the coupling reaction of diazoacetates catalyzed by **1** preferentially proceeded by route 2. The selective formation of *cis*-alkenes from this pathway resembles the observations in $RuCl_2(PPh_3)_3$-catalyzed intermolecular coupling of ethyldiazoacetate.[1s]

Patulolides A (**22**) and B (**23**) are biologically active macrocyclic lactones isolated from *Penicillium urticae* mutant S11R59.[6,7] These lactones can be synthesized through ring-closing esterification[8] or alkene metathesis.[9]

Doyle and co-workers first employed metal-catalyzed intramolecular coupling of **21** to synthesize **22** and **23**.[1q] Using [$Rh_2(CH_3CO_2)_4$] as a catalyst, the reaction afforded a 1:1 mixture of the trans (**22**) and cis isomer (**23**) in an overall yield of 30%, while with catalyst [$Cu(MeCN)_4$]PF_6, a 1:2 mixture of **22**:**23** was formed in 11% isolated yield.[1q]

Under similar conditions, we treated **21** with 1 mol % [Ru(2,6-Cl_2TPP)(CO)] (**1**). After the reaction was completed, the resulting solution was concentrated and the products were identified by ^{1}H NMR spectroscopy. Importantly, only a trace amount of the trans isomer was detected (**22**:**23** < 1:40). Patulolide B (**23**) was isolated in 67% yield (Scheme 2).

Scheme 2



In conclusion, the ruthenium porphyrin **1** is an excellent catalyst for coupling reactions of diazo compounds with remarkable cis selectivity. The mechanism was proposed to involve the reaction of a ruthenium carbene intermediate with a diazo compound. The present protocol provides a convenient entry to *cis*-alkenes, including macrocyclic compounds featuring a *cis*-alkene motif such as Patulolide B, which are of interest in organic synthesis.

Acknowledgment. This work was supported by the Hong Kong Research Grants Council (HKU 7099/01P), the University Development Fund of HKU, and the Area of Excellence Scheme (AoE/P-10/01) established under the University Grants Council of HKSAR. G.Y.L. thanks the Shanghai Institute of Organic Chemistry and the Croucher Foundation of Hong Kong for the postgraduate studentship.

Supporting Information Available: Detailed experimental procedures, spectral data of compounds, and CIF file for the crystal structure of **5e**, along with reaction schemes showing the structural formulas of all the organic compounds involved in this work. This material is available free of charge via the Internet at http://pubs.acs.org.

OL049626A

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