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

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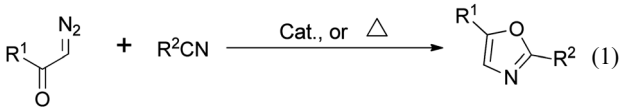
An efficient one-step synthesis of multi-functionalized oxazole derivatives is achieved in high yield by dirhodium(II)-catalyzed reactions of styryl diazoacetate with aryl oximes.

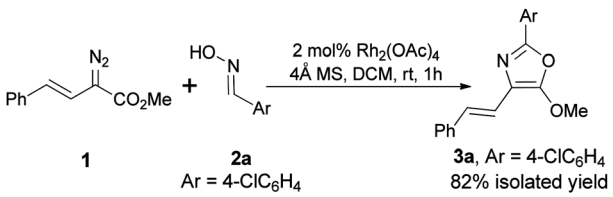
Oxazoles are widely distributed in nature, and many of them have shown biological activities.[1] Because oxazoles are used as building blocks in organic synthesis[2] for α,α-disubstituted amino acids,[3] in cycloaddition reactions,[4] and in the total synthesis of natural products,[5] efficient methods 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–j] 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 (eqn (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 (eqn (2)).



(1)

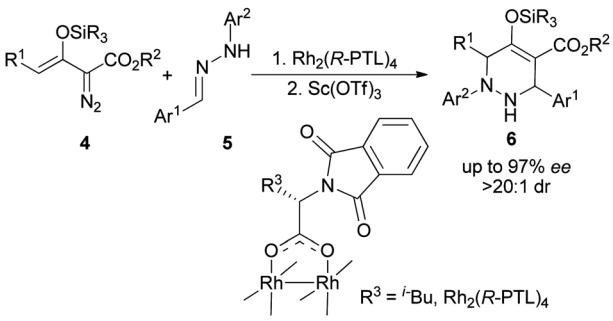
The reaction between styryl diazoacetate **1** and the oxime of 4-chlorobenzaldehyde catalyzed by rhodium acetate yielded the multi-functionalized 4-styryl-5-methoxyoxazole **3a** in 82% isolated yield when 4 Å molecular sieves was used as an additive (eqn (2)). The structure of the generated oxazole 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 (eqn (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]



1 **2a** Ar = 4-ClC$_6$H$_4$ **3a**, Ar = 4-ClC$_6$H$_4$, 82% isolated yield

(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.



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

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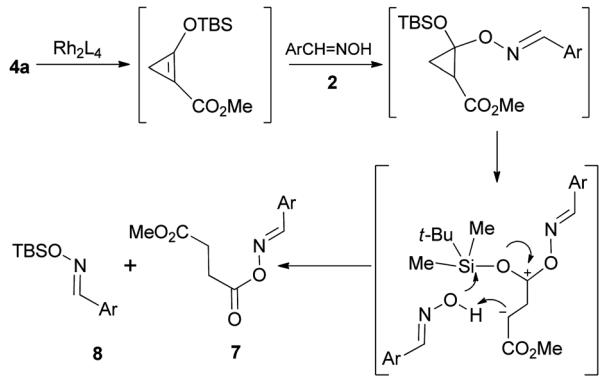
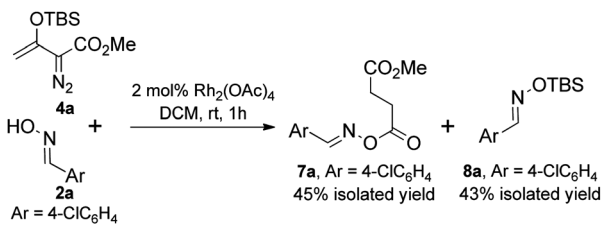


Scheme 2 Pathway to products with enoldiazoacetates.

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 (eqn (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 eqn (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.

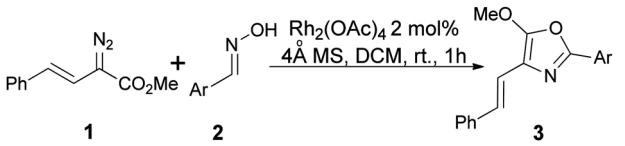


(3)

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 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 (entries 10 and 11).

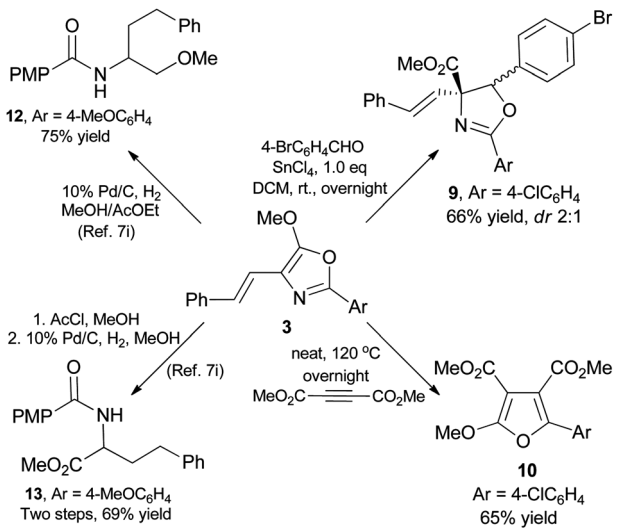
With these results in hand we investigated transformations of functionalized oxazole products to other synthetically interesting motifs (Scheme 3). A Suga–Ibata reaction of oxazole **3a** with an aldehyde for the synthesis of oxazolines was performed.[16] When the reaction was promoted by $SnCl_4$, the 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,

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



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

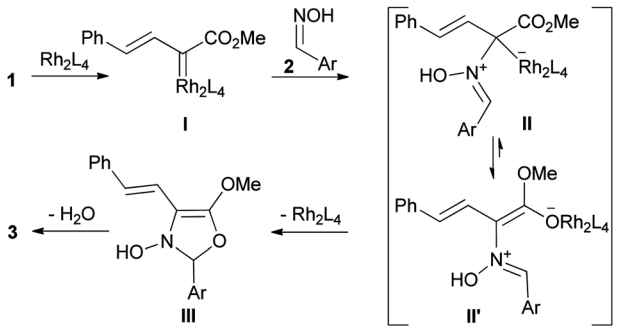
[a] Reactions were carried out over 2 h on a 1.0 mmol scale: **1b** (1.5 mmol), **2** (1.0 mmol), 4 Å MS (100 mg), in 3.0 mL DCM with $Rh_2(OAc)_4$ (2.0 mol%) at room temperature. [b] Isolated yield of **3** (based on limiting reagent **2**).



Scheme 3

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. Dirhodium(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



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

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.

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12 See ESI†.

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