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Efficient synthesis of oxazoles by dirhodium(II)-catalyzed reactions of styryl diazoacetate with oximes

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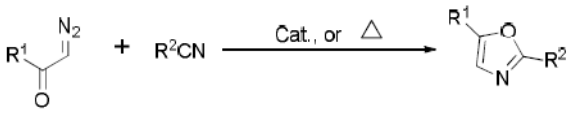
Abstract

An efficient one-step synthesis of multi-functionalized oxazole derivatives is achieved in high yield by dirhodium(II)-catalyzed reactions of styryl diazoacetate with aryl oximes.

Oxazoles are widely distributed in nature, and many of them have shown biological activities.[1] Because oxazoles are used as building blocks in organic synthesis[2] for α,α-disubstituted amino acids,[3] in cycloaddition reactions,[4] and in the total synthesis of natural products,[5] efficient methods for their syntheses continue to be of intense interest.[6] Significant achievements in the synthesis of their core structures that are amenable to further substitutions have been reported,[7] and several transition metal catalyzed methodologies for the functionalization of oxazoles have been developed.[7c-7j] Because these approaches require multistep syntheses, general synthetic processes for functionalized oxazoles having structural diversity and complexity continue to be needed.

Diazo compounds have been extensively studied during the last few decades,[8] and several synthetic methodologies for oxazole formation have been reported,[9] including oxazole syntheses from diazocarbonyl compounds with nitriles catalyzed by transition metal catalysts, Lewis acids or thermal conditions (Eq. 1).[10] However, this transformation has been limited to diazoacetoacetates and diazoketones, and with ethyl diazoacetate the yield of the corresponding 5-alkoxyoxazoles (R^1 = OR) is only 26~31%.[10a] Here we report our recent discovery of a surprisingly efficient dirhodium(II)-catalyzed reaction of styryl diazoacetate with aryl oximes to give 4-styryl-5-methoxyoxazoles directly in high yield under mild conditions (Eq. 2).



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†Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

‡Footnotes should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

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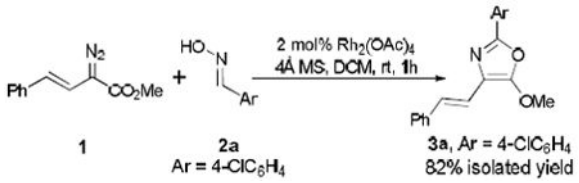
(1)

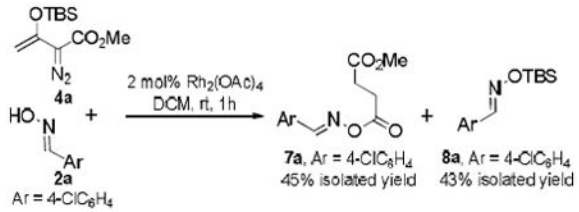
The reaction between styryl diazoacetate **1** and the oxime of 4-chlorobenzaldehyde catalyzed by rhodium acetate yielded the multi-functionalized 4-styryl-5-methoxyoxazole **3a** in 82% isolated yield when 4Å molecular sieves was used as an additive (Eq 2). The structure of the generated oxazole was confirmed by single-crystal X-ray diffraction analysis of its bromo-derivative.[11] This process represents a significant improvement for the synthesis of 5-methoxyoxazoles from diazoacetates compared to previously reported reactions with nitriles (Eq. 1)[10] and for the synthesis of 4-vinyl-5-methoxyoxazoles via a recently reported coupling strategy.[7i] In catalytic reactions with styryldiazoacetates the easily accessible oximes are more reactive than are nitriles and give the corresponding oxazoles in high yield. The reaction of styryl diazoacetate **1** with benzonitrile gives the corresponding oxazole in only 27 % isolated yield under the same reaction conditions.[12]



(2)

Originally we thought that enoldiazoacetates **4** would undergo stepwise [3,3]-cycloaddition with oximes analogous to their asymmetric vinylogous reactions with hydrazones **5** catalyzed by Rh_2(*R*-PTL)$_4$ followed by diastereoselective Sc(OTf)$_3$-catalyzed Mannich addition to form the corresponding tetrahydropyridazine derivatives (**6**, Scheme 1).[13] However, instead of the expected six-membered outcome with enoldiazoacetates, rhodium acetate-catalyzed reactions of oximes occurred by a completely different processes.

The reaction of enoldiazoacetate **4a** with 4-chlorobenzaldehyde oxime **2a** catalyzed by dirhodium(II) acetate gave succinate derivative **7a**[14] and TBS-substituted oxime **8a** as major products (Eq. 3) without any evidence of an OH insertion product at the vinylogous position. This outcome is consistent with initial rhodium acetate catalyzed intramolecular conversion of enoldiazoacetate **4a** to 2-TBSO-cyclopropenecarboxylate[15] followed by oxime addition, ring opening, and TBS transfer (Scheme 2). The outcome described in Eq 3, in contrast with that of Scheme 1, suggests that hydrazones 5 are able to intercept the intermediate metal carbene prior to its intramolecular conversion to 2-TBSO-cyclopropenecarboxylate.



(3)

The substrate scope for reactions of oximes with styryl diazoacetate **1** under optimized dirhodium(II)-catalyzed conditions has been determined, and the results are summarized in Table 1. All of the oxazole products were obtained in good to high yields, and 5-methoxyoxazoles **3** were the sole isolated reaction products. Both electron-deficient and

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electron-rich oximes give good to high yields of oxazoles. The position of the methyl substituent on the hydroxylamine's aryl group has little influence on product yields (entries 7-9). The reaction of styryl diazoacetate **1** with 2-furyl and 2-naphthyl substrates also produced the corresponding oxazoles in 62% and 87% yield, respectively.

With these results in hand we investigated transformations of functionalized oxazole products to other synthetically interesting motifs (Scheme 4). A Suga-Ibata reaction of oxazole **3a** with an aldehyde for the synthesis of oxazolines was performed.[16] When the reaction was promoted by $SnCl_4$, the desired addition product **9** was obtained in 66% isolated yield with 2:1 diastereoselectivity; this compound is a useful precursor of α-amino-β-hydroxyl carboxylic acids having a quaternary carbon center.[17] We also employed oxazole **3a** for 1,3-diplar cycloaddition reactions with dimethyl 2-butynedioate under thermal conditions.[18] These reactions showed 100% conversion when dimethyl 2-butynedioate was the solvent, and furan derivative **10** was isolated as the major product accompanied by a small amount of hydrolyzed furan. Another demonstration of the utility of these 4-styryl-5-methoxyoxazole derivatives, reported by Antilla and coworkers,[7i] is the synthesis of functionalized amino alcohol **12** and amino acid **13** derivatives in high yield.

In summary, we have discovered an efficient dirhodium(II)-catalyzed synthesis of 4-styryl-5-methoxyoxazoles starting from styryl diazoacetate and oximes in high yield under mild conditions. A possible mechanism for formation of 4-styryl-5-methoxy-2-aryloxazoles (**3**) from catalytic reactions between **1** and **2** is described in Scheme 4. Dirihodium(II)-catalyzed dinitrogen extrusion from styryldiazoacetate (**1**) forms metal carbene which reacts with oximes and generates the azomethine yilde (**II**). Rapid equilibration of this intermediate to the corresponding enol anion (**II'**) followed by oxo-Mannich addition to produce the ring-closed structure (**III**), that with final aromatization by dehydration gives oxazole derivatives **3** in high yield. Additional investigations are underway to investigate the scope of these reactions with other vinyldiazoacetates and to ascertain where the crossover point occurs in intermolecular interception of the intermediate metal carbene versus its intramolecular conversion to cyclopropenecarboxylates.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Notes and references

1. a) Palmer, DC., editor. Oxazoles: Synthesis, Reactions and Spectroscopy, Part A. John Wiley & Sons; Hoboken, NJ: 2003. b) Palmer, DC., editor. Oxazoles: Synthesis, Reactions and Spectroscopy, Part B. John Wiley & Sons; Hoboken, NJ: 2004. c) Ikeda Y, Nonaka H, Furumai T, Onaka H, Igarashi Y. J Nat Prod. 2005; 68:1061. [PubMed: 16038549] d) Banks JC, Moody CJ. Tetrahedron Lett. 2009; 50:3371.
2. a) Padwa, A. Progress in Heterocyclic Chemistry. Suschitzky, H.; Scriven, EFV., editors. Vol. 6. Pergamon Press; Oxford: 1994. p. 56-73.b) Lee YJ, Lee JY, Kim MJ, Kim TS, Park HG, Jew SS. Org Lett. 2005; 7:1557. [PubMed: 15816751] c) Arp FO, Fu GC. J Am Chem Soc. 2006; 128:14264. [PubMed: 17076493] d) Vedejs E, Grissom JW. J Am Chem Soc. 1988; 110:3238.
3. a) Shaw SA, Aleman P, Christy J, Kampf JW, Va P, Vedejs E. J Am Chem Soc. 2006; 128:925. [PubMed: 16417383] b) Uraguchi D, Koshimoto K, Miyake S, Ooi T. Angew Chem Int Ed. 2010;

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49:5567.c) Joannesse C, Johnston CP, Concellón C, Simal C, Philp D, Smith AD. Angew Chem Int Ed. 2009; 48:8914.

4. a) Jacobi PA, Lee Kyungae. J Am Chem Soc. 2000; 122:4295.b) Sabot C, Oueis E, Brune X, Renard P. Chem Commun. 2012; 48:768.c) Badillo JJ, Arevalo GE, Fettinger JC, Franz AK. Org Lett. 2011; 13:418. [PubMed: 21186788]
5. a) Li P, Evans CD, Wu Y, Cao B, Hamel E, Joullie MM. J Am Chem Soc. 2008; 130:2351. [PubMed: 18229928] b) Grimley JS, Sawayama AM, Tanaka H, Stohlmeyer MM, Woiwode TF, Wandless TJ. Angew Chem Int Ed. 2007; 46:8157.c) Tanaka H, Sawayama AM, Wandless TJ. J Am Chem Soc. 2003; 125:6864. [PubMed: 12783528] d) Wang Y, Janjic J, Kozmin SA. J Am Chem Soc. 2002; 124:13670. [PubMed: 12431085] e) Smith AB, Minbiole KP, Verhoest PR, Schelhaas M. J Am Chem Soc. 2001; 123:10942. [PubMed: 11686698]
6. a) Zhu C, Yoshimura A, Sointsev PV, Ji L, Wei Y, Nemykin VN, Zhdankin V. Chem Commun. 2012 Accepted Manuscript. 10.1039/C2CC34836Eb) Amaike K, Muto K, Yamaguchi J, Itami K. J Am Chem Soc. 2012; 134:13573. [PubMed: 22870867] c) Cano I, Alvarez E, Nicasio MC, Pérez PJ. J Am Chem Soc. 2011; 133:191. [PubMed: 21171608] d) He W, Li C, Zhang L. J Am Chem Soc. 2011; 133:8482. [PubMed: 21563762]
7. a) Williams DR, Fu L. Org Lett. 2010; 12:808. [PubMed: 20085311] b) Bonne D, Dekhane M, Zhu J. Angew Chem Int Ed. 2007; 46:2485.c) Kitahara M, Umeda N, Hirano K, Satoh T, Miura M. J Am Chem Soc. 2011; 133:2160. [PubMed: 21268615] d) Besselièvre F, Mahuteau-Betzer F, Grierson DS, Piguel S. J Org Chem. 2008; 73:3278. [PubMed: 18348574] e) Verrier C, Martin T, Hoarau C, Marsais F. J Org Chem. 2008; 73:7383. [PubMed: 18702548] f) Miyasaka M, Hirano K, Satoh T, Miura M. J Org Chem. 2010; 75:5421. [PubMed: 20670042] g) Besselièvre F, Piguel S. Angew Chem Int Ed. 2009; 48:9553.h) Cho H, Joseph J, Chang S. Angew Chem Int Ed. 2010; 49:9899.i) Cui S, Wojtas L, Antilla CJ. Org Lett. 2011; 13:5040. [PubMed: 21861479] j) Besselièvre F, Piguel S, Mahuteau-Betzer F, Grierson DS. Org Lett. 2008; 10:4029. [PubMed: 18720988]
8. a) Doyle, MP.; McKervey, MA.; Ye, T. Modern CatalyticMethods for Organic Synthesis with Diazo Compounds. John Wiley & Sins; New York: 1998. b) Davies HM, Beckwith REJ. Chem Rev. 2003; 103:2861. [PubMed: 12914484] (c) Padwa A, Weingarten MD. Chem Rev. 1996; 96:223. [PubMed: 11848752] c) Xu X, Qian Y, Yang L, Hu W. Chem Commun. 2011; 47:797.d) Xu X, Zhou J, Yang L, Hu W. Chem Commun. 2008:6564.
9. a) Shi B, Blake AJ, Lewis W, Campbell IB, Judkins BD, Moody CJ. J Org Chem. 2010; 75:152. [PubMed: 19954177] b) Honey MA, Pasceri R, Lewis W, Moody CJ. J Org Chem. 2012; 77:1396. [PubMed: 22264218] c) Austeri M, Rix D, Zeghida W, Lacour J. Org Lett. 2011; 13:1394. [PubMed: 21341722] d) Linder J, Moody CJ. Chem Commun. 2007:1508.e) Shi B, Blake AJ, Campbell IB, Judkins BD, Moody CJ. Chem Commun. 2009:3291.f) Källström K, Hedberg C, Brandt P, Bayer A, Andersson PG. J Am Chem Soc. 2004; 126:14308. [PubMed: 15521722]
10. a) Doyle MP, Buhro WE, Davidson JG, Elliott RC, Hoekstra JW, Oppenhuizen M. J Org Chem. 1980; 45:3657.b) González-Bobes F, Fenster MDB, Kiau S, Kolla L, Kolotuchin S, Soumeillant M. Adv Synth Catal. 2008; 350:813.c) Lu L, Lu P, Ma S. Eur J Org Chem. 2007:676.d) Clémençon IF, Ganem B. Tetrahedron. 2007; 63:8665.
11. See supporting information for details. CCDC 895782 contains the supplementary crystallographic data for **3b**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
12. See supporting information.
13. Xu X, Zavalij PJ, Doyle MP. Angew Chem Int Ed. 2012; 51 anie.201203962.
14. See supporting information for details and CCDC 895783 contains the supplementary crystallographic data for **7a**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
15. Cyclopropene formation from enoldiazoacetates: Davies HML, Houser JH, Thornley C. J Org Chem. 1995; 60:7529.; Davies HML, Ahmed G, Churchill MR. J Am Chem Soc. 1996; 118:10774.; Xu X, Shabashov D, Zavalij PY, Doyle MP. J Org Chem. 2012; 77:5313. [PubMed: 22621315] ; Xu X, Shabashov D, Zavalij PY, Doyle MP. Org Lett. 2012; 14:800. [PubMed: 22272728]

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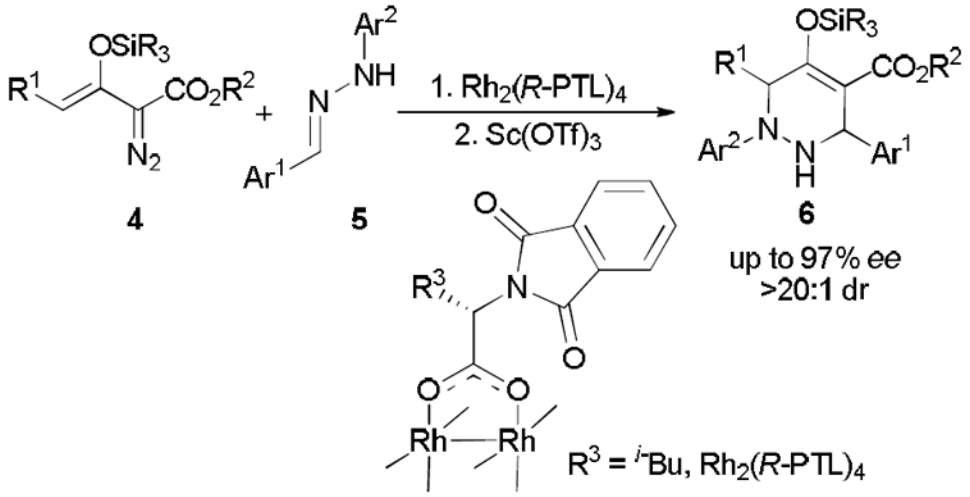
16. a) Suga H, Shi X, Ibata T. J Org Chem. 1993; 58:7397.b) Mitchell JM, Shaw JT. Angew Chem Int Ed. 2006; 45:1722.c) Evans DA, Janey JM, Magomedow N, Tedrow JS. Angew Chem Int Ed. 2001; 40:1884.d) Huang Y, Ni L, Gan H, He Y, Xu J, Wu X, Yao H. Tetrahedron. 2011; 67:2066.
17. a) Suga H, Fujieda H, Hirotau Y, Ibata T. J Org Chem. 1994; 59:3359.b) Suga H, Ikai K, Ibata T. J Org Chem. 1999; 64:7040.c) Griesbeck AG, Bondock S, Lex Johann. J Org Chem. 2003; 68:9899. [PubMed: 14682681]
18. a) Gotthardt H, Huisge R, Bayer H. J Am Chem Soc. 1970; 92:4340.b) Caesar JC, Griffiths DV, Griffiths PA, Tebby JC. J Chem Soc Perkin Trans 1. 1990:2329.c) Sabot C, Oueis E, Brune X, Renard P. Chem Commun. 2012; 48:768.



Scheme 1.
Stepwise formal [3+3]-cycloaddition of hydrazones with enoldiazoacetates

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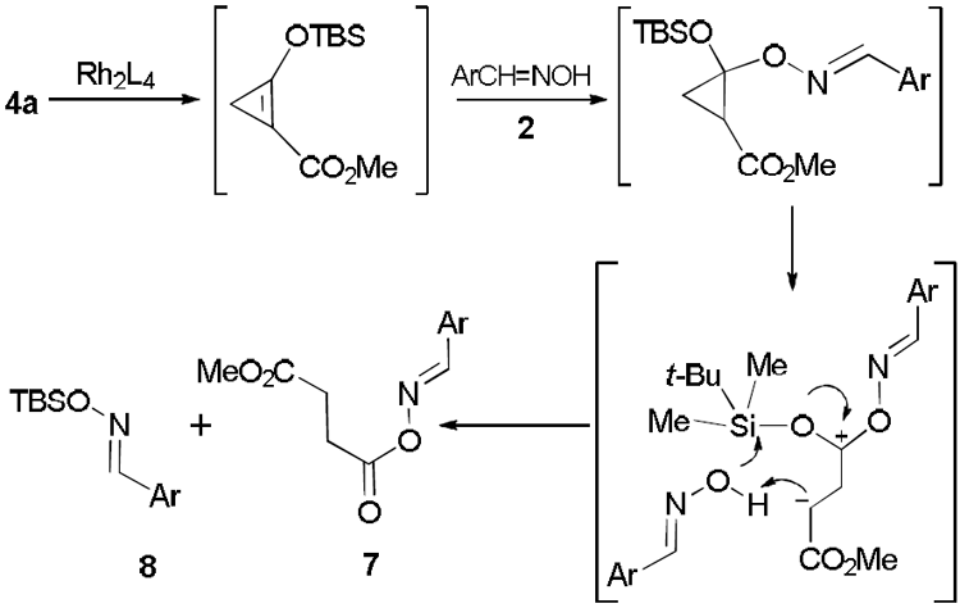
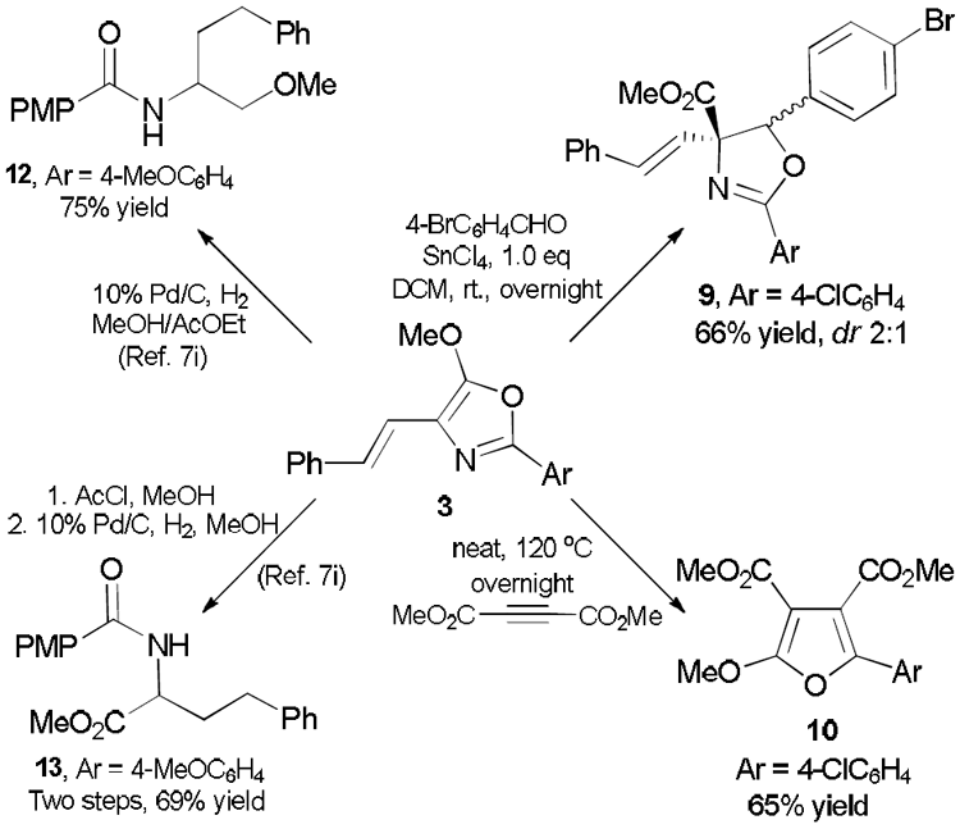


Scheme 2.
Pathway to products with enoldiazoacetates



Scheme 3.

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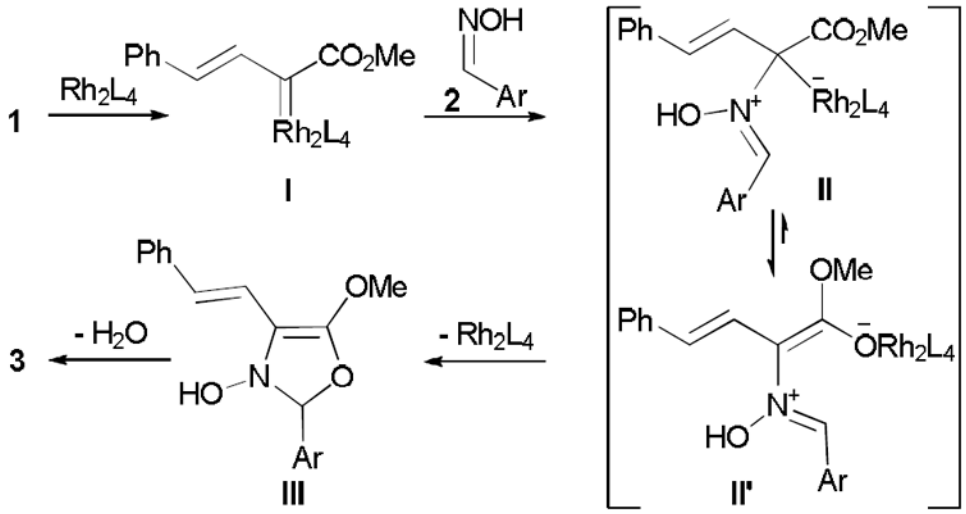

Scheme 4.
Proposed reaction mechanism for oxazole formation from styryldiazoacetate woth oximes

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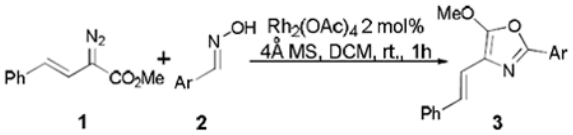
Table 1

Dirhodium(II)-catalyzed oxazole synthesis reaction of styryl diazoacetate **1** with aryl oximes[a]



1 2 3

entry	Ar (2)	3	yield (%)[b]
1	4-ClC_6H_4 (**2a**)	**3a**	82
2	4-BrC_6H_4 (**2b**)	**3b**	89
3	4-FC_6H_4 (**2c**)	**3c**	71
4	Ph (**2d**)	**3d**	83
5	4-$NO_2C_6H_4$ (**2e**)	**3e**	91
6	4-$MeOC_6H_4$ (**2f**)	**3f**	67
7	4-MeC_6H_4 (**2g**)	**3g**	77
8	3-MeC_6H_4 (**2h**)	**3h**	71
9	2-MeC_6H_4 (**2i**)	**3i**	72
10	2-furyl (**2j**)	**3j**	62
11	2-naphthyl (**2k**)	**3k**	87

[a]Reactions were carried out over 2 h on a 1.0 mmol scale: **1b** (1.5 mmol), **2** (1.0 mmol), 4 Å MS (100 mg), in 3.0 mL DCM with $Rh_2(OAc)_4$ (2.0 mol%) at room temperature.

[b]Isolated yield of **3** (based on limiting reagent **2**).