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$Rh_2(OAc)_4$-AgOTf Cooperative Catalysis in Cyclization/Three-Component Reactions for Concise Synthesis of 1,2-Dihydroisoquinolines

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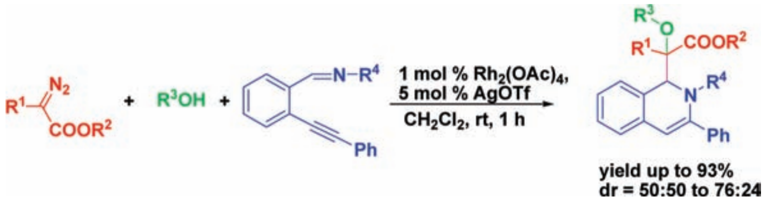
ABSTRACT



Dirhodium acetate and silver triflate cooperatively catalyzed tandem cyclization/three-component reactions of 2-alkynylarylaldimines with diazo compounds and water or alcohols are reported to afford 1,2-dihydroisoquinolines bearing α-hydroxyl-β-amino carboxylate skeleton in high yield.

Tandem or cascade reactions[1] and multicomponent reactions[2] offer significant advantages over traditional approaches for the rapid construction of several bonds in a single synthetic operation. In recent years, cooperative catalysis, including dual-metal catalysis and metal−organo catalysis, has gained much attention owing to its ability to enhance selectivity and reactivity in the reactions.[3] The appropriate combination of compatible cocatalysts can affect the intrinsic reaction kinetics in a designed way to activate the desired component selectively. The 1,2-dihydroisoquinoline derivatives were found in many natural products and pharmaceuticals with remarkable biological activities.[4] Various nucleophiles, such as alkynes, allylstannanes, silyl enol ethers, and active methylene compounds, have been employed in the Lewis acid catalyzed reactions of 2-(1-alkynyl)arylaldimine, leading to 1,2-dihydroisoquinoline derivatives through two possible tandem routes (Scheme 1).[5]

The carbenoid chemistry of transformations through oxonium ylides has received considerable attention in recent years.[6] Recently, we reported a new type of three-component reaction in which ammonium or oxonium ylides generated in situ from diazo compounds with amines or alcohols underwent nucleophilic addition to aldehydes or imines.[7] The

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[1] For recent examples and reviews on tandem or cascade reactions, see: (a) Mitchell, T. A.; Zhao, C.; Romo, D. *Angew. Chem., Int. Ed.* **2008**, *47*, 5026. (b) Chen, J.; Li, C.; An, X.; Zhang, J.; Zhu, X.; Xiao, W. *Angew. Chem., Int. Ed.* **2008**, *47*, 2489. (c) Wang, Q.; Deng, X.; Zhu, B.; Ye, L.; Sun, X.; Li, C.; Zhu, C.; Shen, Q.; Tang, Y. *J. Am. Chem. Soc.* **2008**, *130*, 5408. (d) Wang, J.; Xie, H.; Li, H.; Zu, L.; Wang, W. *Angew. Chem., Int. Ed.* **2008**, *47*, 4177. (e) Wang, L.; Liu, Q.; Wang, D.; Li, X.; Han, X.; Xiao, W.; Zhou, Y. *Org. Lett.* **2009**, *11*, 1119.

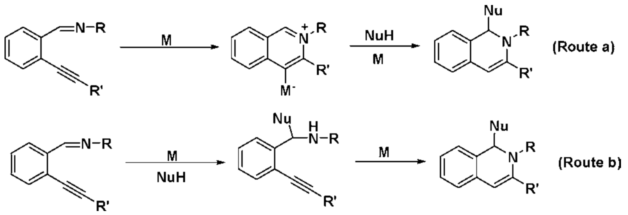
[2] For recent examples and reviews on multicomponent reactions, see: (a) Yue, T.; Wang, M.; Wang, D.; Zhu, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 9454. (b) Jiang, J.; Yu, J.; Sun, X.; Rao, Q.; Gong, L. *Angew. Chem., Int. Ed.* **2008**, *47*, 2458. (c) Xiao, Y.; Zhang, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 1903. (d) Yue, T.; Wang, M.; Wang, D.; Masson, G. *Angew. Chem., Int. Ed.* **2009**, *48*, 6717. (e) Shu, W.; Jia, G.; Ma, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 2788.

[3] For reviews of cooperative catalysis, see: (a) Lee, J. K.; Kung, M. C.; Kung, H. H. *Top Catal.* **2008**, *49*, 136. (b) Park, Y. J.; Park, J. W.; Jun, C. H. *Acc. Chem. Res.* **2008**, *41*, 222. (c) Ko, S.; Kang, B.; Chang, S. *Angew. Chem., Int. Ed.* **2005**, *44*, 455. (d) Jeganmohan, M.; Bhuvaneswari, S.; Cheng, C. H. *Angew. Chem., Int. Ed.* **2009**, *48*, 391. (e) Alexander, D.; Stefan, F. K. *Angew. Chem., Int. Ed.* **2008**, *47*, 2.

[4] For examples, see: (a) Zheng, S.; Chan, C.; Furuuchi, T.; Wright, B. J. D.; Zhou, B.; Guo, J.; Danishefsky, S. D. *Angew. Chem., Int. Ed.* **2006**, *45*, 1754. (b) Vincent, G.; Williams, R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1517. (c) Chen, J.; Chen, X.; Michele, B. C.; Zhu, J. *J. Am. Chem. Soc.* **2006**, *128*, 87.

10.1021/ol902409u

Scheme 1. Two Proposed Reaction Pathways for Tandem Reactions of Various Nucleophiles with 2-(1-Alkynyl)arylaldimine



reaction afforded highly substituted amino acid frameworks with quaternary stereogenic centers in one step. We envisioned that the oxonium ylide, generated in situ from a diazo compound with an alcohol or water, would serve as a nucleophile to attack a Lews acid activated 2-alkynylarylaldimine affording new functionalized 1,2-dihydroisoquinolines bearing an adjacent α-hydroxy-β-amino carboxylate skeleton in one step (Scheme 2). In this multicomponent reaction, two metal catalysts, $Rh_2(OAc)_4$ and a Lewis acid catalyst, must be compatible and activate the desired component selectively.

Scheme 2. 1,2-Dihydroisoquinoline Synthesis via Dual-Metal Co-catalyzed Three-Component Reaction

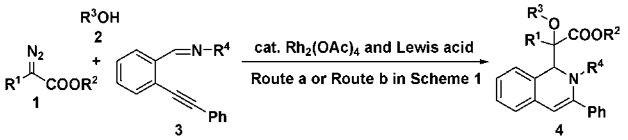
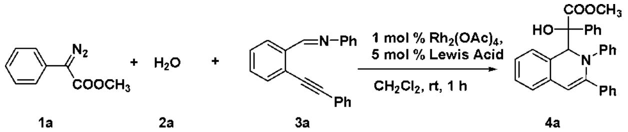


Table 1. Screening for the Lewis acid Co-catalyst for the Three-Component Reaction of **1a**, **2a**, and **3a**[a]



entry	Lewis acid	yield (%)[b]	dr[c]
1		9	50:50
2	$Pd(PPh_3)_4$	0	
3	$PdCl_2(PPh_3)_2$	3	
4	$PdCl_2$	27	45:55
5	$Cu(OTf)_2$	0	
6	CuI	2	
7	$Cu(CN)_4PF_6$	28	46:54
8	AgOTf	83	60:40
9[d]	AgOTf	29	60:40
10[e]	AgOTf	0	
11	$In(OTf)_3$	0	

[a] Reaction conditions: Unless otherwise noted, the reaction was carry out in refluxing CH_2Cl_2 with **1a**:**2a**:**3a** = 1:1.2:1.2, catalyzed by 1 mol % of $Rh_2(OAc)_4$ and 5 mol % of Lewis acid.. [b] Isolated yield based on 2-(1-alkynyl)phenylaldimine **1a.** [c] Determined by ^1H NMR analysis. [d] 1 mol % of catalyst was used. [e] In the absence of $Rh_2(OAc)_4$ catalyst, methyl 2-oxo-2-phenylacetate was isolated.

To verify the practicability of the strategy shown in Scheme 2, our studies commenced with screening of an effective cocatalyst in a reaction of methyl phenyldiazoacetate (**1a**), H_2O (**2a**), and 2-(1-alkynyl)phenylaldimine **3a** and the results are shown in Table 1. In the absence of a Lewis acid cocatalyst, the reaction afforded only 9% yield of desired product **4a** with a significant amount of starting material **3a** recovered (Table 1, entry 1). Soft metal salts such as palladium, copper, or silver with mild Lewis acidity were examined to activate the triple bond functionality of **3a**.[5f] $PdCl_2$ was found to be an effective cocatalyst among the Pd catalysts screened, affording the desired product **4a** in 27% yield (entries 2−4). Similar results were observed with

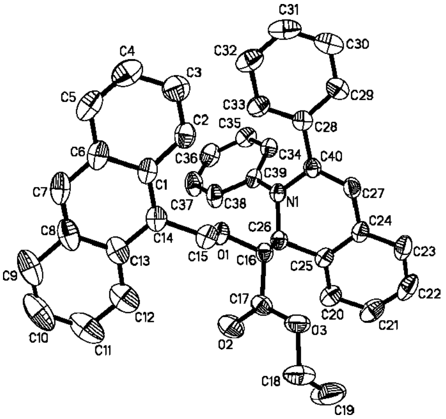


Figure 1. ORTEP representation of the crystal structure of *threo*-**4t**

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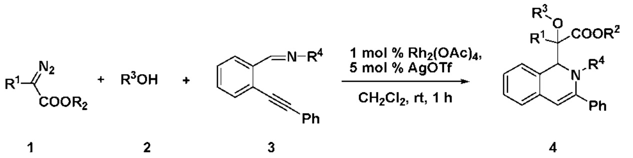
Table 2. Reactions of Diazoacetates **1**, Water or Alcohols **2**, and 2-(1-Alkynyl)phenylaldimines **3** Catalyzed by Silver Triflate and Dirhodium Acetate[a]



1a: R^1 = Ph, R^2 = CH_3
1b: R^1 = *p*-$MeOC_6H_5$, R^2 = CH_3
1c: R^1 = *p*-MeC_6H_5, R^2 = CH_3
1d: R^1 = *m*-BrC_6H_5, R^2 = CH_3
1e: R^1 = *m*-ClC_6H_5, R^2 = CH_3
1f: R^1 = *p*-BrC_6H_5, R^2 = CH_3
1g: R^1 = *p*-$NO_2C_6H_5$, R^2 = CH_3
1h: R^1 = H, R^2 = Et

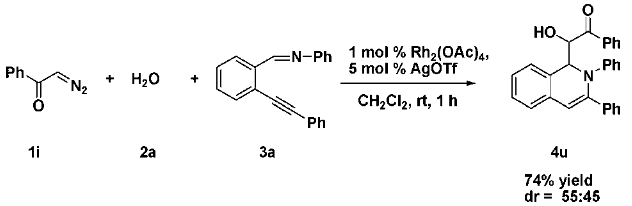
2a: R^3 = H
2b: R^3 = CH_3
2c: R^3 = *i*-Pr
2d: R^3 = *t*-Bu
2e: R^3 = Bn
2f: R^3 = 9-anthryl-CH_2

3a: R^4 = Ph
3b: R^4 = *m*-ClC_6H_5
3c: R^4 = *p*-ClC_6H_5
3d: R^4 = *p*-BrC_6H_5
3e: R^4 = *p*-$NO_2C_6H_5$
3f: R^4 = *o*-OHC_6H_5
3g: R^4 = *p*-$MeOC_6H_5$

entry	1	2	3	4	yield(%)[b]	dr[c]
1	**1a**	**2a**	**3a**	**4a**	83	60:40
2	**1b**	**2a**	**3a**	**4b**	90	56:44
3	**1c**	**2a**	**3a**	**4c**	84	58:42
4	**1d**	**2a**	**3a**	**4d**	80	52:48
5	**1e**	**2a**	**3a**	**4e**	85	53:47
6	**1f**	**2a**	**3a**	**4f**	65	57:43
7	**1g**	**2a**	**3a**		0	
8	**1a**	**2a**	**3b**	**4g**	65	56:44
9	**1a**	**2a**	**3c**	**4h**	67	56:44
10	**1a**	**2a**	**3d**	**4i**	60	59:41
11	**1a**	**2a**	**3e**		0	
12	**1a**	**2a**	**3f**		0	
13	**1h**	**2a**	**3a**	**4j**	92	49:51
14	**1h**	**2a**	**3g**	**4k**	93	54:46
15	**1h**	**2a**	**3b**	***4l***	73	55:45
16	**1h**	**2a**	**3d**	**4m**	71	76:24
17	**1h**	**2a**	**3c**	**4n**	72	68:32
18	**1h**	**2a**	**3e**	**4o**	65	61:39
19	**1h**	**2a**	**3f**		0	
20[d]	**1h**	**2b**	**3a**	**4p**	60	46:54
21[d]	**1h**	**2c**	**3a**	**4q**	55	50:50
22[d]	**1h**	**2d**	**3a**	**4r**	51	61:39
23[d]	**1h**	**2e**	**3a**	**4s**	43	50:50
24[d]	**1h**	**2f**	**3a**	**4t**	34	N.D.[e]

[a] All reactions were carried out in CH_2Cl_2 at rt in the presence of 1 mol % of $Rh_2(OAc)_4$ and 5 mol % of AgOTf with **1**:**2**:**3** = 1.2:1.2:1.0 mmol. [b] Isolated yield based on 2-(1-alkynyl)phenylaldimine **1**. [c] Determined by ^1H NMR analysis of crude products. [d] 4 Å MS (100 mg) was added. [e] Only one diastereomer was isolated after chromatography purification.

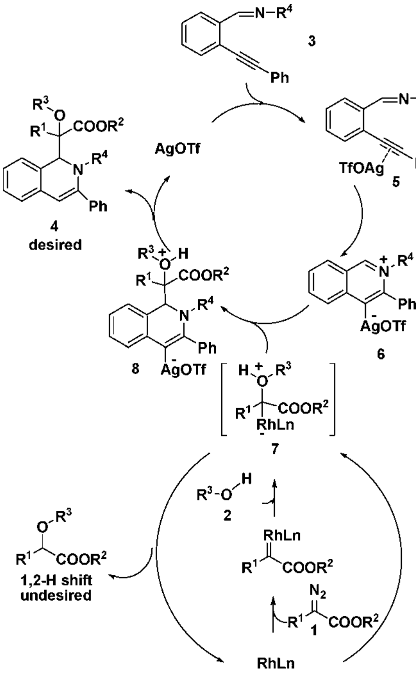
Scheme 3. Reaction of Diazo Compound **1i**, Water **2**, and 2-(1-Alkynyl)phenylaldimine **3a**



copper catalysts (entries 5−7). Gratifyingly, AgOTf was found to be the best cocatalyst to give **4a** in 83% islolated yield (entry 8). The yield dramatically decreased to 29% while decreasing the catalyst loading of AgOTf from 5 mol % to 1 mol % (entry 9). Silver salts were reported to effectively catalyze diazo decomposition of donor/acceptor diazo compounds.[8] In this study, by using AgOTf catalyst alone in the absence of $Rh_2(OAc)_4$, we isolated methyl 2-oxo-2-phenylacetate together with a significant amount of unreacted starting material **3a** (entry 10). Another Lewis acid $In(OTf)_3$, which was demonstrated as an effective catalyst in the reactions of tandem nucleophilic addition and cyclization of 2-alkynylarylaldimines,[5a] was ineffective in the current reaction (entry 11).

To demonstrate the generality of this method, the substrate scope of the reaction was investigated under optimized conditions [AgOTf (5 mol %), $Rh_2(OAc)_4$ (1 mol %), CH_2Cl_2, rt, 1 h], and the results are summarized in Table 2. The chemo- and stereoselectivities of the reactions were found to be dependent on electronic and steric features of the substrates used. In the reactions of methyl aryldiazoacetates **1a**−**g** with H_2O and 2-(1-alkynyl)phenylaldimines **3a**−**f**, electron-rich substrates **1** and **3** gave a higher yield of the product (Table 2, entries 1−12). For example, the use of methyl *p*-MeO-phenyldiazoacetate (**1b**) furnished the reaction in 90% yield (entry 2), while electron-deficient methyl *p*-NO_2-phenyldiazoacetate (**1g**) or N-*p*-NO_2-phenyl 2-(1-alkynyl)phenylaldimine (**3e**) gave no desired three-component product (entries 7 and 11). The reaction was not limited to aryldiazoacetates, as good yields of the desired

Scheme 4. Plausible Reaction Mechanism of $Rh_2(OAc)_4$ and AgOTf Co-catalyzed Tandem Cyclization/Three-Component Reaction



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products were also obtained by using ethyl diazoacetate (**1h**) (entries 13−18 and 20−24). Sterically hindered *N*-aryl 2-(1-alkynyl)phenylaldimine **3f** bearing an ortho substituent on the *N*-aryl group gave no desired product both in the reactions with aryldiazoacetate **1a** or ethyl diazoacetate (**1h**) (entries 12 and 19). Diastereoselectivity was generally poor in the reaction. The highest dr of 76:24 was observed in the reaction of ethyl diazoacetate, H_2O, and N-*p*-Br-phenyl 2-(1-alkynyl)phenylaldimine **3d** (entry 16). Interestingly, electron-deficient substrate **3e**, which was inactive toward methyl phenyldiazoacetate, reacted well with ethyl diazoacetate and H_2O affording the corresponding product **4o** in 65% yield with a dr of 61:39 (entry 18). Alcohols **2b−f** were also used to replace H_2O in the reaction to give the corresponding products **4p−t** in moderate yield (entries 20−24). The structure and relative configuration of isomer *threo*-**4t** was confirmed by single-crystal X-ray analysis (Figure 1).

The reaction was extended to additional diazo compounds. Diazo ketone **1i** was employed in the reaction with H_2O and **3a** to afford the desired product **4u** in 74% yield (Scheme 3).

The exact reaction pathway leading to the three-component adducts is unclear yet, but we prefer a reaction pathway shown in Scheme 4. The isoquinolinium intermediate **6** is formed by nucleophilic attack of the imine nitrogen atom to the AgOTf-coordinated alkyne **5**. The existence of the isoquinolinium intermediate **6** has been reported by Yamamoto in the reaction of **3a** with AgOTf in the absence of any pronucleophiles.[5b,9] In another catalytic cycle, an oxonium ylide intermediate **7** is formed,[7c] which undergoes a Mannich-type reaction via a proposed intermediate **8** to afford the desired product **4**.

In summary, we have reported a cooperative catalyst combination, $Rh_2(OAc)_4$ and AgOTf, which is effective for a tandem cyclization/three-component reaction of 2-alkynylarylaldimines, diazo compounds, and water or alcohols to afford functionalized 1,2-dihydroisoquinolines in moderate to high yield. Further investigation to improve diastereoselectivity and to study an asymmetric version of the current reaction is in progress in our laboratory.

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Supporting Information Available: Experimental procedures, characterization data, and copies of ^{1}H and ^{13}C NMR of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) A less soluble solid was formed prior to the last addition of a diazo compound, suggesting the formation of **6**.