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Ruthenium(II) Porphyrin Catalyzed Tandem Carbonyl Ylide Formation and 1,3-Dipolar Cycloaddition Reactions of α-Diazo Ketones

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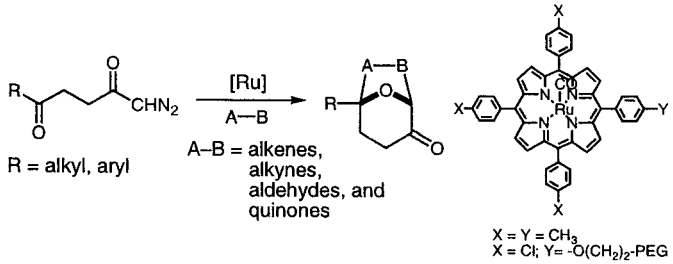
ABSTRACT



The ruthenium porphyrin-catalyzed reactions of diazo ketones with π-unsaturated compounds via carbonyl ylide formation/cycloaddition cascade exhibit product yields and selectivities comparable to the analogous reactions with dirhodium carboxylates as catalysts. By grafting a ruthenium porphyrin on poly(ethylene glycol) (Zhang, J.-L.; Che, C.-M. *Org. Lett.* 2002, *4*, 1911), a recyclable catalytic system is developed with over 5700 product turnovers attained for the reaction of 1-diazo-2,5-hexanedione with dimethyl acetylenedicarboxylate.

Dipolar cycloaddition of carbonyl ylides to multiple-bonded dipolarophiles is a powerful strategy for construction of carbocyclic ring systems in a regio- and stereocontrolled manner.[1] Dirhodium carboxylates are proven to be effective catalysts for the tandem carbonyl ylide/1,3-dipolar cycloaddition reactions, and a highly reactive rhodium-carbenoid intermediate is widely postulated.[2] Indeed, Rh-catalyzed carbonyl ylide formation/cycloaddition cascade reactions have been successfully employed for stereoselective synthesis of highly functionalized oxygen heterocycles and natural products (Figure 1).[2a,3] Apart from dirhodium carboxylates, few transition-metal complexes are known to exhibit similar activities.[4]

Extensive studies by us[5] and others[6] showed that ruthenium porphyrins are versatile catalysts for C−O and C−N bond formations. Recently, ruthenium porphyrin-catalyzed car-

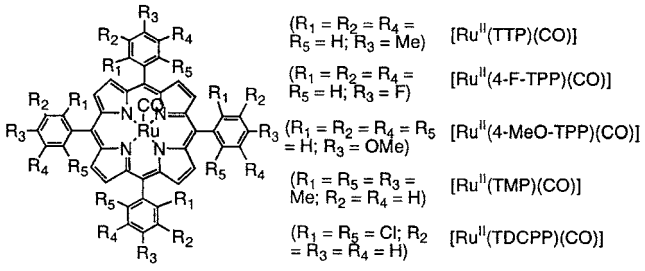


Figure 1. Ruthenium porphyrins.

(1) (a) Ho, T. L. *Tandem Organic Reactions*; John Wiley and Sons: New York, 1992. (b) Moore, W. H.; Decker, O. H. W. *Chem. Rev.* **1986**, *86*, 821. (c) *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley-Interscience: New York, 1984.

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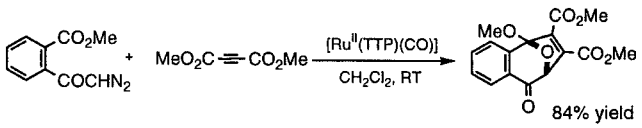
benoid transformations using diazo compounds has received a growing interest.[7−8] Our recent study revealed that a D_4-symmetric chiral ruthenium-carbene porphyrin complex, [Ru^{II}(D_4-Por*)(CO)] (D_4-H_2Por* = 5,10,15,20-tetrakis-[(1*S*,4*R*,5*R*,8*S*)-1,2,3,4,5,6,7,8-octahydro-1,4:5,8-dimethanoanthracen-9-yl]porphyrin), is an effective catalyst for highly regio- and enantioselective intermolecular cyclopropanation of styrenes with high product turnovers using ethyl diazoacetate as carbene source.[7b,h] Considering the lower cost of Ru vs Rh, the high structural diversity, and the remarkable product turnovers of metalloporphyrin catalysts, *we anticipate that ruthenium porphyrins such as the ones depicted in Figure 1 would be an attractive alternative to dirhodium carboxylates as catalysts for carbenoid-mediated transformations*.

In view of the synthetic usefulness of the tandem carbonyl ylide formation/cycloaddition methodology in organic synthesis, we set forth to develop a ruthenium porphyrin-based catalytic system for this important class of reactions. In this work, we employed a ruthenium porphyrin supported on poly(ethylene) glycol (PEG) as recyclable catalyst[9] for the catalytic cycloaddition of 1-diazo-2,5-hexanedione (**1a**) with DMAD, and more than 5700 product turnovers have been achieved through seven successive reactions.

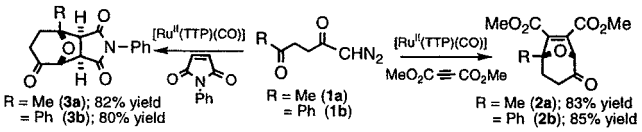
To begin our study, we examined the reaction of *o*-(methoxycarbonyl)-α-diazoacetophenone.[10] When the diazoacetophenone was added slowly over 2 h through a syringe pump to a CH_2Cl_2 solution containing DMAD (1.2 equiv) and [Ru^{II}(TTP)(CO)] (1 mol %), the desired cycloadduct was isolated in 84% yield (Scheme 1).

Scheme 1



The reactivity of conformationally flexible diazo ketones **1a**,**b** containing a 2,5-pentanedione backbone has been examined (Scheme 2). The diazo ketones were derived from

Scheme 2

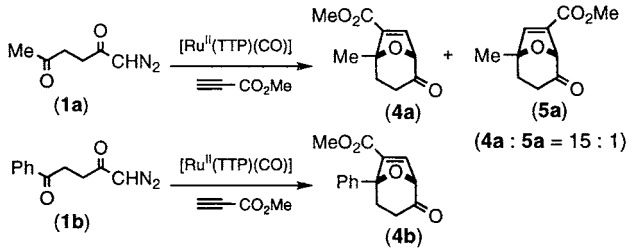


levulinic acid and 3-benzoylpropionic acid according to reported procedures.[11] Under the Ru-catalyzed conditions, **1a** and **1b** were found to undergo facile cycloaddition with DMAD (1.2 equiv), furnishing **2a**,**b** in ca. 85% isolated yields (Scheme 2). It is noteworthy that comparable product yields [90% (**2a**); 88% (**2b**)] were obtained using [Rh_2(CH_3CO_2)$_4$] as catalyst.

With activated alkenes such as *N*-phenylmaleimide as dipolarophile, the Ru-catalyzed decomposition of **1a**,**b** gave *exo*-**3a**,**b** exclusively in 80−82% yields (Scheme 2). The stereochemical assignment was made by comparison with the reported spectral data.[11]

When an unsymmetrical methyl propiolate was employed as dipolarophile (Scheme 3), the Ru-catalyzed reaction of

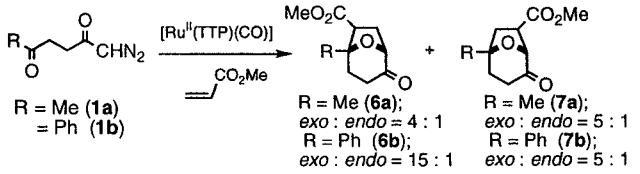
Scheme 3



1a gave two regioisomeric cycloadducts **4a** and **5a** in 80% overall isolated yield, where **4a** was produced preferentially (**4a**/**5a** = 15:1) on the basis of ^{1}H NMR analysis of the reaction mixture. In this work, the analogous [Rh_2(CH_3CO_2)$_4$]-catalyzed reaction was found to give a slightly lower regioselectivity (**4a**/**5a** = 8:1). The phenyl-substituted derivative **1b** reacted with methyl propiolate to afford **4b** as the only product (ca. 77%) under the Ru-/Rh-catalyzed conditions (Scheme 3).

Analogous to the Rh-catalyzed reaction,[11] the [Ru^{II}(TTP)(CO)]-catalyzed reaction of **1a** with methyl acrylate produced a mixture of four diastereomeric cycloadducts: *exo*-/*endo*-**6a** and *exo*-/*endo*-**7a** (Scheme 4), isolated in 85% overall

Scheme 4



yield. Individual compounds were characterized spectroscopically with reference to the literature data.[11] On the basis of ^{1}H NMR analysis of the crude reaction mixture, the regioselectivity (**6a**/**7a**) was determined to be 2.5:1 with exo/endo ratios of 4:1 (**6a**) and 5:1 (**7a**).

Both CH_2Cl_2 and C_6H_6 are equally effective as solvent for the ruthenium porphyrin-catalyzed cycloaddition reac-

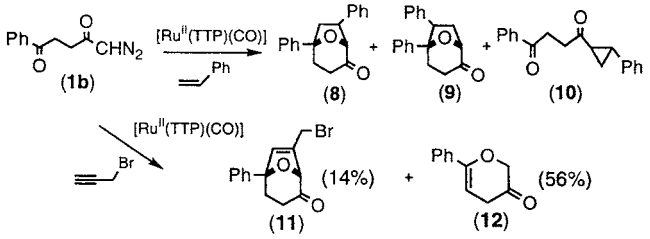
(2) (a) Hodgson, D. M.; Stupple, P. A.; Pierard, F. Y. T. M.; Labande, A. H.; Johnstone, C. *Chem. Eur. J.* **2001**, *7*, 4465. (b) Hodgson, D. M.; Pierard, F. Y. T. M.; Stupple, P. A. *Chem. Soc. Rev.* **2001**, *30*, 50. (c) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; John Wiley and Sons: New York, 1998; Chapter 7, 397. (d) Kitagaki, S.; Anada, M.; Kataoka, O.; Matsuno, K.; Umeda, C.; Watanabe, N.; Hashimoto, S.-I. *J. Am. Chem. Soc.* **1999**, *121*, 1417. (e) Padwa, A.; Weingarten, M. D. *Chem. Rev.* **1996**, *96*, 223.

tions. When the cycloaddition of **1a** with methyl acrylate was performed in C_6H_6, **6a** and **7a** were obtained in 73% overall yield. On the basis of ^{1}H NMR analysis, the regioselectivity (**6a**/**7a** = 3:1) and stereoselectivities [exo/endo ratio = 4:1 (**6a**) and 5:1 (**7a**)] were found to be identical to the corresponding values when CH_2Cl_2 was used as the solvent.

A similar reaction of **1b** with methyl acrylate produced four diastereomeric cycloadducts *exo*-/*endo*-**6b** and *exo*-/*endo*-**7b** (Scheme 4), which were isolated in 78% overall yield. ^{1}H NMR analysis of the reaction mixture revealed the regioisomeric (**6b**/**7b**) ratio = 5:1 and the *exo*/*endo* ratios being 15:1 (**6b**) and 5:1 (**7b**). The observed product yields and selectivities for the Ru-catalyzed cycloadditions are similar to that reported for the analogous Rh-catalyzed reactions.[11]

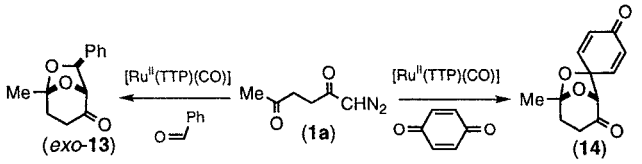
Dropwise addition of **1b** to a CH_2Cl_2 solution of styrene (5 equiv) and [Ru^{II}(TTP)(CO)] (1 mol %) resulted in cyclopropanation predominantly, and cyclopropane **10** was isolated in 55% yield with the anti/syn ratio = 8.5:1. Yet, cycloadducts **8** and **9** were obtained in 28% overall yield (Scheme 5) and characterized spectroscopically.[11] The regioselectivity of the cycloaddition (**8**:**9**) was determined to be 7:1 with the *exo*/*endo* ratios = 26:1 (**8**) and 5:1 (**9**) based on ^{1}H NMR analysis of the reaction mixture. The Ru-catalyzed reaction of **1b** with propargylic bromide afforded the cycloadduct **11** in only 14% yield by the carbonyl ylide formation/1,3-dipolar cycloaddition cascade. The enol ether **12** was isolated as the major product (56% yield), which was probably formed via 1,4-hydrogen shift of the carbonyl ylide intermediate.

Scheme 5



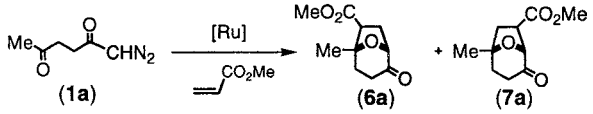
The C=O bond of benzaldehyde is also an effective dipolarophile. Treatment of **1a** with benzaldehyde (5 equiv) and [Ru^{II}(TTP)(CO)] (1 mol %) in CH_2Cl_2 at room temperature afforded the 1:1 cycloadduct *exo*-**13** exclusively in 73% yield (Scheme 6). Unlike the related Rh-catalyzed reaction,[11] formation of the [2:1] cycloadduct was not observed in this work. With *p*-quinone as dipolarophile,[3d] cycloaddition to the C=O bond occurred preferentially to give **14** in 72% isolated yield. By ^{1}H NMR analysis, the C=C cycloadduct was detected in <10% yield. A similar finding was observed for the analogous [$Rh_2(CH_3CO_2)_4$]-catalyzed reaction (**14**: 76% isolated yield).

Scheme 6



Employing **1a** and methyl acrylate as substrates, the effect of the porphyrin structure on the Ru-catalyzed cycloaddition has been examined. As depicted in Table 1, the regio- and stereoselectivities show modest variation with the porphyrin structure. The sterically bulky [Ru^{II}(TMP)(CO)] and [Ru^{II}(TDCPP)(CO)] were found to exhibit comparable activities to [Ru^{II}(TTP)(CO)] and [$Rh_2(CH_3CO_2)_4$].

Table 1. Effect of Ruthenium Porphyrin Catalysts on the Cyclization of Diazo Compound **1a** with Methyl Acrylate



entry	Ru catalyst[a]	% yield[b] (**6a** + **7a**)	regioselectivity[c] (**6a**/**7a**)	exo/endo[c] **6a**	exo/endo[c] **7a**
1	[Ru^{II}(TTP)(CO)]	85	2.5:1	4:1	5:1
2	[Ru^{II}(4-OMe-TPP)(CO)]	80	2.6:1	3.8:1	7:1
3	[Ru^{II}(4-F-TPP)(CO)]	82	3:1	3.9:1	7:1
4	[Ru^{II}(TMP)(CO)]	83	4.8:1	3.8:1	3.3:1
5	[Ru^{II}(TDCPP)(CO)]	78	4.5:1	3.2:1	3.3:1
6	[$Rh_2(CH_3CO_2)_4$]	87	2:1	3:1	3:1

[a] [H_2TTP] = *meso*-tetrakis(4-tolyl)porphyrin; [H_2-4-OMe-TPP] = *meso*-tetrakis(4-methoxyphenyl)porphyrin; [H_2-4-F-TPP] = *meso*-tetrakis(4-fluorophenyl)porphyrin; [H_2TMP] = *meso*-tetrakis(mesityl)porphyrin; [H_2TDCPP] = *meso*-tetrakis(2,6-dichlorophenyl)porphyrin. [b] Isolated yield. [c] Based on ^{1}H NMR analysis of the reaction mixture.

When 1-diazo-9-decene-2,5-dione (Scheme 7)[12] containing a tethered terminal C=C bond was added slowly to a CH_2Cl_2 solution of [Ru^{II}(TTP)(CO)] (1 mol %), hexahydro-1*H*-

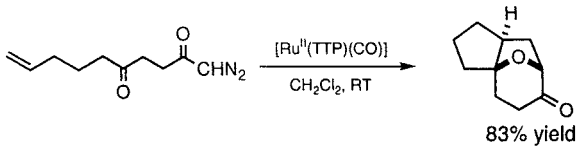
(3) Recent examples, see: (a) Hodgson, D. M.; Avery, T. D.; Donohue, A. C. *Org. Lett.* **2002**, *4*, 1809. (b) Wood, J. L.; Thompson, B. D.; Yusuff, N.; Pflum, D. A.; Matthäus, M. S. P. *J. Am. Chem. Soc.* **2001**, *123*, 2097. (c) Chiu, P.; Chen, B.; Cheng, K.-F. *Org. Lett.* **2001**, *3*, 1721. (d) Pirrung, M. C.; Kaliappan, K. P. *Org. Lett.* **2000**, *2*, 353.

(4) (a) Ibata, T.; Jitsuhiro, K.; Tsubokura, Y. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 240. (b) Ibata, T.; Jitsuhiro, K. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 3582.

(5) (a) Zhang, R.; Yu, W.-Y.; Sun, H.-Z.; Liu, W.-S.; Che, C.-M. *Chem. Eur. J.* **2002**, *8*, 2495. (b) Liang, J.-L.; Huang, J.-S.; Yu, X.-Q.; Zhu, N.-Y.; Che, C.-M. *Chem. Eur. J.* **2002**, *8*, 1563. (c) Zhang, R.; Yu, W.-Y.; Wong, K.-Y.; Che, C.-M. *J. Org. Chem.* **2001**, *66*, 8145. (d) Yu, X.-Q.; Huang, J.-S.; Zhou, X.-G.; Che, C.-M. *Org. Lett.* **2000**, *2*, 2233. (e) Zhang, R.; Yu, W.-Y.; Lai, T.-S.; Che, C.-M. *Chem. Commun.* **1999**, 409. (f) Au, S.-M.; Huang, J.-S.; Yu, W.-Y.; Fung, W.-H.; Che, C.-M. *J. Am. Chem. Soc.* **1999**, *121*, 9120. (g) Lai, T.-S.; Zhang, R.; Cheung, K.-K.; Kwong, H.-L.; Che, C.-M. *Chem. Commun.* **1998**, 1583.

(6) (a) Gross, Z.; Ini, S. *Org. Lett.* **1999**, *1*, 2077. (b) Berkessel, A.; Frauenkron, M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2265. (c) Groves, J. T.; Roman, J. S. *J. Am. Chem. Soc.* **1995**, *117*, 5594. (d) Higuchi, T.; Ohtake, H.; Hirobe, M. *Tetrahedron Lett.* **1989**, *30*, 6545. (e) Groves, J. T.; Quinn, R. *J. Am. Chem. Soc.* **1985**, *107*, 5790.

Scheme 7



3a,7-epoxyazulen-6(7*H*)-one was formed presumably via intramolecular 1,3-dipolar cycloaddition (Scheme 7). The cycloadduct was isolated in 83% yield after column chromatography and was characterized spectroscopically.[12]

Previously, we[13a−c] and others[13d] reported that ruthenium porphyrin complexes can be grafted onto various insoluble solid supports such as Merrifield resin,[13a] mesoporous molecular sieves (MCM-41)[13b−c] and some highly cross-linked polymers[13d] for heterogeneous organic oxidations.[13] Recently, we developed a ruthenium porphyrin catalyst supported on poly(ethylene glycol) (Figure 2).[9] This supported ruthenium porphyrin catalyst has been shown to display excellent reactivities toward alkene epoxidations and cyclopropanations, and yet the catalyst is readily recovered and reused without loss of catalytic activity.[9]

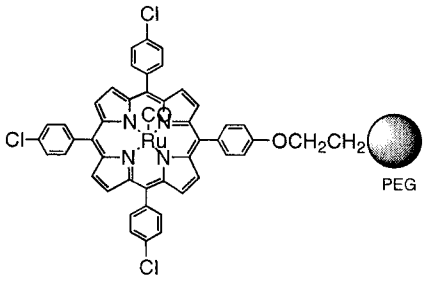
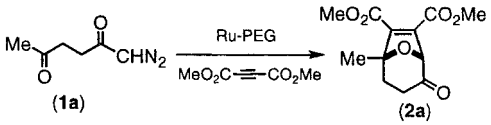


Figure 2. Soluble polymer-supported ruthenium porphyrin (Ru-PEG).

In this work, a recyclable catalytic system for the tandem carbonyl ylide formation/cyclization reaction was developed. Addition of **1a** to CH_2Cl_2 containing DMAD and the Ru-PEG catalyst (0.1 mol %) over 30 h at room temperature afforded **2a** in 85% yield with 850 turnovers. The Ru-PEG catalyst was recovered and subjected to another six consecutive reactions (see the Supporting Information for details); the results are listed in Table 2. No apparent loss of catalytic activity was observed, and a total product turnover of 5720 was attained.

Table 2. Recyclable Ru−PEG Catalyst for Tandem Carbonyl Ylide Formation/Cycloaddition Reaction



reaction run	% yield	turnovers
1	85	850
2	83	830
3	83	830
4	81	810
5	82	820
6	80	800
7	78	780

Acknowledgment. This work is supported by the Area of Excellence Scheme (AoE/P-10-01) established under the University Grants Council (HKSAR), The University of Hong Kong (Generic Drugs Research Program), and the Hong Kong Research Grants Council (HKU7077/01P). Dr. Pauline Chiu is gratefully acknowledged for helpful discussions.

Supporting Information Available: Detailed experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) (a) Zheng, S.-L.; Yu, W.-Y.; Che, C.-M. *Org. Lett*. **2002**, *4*, 889. (b) Che, C.-M.; Huang, J.-S.; Lee, F.-W.; Li, Y.; Lai, T.-S.; Kwong, H.-L.; Teng, P.-F.; Lee, W.-S.; Lo, W.-C.; Peng, S.-M.; Zhou, Z.-Y. *J. Am. Chem. Soc*. **2001**, *123*, 4119. (c) Li, Y.; Huang, J.-S.; Zhou, Z.-Y.; Che, C.-M. *J. Am. Chem. Soc*. **2001**, *123*, 4843. (d) Galardon, E.; Le Maux, P.; Simonneaux, G. *Tetrahedron* **2000**, *56*, 615. (e) Gross, Z.; Galili, N.; Simkhovich, L. *Tetrahedron Lett*. **1999**, *40*, 1571. (f) Frauenkron, M.; Berkessel, A. *Tetrahedron Lett*. **1997**, *38*, 7175. (g) Galardon, E.; Le Maux, P.; Simonneaux, G. *J. Chem. Soc., Chem. Commun*. **1997**, 927. (h) Lo, W.-C.; Che, C.-M.; Cheng, K.-F.; Mak, T. C.-W. *J. Chem. Soc., Chem. Commun*. **1997**, 1205.

(8) For examples, see: (a) Klose, A.; Solari, E.; Floriani, C.; Geremia, S.; Randaccio, L. *Angew. Chem., Int. Ed*. **1998**, *37*, 148. (b) Galardon, E.; Le Maux, P.; Toupet, L.; Simonneaux, G. *Organometallics* **1998**, *17*, 565.

(9) Zhang, J.-L.; Che, C.-M. *Org. Lett*. **2002**, *4*, 1911.

(10) Padwa, A.; Fryxell, G. E.; Zhi, L. *J. Org. Chem*. **1988**, *53*, 2875.

(11) Padwa, A.; Fryxell, G. E.; Zhi, L. *J. Am. Chem. Soc*. **1990**, *112*, 3100.

(12) Padwa, A.; Hornbuckle, S. F.; Fryxell, G. E.; Stull, P. D. *J. Org. Chem*. **1989**, *54*, 817.

(13) (a) Yu, X.-Q.; Huang, J.-S.; Yu, W.-Y.; Che, C.-M. *J. Am. Chem. Soc*. **2000**, *122*, 5337. (b) Liu, C.-J.; Yu, W.-Y.; Li, S.-G.; Che, C.-M. *J. Org. Chem*. **1998**, *63*, 7364. (c) Liu, C.-J.; Li, S.-G.; Pang, W.-Q.; Che, C.-M. *Chem. Commun*. **1997**, 65. (d) Nestler, O.; Severin, K. *Org. Lett*. **2001**, *3*, 3907.