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A Dramatic Substituent Effect in Silver(I)-Catalyzed Regioselective Cyclization of *ortho*-Alkynylaryl Aldehyde Oxime Derivatives

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Abstract: A dramatic substituent effect was found in the silver(I)-catalyzed cyclization reaction of *ortho*-alkynylaryl aldehyde oxime derivatives. When R is an alkyl group, the Ag(I)-catalyzed reaction in dimethylacetamide at 110 °C (conditions A) affords isoquinolines in good to excellent yields, in contrast, isoquinolin-1(2*H*)-ones were produced in moderate to high yields under conditions B (dimethylformamide, room temperature) when R is an acetyl group. A plausible mechanism was proposed for this *product selectivity control reaction (PSCR)* by subtle structure modification.

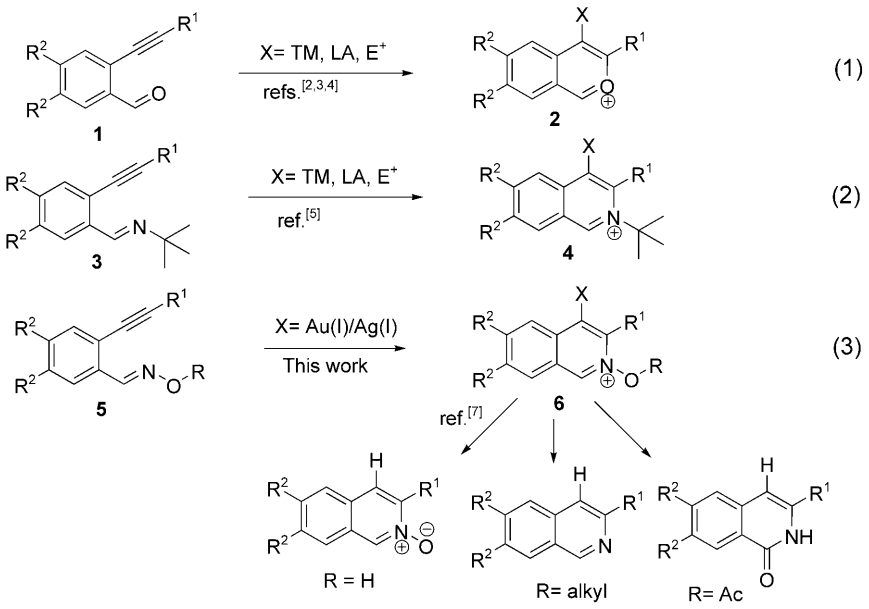
Keywords: alkynes; cyclization; regioselectivity; silver

The selective synthesis of different products from the same starting materials by simple subtle structure modification or catalyst selection is an interesting but often troublesome topic for chemists.[1] The chemistry of *ortho*-alkynylaryl aldehydes **1** mediated with transition metals, Lewis acids or electrophiles to generate a pyrylium intermediate **2** which then undergoes many transformations to afford versatile useful organic building blocks has been well studied[2] by several groups such as those of Yamamoto[3] and Barluenga.[4] Recently, The cyclization of their imine analogues **3**[2i] has been also developed by Larock,[5] leading to an efficient synthesis of isoquinoline derivatives *via* the intermediate pyrridinium **4**. During our exploration of novel product selectivity control reactions (PSCR),[6] we envisaged that *ortho*-alkynylaryl aldehyde oxime derivatives **5** catalyzed by transition metal complexes or Lewis acids would afford an intermediate pyrridinium **6** and subsequent transformations of which might depend on the type of substituent R of **6** (Scheme 1).

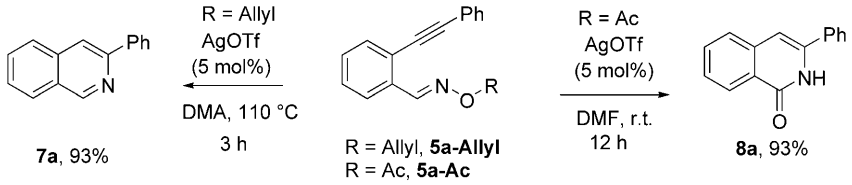
We report herein that, under the catalysis of AgOTf, the cyclization of **5** can regioselectively give three different products, i.e., isoquinoline *N*-oxides,[7] isoquinolines[8] or isoquinolin-1(2*H*)-ones.[9] The type of the R group of the oximes controls the product selectivity.

Initially, we tested the cyclization pattern of (*E*)-2-(2-phenylethynyl)benzaldehyde *O*-allyl oxime **5a-Allyl** and (*E*)-2-(2-phenylethynyl)benzaldehyde *O*-acetyl oxime **5a-Ac** in the presence of catalytic amounts of various catalysts (see Tables 1 and 2 in the Supporting Information). After numerous attempts, we were pleased to find that the cyclization reaction of **5a-Allyl** proceeds smoothly in DMA at 110 °C under the catalysis of 5 mol% of AgOTf to afford isoquinoline **7a** in 93% yield (Conditions A), whereas isoquinolin-1(2*H*)-one **8a** was produced in the same yield from the corresponding (*E*)-2-(2-phenylethynyl)benzaldehyde *O*-acetyl oxime **5a-Ac** in DMF at room temperature (Conditions B), which verified our hypothesis that the R group of the oxime indeed controls the cyclization pattern (Scheme 2).

In order to study the scope of this transformation, various substituted *ortho*-alkynylaryl aldehyde *O*-methyl or *O*-acetyl oximes **5** were studied and the results are summarized in Table 1. Several points are noteworthy: (1) isoquinolines could be obtained exclusively in good to excellent yields from the cylization reaction of corresponding *O*-methyl oximes **5-Me** under Conditions A; (2) the cyclization reaction of *O*-acetyl oximes **5-Ac** produces isoquinolin-1(2*H*)-ones in moderate to excellent yields under Conditions B; (3) aryl, cyclohexenyl, alkyl groups can be introduced



Scheme 1.



Scheme 2. The substituent controls the product selectivity.

at the R^1 position and tolerated; (4) a cyclopropyl group at R^1 was kept untouched in both cases; (5) the reaction of **5g-Ac** gives 3-vinylisoquinoline **7g′** by elimination of one molecule of HOAc under Conditions A, whereas the normal cycloisomerization product **8g** without HOAc elimination was formed in 63% yield under Conditions B (entries 13 and 14).

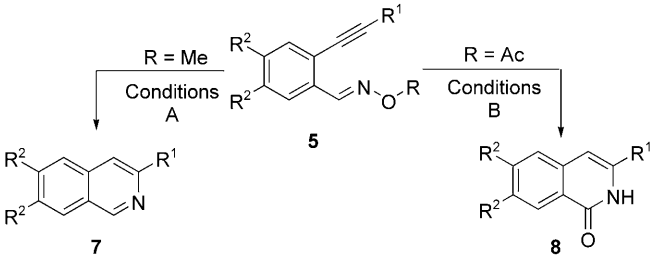
Furthermore, substrates **5j** and **5k** without an aromatic ring were prepared and tested for the purpose of studying the effect of the aromatic ring (Scheme 3). We found that the cyclization reaction of **5j-Me** did not work so well under Conditions A and gives 3-phenyl-5,6,7,8-tetrahydroisoquinoline **7j**[10] in only 37% yield. A better yield (63%) could be given by using $Ph_3PAuOTf$ (generated *in situ* from $Ph_3PAuCl/AgOTf$) as catalyst [Eq. (4)]. $Ph_3PAuOTf$ also showed better catalytic activity than AgOTf in the cyclization of **5k-Me** leading to 2,5-diphenylpyridine **7k** [Eq. (5)]. It is quite surprising to find that the reactions of the corresponding *O*-acetyl oximes **5j-Ac** and **5k-Ac** are complicated under Conditions B or other conditions even when using $Ph_3PAuOTf$ as catalyst.

Where the OMe group goes in the cyclization of *O*-methyl oximes is the next question which should be answered. Thus, *O*-benzyl oxime **5a-Bn** was prepared and the cyclization reaction of which was studied (Scheme 4). It is interesting to find that one equivalent of benzaldehyde was formed along with the product **7a**, which gives further information to help us understand the reaction mechanism.

Based on the above results, one plausible mechanism of this Ag(I)-catalyzed regioselective cyclization of *ortho*-alkynylaryl aldehyde oxime derivatives **5** leading to different products is depicted in Scheme **5**. Intermediate **6a** was initially formed *via* AgOTf-mediated cyclization, which would undergo fragmentation of the methoxy group to give intermediate **9** and one molecular of CH_2O, when R is a methyl group. The subsequent protonation of intermediate **9** would afford the isoquinoline product. In contrast, the intermediate **6b** would undergo a cycloisomerization reaction to form intermediate **10** when R is an acetyl group. Intermediate **10** would undergo protonation to afford 1-acetoxyisoquinoline **11**, which could be isolated in very low yield under some screening conditions. Subsequent hydrolysis of **11** gives the final isoquinolin-1(2*H*)-ones **8**.

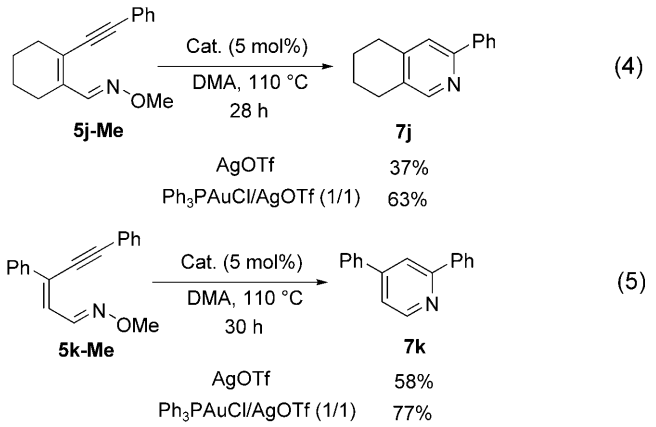
In conclusion, we have developed an efficient Ag(I)-catalyzed regioslective cyclization reaction of

Table 1. Ag(I)-catalyzed regioselective cyclization of *ortho*-alkynylaryl aldehyde oxime derivatives.



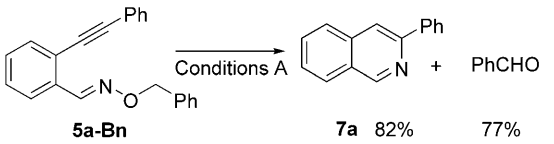
Entry	$R^2/R^1/R$ (**5**)	Conditions[a]	Time [h]	Yield[b] [%]
1	H/Ph/Me (**5a-Me**)	A	4	**7a** (84)
2	H/Ph/Ac (**5a-Ac**)	B	12	**8a** (93)
3	H/1-naphthyl/Me (**5b-Me**)	A	12	**7b** (81)
4	H/1-naphthyl/Ac (**5b-Ac**)	B	20	**8b** (80)
5	H/*n*-Bu/Me (**5c-Me**)	A	8	**7c** (76)
6	H/*n*-Bu/Ac (**5c-Ac**)	B	8	**8c** (78)
7	H/cyclopropyl/Me (**5d-Me**)	A	8	**7d** (72)
8	H/cyclopropyl/Ac (**5d-Ac**)	B	8	**8d** (91)
9	H/1-cyclohexenyl/Me (**5e-Me**)	A	6	**7e** (85)
10	H/1-cyclohexenyl/Ac (**5e-Ac**)	B	10	**8e** (88)
11	H/Allyl-N(Ts)CH_2/Me (**5f-Me**)	A	10	**7f** (71)
12	H/Allyl-N(Ts)CH_2/Ac (**5f-Ac**)	B	20	**8f** (83)
13	H/$AcOC_2H_4$/Me (**5g-Me**)	A	24	**7g′** (62)
14	H/$AcOC_2H_4$/Ac (**5g-Ac**)	B	10	**8g** (63)
15	MeO/Ph/Me (**5h-Me**)	A	12	**7h** (75)
16	MeO/Ph/Ac (**5h-Ac**)	B	10	**8h** (77)
17	MeO/*n*-Bu/Me(**5i-Me**)	A	36	**7i** (79)
18	MeO/*n*-Bu/Ac(**5i-Ac**)	B	7	**8i** (58)

[a] *Conditions A:* AgOTf (5 mol%), DMA, 110 °C; *Conditions B:* AgOTf (5 mol%), DMF, room temperature.
[b] Yield is isolated yield.

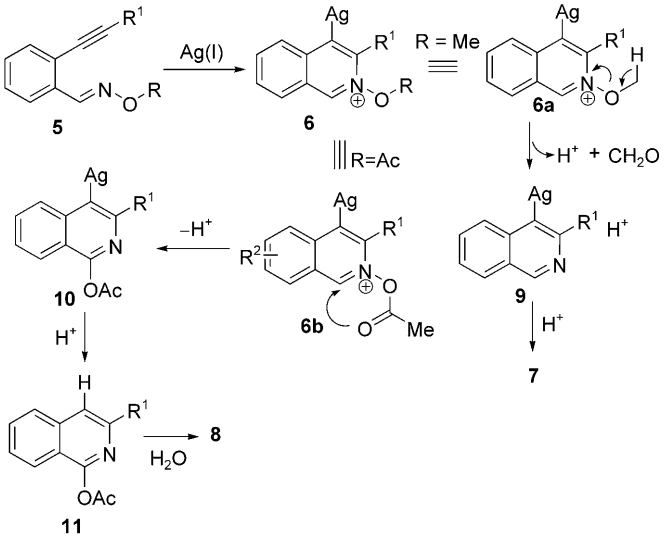


Scheme 3.

ortho-alkynylaryl aldehyde oxime derivatives **5** leading to isoquinolines or isoquinolin-1(2*H*)-ones, respectively, whereby the type of the R group of the oximes controls the product selectivity. The scope, mechanism, and synthetic applications of this transformation are being investigated in this laboratory.



Scheme 4.



Scheme 5. Plausible mechanism for the cyclization reaction.

Experimental Section

Typical Procedure for Ag(I)-Catalyzed Cyclization of *ortho*-Alkynylaryl Aldehyde Oxime Derivatives

*Synthesis of **7a** under Conditions A:* To a solution of (*E*)-2-(2-phenylethynyl)benzaldehyde *O*-methyl oxime (117.5 mg, 0.50 mmol) in 3 mL DMA was added AgOTf (6.50 mg, 0.025 mmol) under argon protection, the mixture was stirred at 110 °C and the reaction was complete after 4 h as was determined by TLC analysis. After cooling down to room temperature, 15 mL of water were added and the mixture was extracted with EtOAc three times. The combined organic layers were washed with saturated brine solution and dried over $MgSO_4$. After filtration and evaporation, the residue was purified by column chromatography on silica gel (hexanes:EtOAc = 20:1) to afford **7a**; yield: 86.3 mg (84%).

*Synthesis of **8a** under Conditions B:* To a solution of (*E*)-2-(2-phenylethynyl)benzaldehyde *O*-acetyl oxime (126.5 mg, 0.50 mmol) in 3 mL DMF was added AgOTf (6.50 mg, 0.025 mmol) under argon protection, the mixture was stirred at room temperature and the reaction was complete after 12 h as was determined by TLC analysis. 15 mL of water were added and the mixture was extracted by EtOAc three

times. The combined organic layers were washed with saturated brine solution and dried over $MgSO_4$. After filtration and evaporation, the residue was purified by column chromatography on silica gel (DCM:EtOAc = 5:1) to afford **8a**; yield: 102.6 mg (93%).

Supporting Information

Experimental details and copies of $^1H/^{13}C$ NMR spectra of all new compounds are available as supporting information.

Acknowledgements

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