Ruthenium-catalyzed efficient routes to oxindole derivatives

Khalil Tabatabaeian, Manouchehr Mamaghani, Nosratollah Mahmoodi, and Alireza Khorshidi

Abstract: Ruthenium-catalyzed preparation of oxindoles from one-pot trimerization of indoles under oxidative conditions and from electrophilic substitution reaction of indoles with isatins or isatin-derived imines under very mild reaction conditions is reported.

Key words: ruthenium, oxindoles, isatins, indoles, oxidative conditions.

Résumé : On a réalisé la préparation d'oxindoles par la réaction de trimérisation monotope d'indoles dans des conditions oxydantes et catalysée par le ruthénium ainsi que par la réaction de substitution électrophile d'indoles avec des isatines ou des imines dérivées de l'isatine, dans des conditions réactionnelles très douces.

Mots-clés : ruthénium, oxindoles, isatines, indoles, conditions oxydantes.

[Traduit par la Rédaction]

Introduction

Various indole derivatives occur in many pharmacologically and biologically active compounds,[1] and the chemistry of indoles has been and continues to be one of the most active areas of heterocyclic chemistry.[2,3] Isatins are also familiar for their biological activity. Oxindoles are well-known amongst different isatin derivatives and are useful as antibacterials, antiinflammatories, and laxatives.[4,5] Although these heterocyclic compounds were recently isolated from plants, for example, the marine alkaloid Convolutamydine A from the marine bryozoan *Amathia convoluta*,[6] oxindole derivatives have been prepared by different methods, such as the reaction of indoles and isatin in acid conditions,[7] silica sulfuric acid catalysis,[8] $KAl(SO_4)_2$ catalysis under microwave conditions,[9] bismuth triflate catalysis,[10] and few others. All of these methods have their own drawbacks, such as long reaction times, non-environment-friendly solvents, low yields of products, and so forth. Recently, we have been involved in the study of the catalytic activity of ruthenium towards organic reactions.[11–14] As a matter of fact, many organic transformations, which involve ruthenium species as catalyst, are known and well-documented.[15–17] We found that ruthenium chloride hydrate smoothly acts as homogeneous catalyst in one-pot trimerization of indoles under oxidative conditions and also in condensation of indoles with isatins or isatin-derived imines, providing the desired oxindoles in high yields under mild reaction conditions and using a relatively easy work-up.

Received 2 March 2009. Accepted 28 May 2009. Published on the NRC Research Press Web site at canjchem.nrc.ca on 7 August 2009.

K. Tabatabaeian,[1] M. Mamaghani, N. Mahmoodi, and A. Khorshidi. Department of Chemistry, Faculty of Sciences, The University of Guilan, P. O. Box: 41335-1914, Iran.

[1]Corresponding author (e-mail: Taba@guilan.ac.ir).

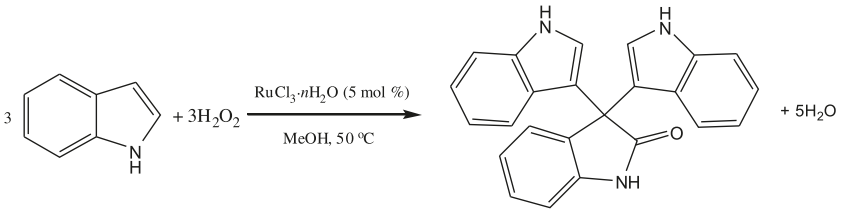
Results and discussion

A recent report on the trimerization of indole through laccase catalysis,[18] along with previous reports, such as iodine-catalyzed trimerization,[19] prompted us to evaluate the trimerization of indoles under ruthenium catalysis. We have recently reported the efficient condensation of indoles with aldehydes or ketones using $RuCl_3{\cdot}nH_2O$ as homogeneous catalyst.[11] To obtain oxindoles directly from indoles, as it is shown in Scheme 1, the scheme of reaction involves in situ oxidation to isatins and then condensation of the latter with excess indoles.

In an optimized procedure, treatment of indole (3 mmol) with hydrogen peroxide (3 mmol) in the presence of $RuCl_3{\cdot}nH_2O$ (5 mol%) in methanol (5 mL) at 50 °C for 120 min gave the corresponding 3,3-di(1*H*-indole-3-yl)indolin-2-one as a white solid precipitate, which was easily purified (see Experimental section). NMR data were consistent with those previously reported for 3,3-di(1*H*-indole-3-yl)indolin-2-one (**1a**),[20] while laccase catalysis was shown to produce 2,2-di(1*H*-indol-3-yl)indolin-3-one.[18] From a mechanistic point of view, initial oxidation of indole to isatin followed by the coordination of C3-located carbonyl group of isatin with ruthenium and then aldol condensation may be responsible for the formation of products, while laccase catalysis proceeds via a different pathway.[18] A mechanistic pathway for oxidation under ruthenium catalysis could be found in our previous report.[14] As shown in Table 1, indoles bearing substitution on 2- or 3-position failed to produce the desired products (Table 1, entries 5 and 6) probably because of oxidation to products other than isatin.

To further explore the formation of oxindoles, the condensation reaction of indoles and isatins was examined. In the condensation of indole (2 mmol) with isatin (1 mmol) in the presence of $RuCl_3{\cdot}nH_2O$ catalyst (5 mol%) in methanol (3 mL) at 50 °C, the reaction furnished an excellent yield of the product **1a** in a rather short time (95%, 5 min). This may be due to the fact that the product is insoluble in the

Scheme 1. Trimerization of indole under oxidative conditions.



reaction solvent. As shown in Table 2, this method worked with a variety of substrates. In most cases, the products are insoluble in the reaction solvent, and a simple filtration and rinsing (with methanol) work-up provides spectroscopically pure products. One interesting example is the reaction of 3-methylindole with isatin (Table 2, entry 4), which provided the alcohol product **4b**, while other reported methods failed for this reaction. $RuCl_3 \cdot nH_2O$ was found to be an efficient catalyst in the view of handling, temperature, yields, and reaction times as indicated in comparison with the reported methods.[7–10]

Although bis-indolylalkanes were usually prepared by nucleophilic addition of indoles to aldehydes, the addition of indoles to Schiff bases is also studied. However, the reactivity of Schiff bases is lower in comparison with aldehydes. Some reports in this context involve the reaction of indoles with aromatic aldimines in low-to-moderate yields in the presence of BF_3 etherate or Me_3SiCl,[21] $InCl_3$-catalyzed addition to aromatic aldimines in an extremely difficult procedure,[22] and the addition of indoles to *N-tert*-butanesulfinylaldimines, which requires long reaction times.[23] We found that isatin-derived imines bearing an electron-withdrawing group on the amine moiety, also, react with indoles in a smooth fashion to provide the desired oxindoles as an alternative route (Scheme 2). Typical results in this context are listed in Table 3. To ensure that the products were not formed from isatin due to hydrolysis of aldimine in the presence of Ru^{III}, a control reaction was set up without indole, and no isatin was detected (checked by TLC). To the best of our knowledge, this is the first report on efficient addition of indoles to aldimines. Here again, the unique feature of the protocol is the insolubility of the products in the reaction solvent, offering an easy work-up.

Conclusion

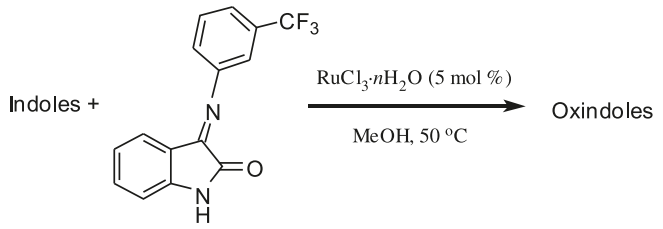
In conclusion, we have developed convenient routes to oxindole derivatives.

Experimental

General

IR spectra were recorded on a Shimadzu FTIR-8400S spectrometer. ^1H NMR spectra were obtained on a Bruker DRX-500 Avance spectrometer and ^{13}C NMR spectra were obtained on a Bruker DRX-125 Avance spectrometer. Chemical shifts of ^1H and ^{13}C NMR spectra were expressed in ppm downfield from tetramethylsilane. Melting points were measured on a Büchi Melting Point B-540 instrument and are uncorrected. Elemental analyses were performed by a Carlo-Erba EA1110 CNNO-S analyzer and agreed with the calculated values. Microwave irradiation was performed in a LBP125 microwave oven.

Scheme 2. Ru^{III}-catalyzed condensation of indoles with an isatin-derived aldimine.



Materials

All materials were purchased from Merck and used without further purification.

General procedure for trimerization of indoles under oxidative condensations

To a solution of indole (3 mmol) and $RuCl_3 \cdot nH_2O$ (10.7 mg, 0.05 mmol) in methanol, H_2O_2 (340 mg of a 30% solution) was added, and the reaction mixture was heated in an oil bath at 50 °C under reflux conditions for the time specified in Table 1. After completion of the reaction, the white solid precipitate was filtered and washed with cold methanol until removal of all traces of impurities (checked by TLC), providing the product **1a** (273 mg, 75%). The same procedure was used for the other products, except for products **3a** (Table 1, entry 3), **4b**, and **5b** (Table 2, entries 4 and 5, respectively), which were purified by preparative TLC (*n*-hexane/ethyl acetate 10:5).

Characterization data for the products

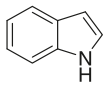
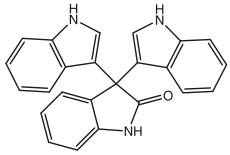
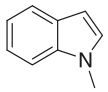
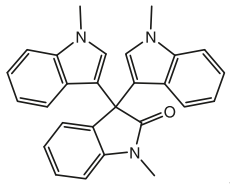
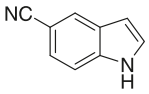
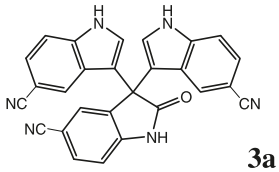
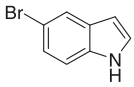
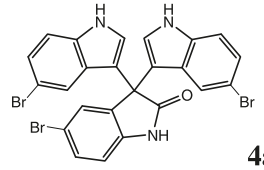
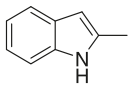
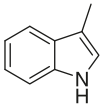
3,3-Di(1H-indol-3-yl)indolin-2-one, 1a

White solid, mp 310–312 °C. IR (KBr) ν (cm^{-1}): 758, 1012, 1103, 1336, 1473, 1614, 1706, 3056, 3280, 3323, 3427. ^1H NMR (500 MHz, $CDCl_3$, 25 °C) δ: 6.51 (2H, t, J = 7.5 Hz), 6.59 (1H, t, J = 7.5 Hz), 6.62 (2H, s), 6.69 (1H, d, J = 7.7 Hz), 6.72 (2H, t, J = 7.5 Hz), 6.88 (1H, t, J = 7.6 Hz), 6.97 (1H, d, J = 7.4 Hz), 7.02 (4H, t, J = 7.65 Hz), 9.78 (1H, s), 9.89 (2H, s) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C) δ: 53.41, 110.48, 112.47, 115.14, 119.01, 119.13, 121.62, 122.26, 125.05, 125.21, 126.55, 128.70, 135.45, 137.77, 142.17, 179.60 ppm. Anal. calcd. for $C_{24}H_{17}N_3O$: C, 79.32; H, 4.72; N, 11.56. Found: C, 79.35; H, 4.75; N, 11.55.

1-Methyl-3,3-bis(1-methyl-1H-indol-3-yl)indolin-2-one, 2a

White solid, mp 232–234 °C. IR (KBr) ν (cm^{-1}): 742, 1014, 1083, 1128, 1157, 1251, 1334, 1371, 1467, 1608, 1714, 2925, 3051. ^1H NMR (500 MHz, $CDCl_3$, 25 °C) δ: 3.40 (3H, s), 3.74 (6H, s), 6.92 (2H, s), 6.99 (2H, t, J = 7.4 Hz), 7. 04 (1H, d, J = 7.8 Hz), 7.08 (1H, t, J = 7.5 Hz), 7.21 (2H, t, J = 7.5 Hz), 7.32 (2H, d, J = 8.3 Hz), 7.35 (2H,

Table 1. Ru-catalyzed trimerization of indoles under oxidative conditions.

Entry[a]	Indole	Product	Time (min)	Yield[b](%)
1		 **1a**	120	75[c]
2		 **2a**	80	80[c]
3		 **3a**	150	65
4		 **4a**	150	68
5		—	—	—
6		—	—	—

[a] All products were characterized by ^{1}H NMR, ^{13}C NMR, and IR data.
[b] Isolated yields.
[c] Identified by comparison with authentic samples.[20]

d, *J* = 8.1 Hz), 7.38 (1H, t, *J* = 7.4 Hz), 7.51 (1H, d, *J* = 7.3 Hz) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C) δ: 27.08, 33.20, 53.19, 108.62, 109.72, 114.17, 119.43, 121.84, 121.96, 123.13, 125.72, 126.89, 128.46, 129.19, 134.74, 138.20, 143.38, 178.30 ppm. Anal. calcd. for $C_{27}H_{23}N_3O$: C, 79.97; H, 5.72; N, 10.36. Found: C, 79.95; H, 5.74; N, 10.35.

3,3-Di(5-cyano-1H-indole-3-yl)-5-cyanoindolin-2-one, 3a

White solid, mp 289–291 °C. IR (KBr) ν (cm^{-1}): 754, 812, 1470, 1618, 1704, 2224, 3259, 3340. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) δ: 6.94 (2H, d, *J* = 2.5 Hz), 7.01 (1H, d, *J* = 8.3 Hz), 7.18 (2H, dd, *J* = 8.3, 1.3 Hz), 7.29 (1H, d, *J* = 8.5 Hz), 7.33 (2H, d, *J* = 8.3 Hz), 7.53 (1H, s), 7.69 (2H, s), 10.45 (1H, s), 10.78 (2H, s) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C) δ: 53.10, 102.13, 110.87, 113.19, 115.98, 121.44, 122.60, 124.68, 125.39, 125.99, 126.98, 128.84, 133.86, 139.47, 141.49, 179.70 ppm. Anal. calcd. for $C_{27}H_{14}N_6O$: C, 73.96; H, 3.22; N, 19.17. Found: C, 74.01; H, 3.24; N, 19.17.

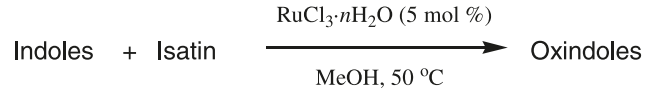
3,3-Di(5-bromo-1H-indole-3-yl)-5-bromoindolin-2-one, 4a

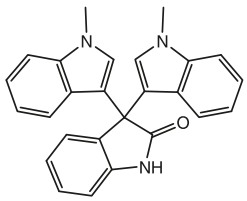
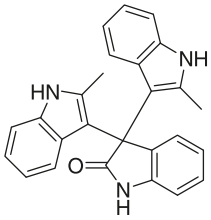
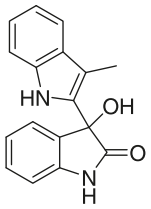
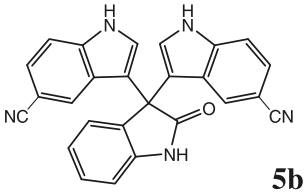
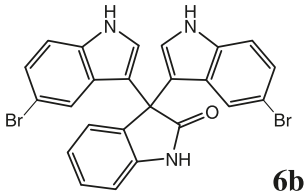
White solid, mp 286–288 °C. IR (KBr) ν (cm^{-1}): 653, 677, 751, 799, 888, 1103, 1464, 1618, 1714, 3281, 3323, 3429. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) δ: 6.85 (2H, s), 6.96 (1H, d, *J* = 8.5 Hz), 7.02 (2H, dd, *J* = 8.7, 1.7 Hz), 7.10 (1H, d, *J* = 8.5 Hz), 7.16 (2H, d, *J* = 8.5 Hz), 7.27 (1H, s), 7.40 (2H, s), 9.99 (1H, s), 10.33 (2H, s) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C) δ: 53.75, 110.54, 112.87, 113.65, 114.66, 122.65, 123.99, 124.65, 125.68, 126.49, 127.99, 128.49, 134.35, 136.40, 141.89, 179.86 ppm. Anal. calcd. for $C_{24}H_{14}Br_3N_3O$: C, 48.03; H, 2.35; N, 7.00. Found: C, 48.07; H, 2.33; N, 7.03.

3,3-Di(2-methyl-1H-indole-3-yl)indolin-2-one, 3b

White solid, mp 297–299 °C. IR (KBr) ν (cm^{-1}): 611, 686, 740, 760, 1018, 1176, 1298, 1421, 1458, 1616, 1712, 2927, 3055, 3330, 3417. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) δ: 2.11 (3H, s), 2.30 (3H, s), 6.41 (1H, d, *J* = 7.6 Hz), 6.80–6.85 (3H, m), 6.98–7.09 (4H, m), 7.37 (2H,

Table 2. Ru^{III}-catalyzed condensation of indoles with isatin.



Entry[a]	Indole	Product	Time (min)	Yield[b] (%)
1	Indole	**1a**	5	95[c]
2	1-Methylindole	 **2b**	5	90[c]
3	2-Methylindole	 **3b**	5	98
4	3-Methylindole	 **4b**	60	75
5	5-Cyanoindole	 **5b**	30	78
6	5-Bromoindole	 **6b**	10	92

[a]All products were characterized by ^{1}H NMR, ^{13}C NMR, and IR data.
[b]Isolated yields.
[c]Identified by comparison with authentic sample.[20]

d, J = 7.5 Hz), 7.82 (1H, d, J = 7.6 Hz), 7.92 (1H, d, J = 8.2 Hz), 10.39 (1H, s), 10.51 (1H, s), 10.92 (1H, s) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C) δ: 13.87, 14.05, 53.28, 110.21, 110.29, 111.21, 111.27, 118.78, 118.84, 120.15, 120.21, 120.46, 120.63, 122.13, 126.32, 127.90, 128.54, 128.68, 132.84, 134.81, 135.76, 135.83, 136.44, 142.06, 180.21 ppm. Anal. calcd. for $C_{26}H_{21}N_3O$: C, 79.77; H, 5.41; N, 10.73. Found: C, 79.78; H, 5.40; N, 10.72.

*3-Hydroxy-3-(3-methyl-1*H*-indol-2-yl)indolin-2-one, 4b*

White solid. IR (KBr) ν (cm^{-1}): 748, 1001, 1064, 1093, 1124, 1209, 1242, 1328, 1467, 1622, 1685, 1716, 2833, 2941,

Table 3. Ru^{III}-catalyzed condensation of indoles with aldimine.

Entry[a]	Indole	Product	Time (min)	Yield[b] (%)
1	Indole	**1a**	1	85[c]
2	1-Methylindole	**2b**	15	88[c]
3	2-Methylindole	**3b**	20	75
4	5-Cyanoindole	**5b**	60	67
5	5-Bromoindole	**6b**	60	70

[a]All products were characterized by ^{1}H NMR, ^{13}C NMR, and IR data.
[b]Isolated yields.
[c]Identified by comparison with authentic samples.[20]

3222, 3357. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) δ: 2.01 (1H, br), 2.08 (3H, s), 6.90 (1H, d, J = 7.8 Hz), 7.16 (1H, t, J = 7.1 Hz), 7.21 (1H, t, J = 7.0 Hz), 7.29–7.34 (3H, m), 7.44 (1H, d, J = 7.4 Hz), 7.58 (1H, d, J = 7.8 Hz), 8.30 (1H, s), 8.75 (1H, s) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C) δ: 9.59, 97.47, 110.74, 111.17, 111.38, 119.12, 119.93, 122.81, 123.69, 126.55, 129.62, 129.77, 130.24, 131.28, 135.37, 140.91, 178.08 ppm. Anal. calcd. for $C_{17}H_{14}N_2O_2$: C, 73.37; H, 5.07; N, 10.07. Found: C, 73.43; H, 5.10; N, 10.09.

3,3-Di(5-cyano-1*H*-indole-3-yl)indolin-2-one, 5b

White solid, mp 273–275 °C. IR (KBr) ν (cm^{-1}): 752, 810, 1101, 1228, 1346, 1469, 1618, 1670, 1706, 2223, 3259, 3338. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) δ: 6.87 (1H, t, J = 7.0 Hz), 6.91–6.95 (3H, m), 7.10–7.18 (4H, m), 7.31 (2H, d, J = 8.3 Hz), 7.62 (2H, s), 9.98 (1H, s), 10.64 (2H, s) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C) δ: 52.93, 102.03, 110.85, 113.14, 115.98, 121.45, 122.59, 124.62, 125.32, 125.99, 126.98, 128.81, 133.79, 139.47, 141.39, 179.39 ppm. Anal. calcd. for $C_{26}H_{15}N_5O$: C, 75.53; H, 3.66; N, 16.94. Found: C, 75.55; H, 3.65; N, 16.94.

3,3-Di(5-bromo-1*H*-indole-3-yl)indolin-2-one, 6b

White solid, mp 264–266 °C. IR (KBr) ν (cm^{-1}): 651, 675, 750, 798, 885, 1101, 1463, 1562, 1616, 1712, 3280, 3323, 3427. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) δ: 6.75 (2H, d, J = 2.4 Hz), 6.79 (1H, t, J = 7.4 Hz), 6.86 (1H, d, J = 7.7 Hz), 6.97 (2H, dd, J = 8.6, 1.7 Hz), 7.02–7.08 (4H, m), 7.32 (2H, d, J = 1.3 Hz), 9.87 (1H, s), 10.12 (2H, s) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C) δ: 53.65, 110.43, 112.32, 113.51, 114.64, 122.27, 123.65, 124.47, 125.42, 126.29, 127.89, 128.40, 134.26, 136.29, 141.50, 179.64 ppm. Anal. calcd. for $C_{24}H_{15}Br_2N_3O$: C, 55.31; H, 2.90; N, 8.06. Found: C, 55.35; H, 2.92; N, 8.05.

Acknowledgements

The authors are grateful to the Research Council of Guilan University for the partial support of this study.

References

(1) Zhang, H.-C.; Ye, H.; Moretto, A. F.; Brumfield, K. K.; Maryanoff, B. E. *Org. Lett.* **2000**, *2* (1), 89–92. doi:10.1021/ol991255o. PMID:10814253.

(2) Gilchrist, T. L. In *Heterocyclic chemistry*; Academic Press: London, 1997; p. 231.

(3) Humphrey, G. R.; Kuethe, J. T. *Chem. Rev.* **2006**, *106* (7), 2875–2911. doi:10.1021/cr0505270. PMID:16836303.

(4) Popp, F. D. *J. Heterocycl. Chem.* **1984**, *21* (5), 1367–1368. doi:10.1002/jhet.5570210523.

(5) Garrido, F.; Ibanez, J.; Gonalons, E.; Giraldez, A. *Eur. J. Med. Chem.* **1975**, *10*, 143.

(6) Kamano, Y.; Zhang, H. P.; Ichihara, Y.; Kizu, H.; Komiyama, K.; Itokawa, H.; Pettit, G. R. *Tetrahedron Lett.* **1995**, *36* (16), 2783–2784. doi:10.1016/0040-4039(95)00395-S.

(7) Bergman, J.; Eklund, N. *Tetrahedron* **1980**, *36* (10), 1445–1450. doi:10.1016/0040-4020(80)85060-5.

(8) Mohammadizadeh, M. R.; Karimi, A. R. *Catal. Commun.* **2006**, *7* (10), 752–755. doi:10.1016/j.catcom.2006.01.026.

(9) Azizian, J.; Mohammadi, A. A.; Karimi, N.; Mohammadizadeh, M. R. *J. Chem. Res. Synop.* **2004**, *6*, 424.

(10) Yadav, S. S.; Subbareddy, B. V.; Kamakolanu, U. G. *Synthesis* **2006**, *2006* (24), 4121–4123. doi:10.1055/s-2006-950373.

(11) Tabatabaeian, K.; Mamaghani, M.; Mahmoodi, N. O.; Khorshidi, A. *Can. J. Chem.* **2006**, *84* (11), 1541–1545. doi:10.1139/V06-159.

(12) Tabatabaeian, K.; Mamaghani, M.; Mahmoodi, N. O.; Khorshidi, A. *J. Mol. Catal. A* **2007**, *270* (1-2), 112–116. doi:10.1016/j.molcata.2007.01.038.

(13) Tabatabaeian, K.; Mamaghani, M.; Mahmoodi, N. O.; Khorshidi, A. *Tetrahedron Lett.* **2008**, *49* (9), 1450–1454. doi:10.1016/j.tetlet.2008.01.001.

(14) Tabatabaeian, K.; Mamaghani, M.; Mahmoodi, N. O.; Khorshidi, A. *Catal. Commun.* **2008**, *9* (3), 416–420. doi:10.1016/j.catcom.2007.07.024.

(15) Murahashi, S.-I. In *Ruthenium in organic synthesis*; Wiley-VCH: New York, 2004.

(16) Bruneau, C.; Dixneuf, P. H. In *Ruthenium catalysts and fine chemistry*; Springer, 2004.

(17) Murai, S. In *Activation of unreactive bonds and organic synthesis*; Springer, 1999.

(18) Ganachaud, C.; Garfagnoli, V.; Tron, T.; Iacazio, G. *Tetrahedron Lett.* **2008**, *49* (15), 2476–2478. doi:10.1016/j.tetlet.2008.02.021.

(19) Janosik, T.; Bergman, J. *Heterocycles* **2002**, *57* (7), 1273. doi:10.3987/COM-02-9477.

(20) Wang, S.-Y.; Ji, S.-J. *Tetrahedron* **2006**, *62* (7), 1527–1535. doi:10.1016/j.tet.2005.11.011.

(21) Banerji, J.; Kumar, M.; Sarkar, S. *Indian J. Chem.* **1983**, *22*, 27.

(22) Wynne, J. H.; Stalick, W. M. *J. Org. Chem.* **2002**, *67* (16), 5850–5853. doi:10.1021/jo020049i. PMID:12153292.

(23) Bowen, K.; Qin, Y.; He, Q.; Huang, Z.; Wang, F. *Tetrahedron Lett.* **2005**, *46* (10), 1751–1753. doi:10.1016/j.tetlet.2004.12.140.