ORGANIC LETTERS

2010
Vol. 12, No. 24
5688−5691

Rhodium(III)-Catalyzed Synthesis of Isoquinolines from Aryl Ketone *O*-Acyloxime Derivatives and Internal Alkynes

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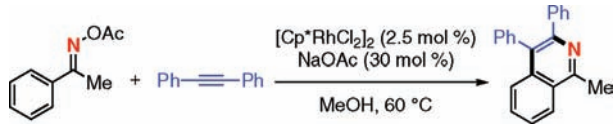
Received October 16, 2010

ABSTRACT



A synthetic method of isoquinolines from aryl ketone *O*-acyloxime derivatives and internal alkynes has been developed using $[Cp^*RhCl_2]_2$−NaOAc as the potential catalyst system. The present transformation is carried out by a redox-neutral sequence of C−H vinylation via *ortho*-rhodation and C−N bond formation of the putative vinyl rhodium intermediate on the oxime nitrogen, where the N−O bond of oxime derivatives could work as an internal oxidant to maintain the catalytic cycle.

Chemical transformation via catalytic C−H bond activation by various transition metal complexes is a powerful and attractive tool in organic synthesis.[1] In the process of the C−H functionalization, suitable heteroatoms in the substrates are commonly utilized to direct a metal complex to the specific proximal C−H bond. Among such directing groups, an sp^2 nitrogen atom of the imine derivatives has played a crucial role in numerous examples of the C−H bond activation with the rational catalyst design,[2] while these nitrogen atoms have rarely been involved for a new bond constructed in the reaction processes.[3] In recent elegant precedents, Fagnou[4] and Miura-Satoh[5] have independently reported the Rh(III)-catalyzed oxidative isoquinoline synthesis using *N*-*t*-Bu aryl aldimines and benzophenone *N*-H imines, respectively, as a nitrogen containing source via *ortho*-aryl C−H rhodation followed by internal alkyne insertion and C−N reductive elimination, where stoichiometric use of $Cu(OAc)_2$ as an external oxidant is indispensable to regenerate the active Rh(III) catalyst.

To achieve the catalytic process for the synthesis of isoquinolines that bears flexibility on the functional groups and proceeds under milder reaction conditions, our attention

(1) For recent reviews, see: (a) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624. (b) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (c) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Commun.* **2010**, *46*, 677. (d) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792. (e) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094. (f) Kulkarni, A. A.; Daugulis, O. *Synthesis* **2009**, 4087. (g) Kakiuchi, F.; Kochi, T. *Synthesis* **2008**, 3013.

(2) For selected reports on the *ortho*-metallation−C-C bond formation sequence of aldimine and ketimine derivatives, see: (a) Gao, K.; Lee, P.-S.; Fujita, T.; Yoshikai, N. *J. Am. Chem. Soc.* **2010**, *132*, 12249. (b) Yoshikai, N.; Matsumoto, A.; Norinder, J.; Nakamura, E. *Angew. Chem., Int. Ed.* **2009**, *48*, 2925. (c) Kuninobu, Y.; Kikuchi, K.; Tokunaga, Y.; Nishina, Y.; Takai, K. *Tetrahedron* **2008**, *64*, 5974. (d) Kuninobu, Y.; Tokunaga, Y.; Kawata, A.; Takai, K. *J. Am. Chem. Soc.* **2006**, *128*, 202. (e) Thalji, R. K.; Ahrendt, K. A.; Bergman, R. G.; Ellman, J. A. *J. Org. Chem.* **2005**, *70*, 6775. (f) Ueura, K.; Satoh, T.; Miura, M. *Org. Lett.* **2005**, *7*, 2229. (g) Lim, S.-G.; Ahn, J.-A.; Jun, C.-H. *Org. Lett.* **2004**, *6*, 4687. (h) Thalji, R. K.; Ahrendt, K. A.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2001**, *123*, 9692.

(3) For utilization of 6p-electrocyclization of azatrienes generated by *ortho*-vinylation, see: (a) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 3645. (b) Yotphan, S.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 2452. (c) Parthasarathy, K.; Jeganmohan, M.; Cheng, C.-H. *Org. Lett.* **2008**, *10*, 325. (d) Lim, S.-G.; Lee, J. H.; Moon, C. W.; Hong, J.-B.; Jun, C.-H. *Org. Lett.* **2003**, *5*, 2759.

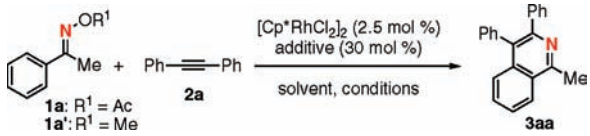
(4) Guimond, N.; Fagnou, K. *J. Am. Chem. Soc.* **2009**, *131*, 12050.

(5) Fukutani, T.; Umeda, N.; Hirano, K.; Satoh, T.; Miura, M. *Chem. Commun.* **2009**, 5141.

10.1021/ol102504b
Published on Web 11/17/2010

has been drawn to the potential chemical reactivity of readily available aryl ketoxime derivatives.[6] Herein, we wish to report the preliminary result of an efficient C−C and C−N bond formation sequence[7] to prepare highly substituted isoquinolines utilizing aryl ketone *O*-acetyloximes and 3-phenylisoxazol-5-ones with internal alkynes under the catalytic redox-neutral[8,9] $[Cp^*RhCl_2]_2$−NaOAc system, where the N−O bond of oxime derivatives could work as an internal oxidant to maintain the catalytic cycle.

Table 1. Optimization of Reaction Conditions



entry	oximes	additive	solvent	conditions	yield of **3aa**[b]
1	**1a**	none	MeOH	60 °C, 7 h	0[c]
2	**1a**	NaOAc	MeOH	60 °C, 6 h	82
3	**1a**	CsOAc	MeOH	60 °C, 4 h	80
4	**1a**	CsOAc	*t*-BuOH	80 °C, 7 h	14[c]
5	**1a**	CsOAc	DMF	80 °C, 23 h	4[c]
6	**1a′**	NaOAc	MeOH	60 °C, 19 h	13 (64)[d]

[a] Reactions were carried out on the scale of 0.3 mmol of **1a** and **2a** in MeOH (0.2 M) under a N_2 atmosphere. [b] Isolated yields. [c] NMR yields from the crude mixture. [d] Recovery yield of **1a′**.

We embarked on the investigation with reactions of acetophenone *O*-acetyloxime (**1a**) and diphenylacetylene (**2a**), and Table 1 lists representative data using $[Cp^*RhCl_2]_2$ as a catalyst.[10] Although no reaction was observed with only $[Cp^*RhCl_2]_2$ in MeOH (entry 1), addition of a metal acetate as a cocatalyst (30 mol %) resulted in the formation of isoquinoline **3aa** in good yields at 60 °C (entries 2 and 3).[11] Other solvents such as *t*-BuOH and DMF were not viable for this transformation (entries 4 and 5). The reaction of *O*-methyloxime **1a′** was sluggish, affording isoquinoline **1aa** in 13% yield with 64% recovery of oxime **1a′** even after 19 h (entry 6). This indicates that the leaving group reactivity (as $-OR^1$) is essential for this isoquinoline formation.

By utilizing the $[Cp^*RhCl_2]_2$−NaOAc catalytic system (Table 1, entry 2), the scope of the isoquinoline formation was investigated (Table 2).[12] The present process showed wide substrate tolerance with internal alkynes (entries 1−5). Insertion of an unsymmetrical alkyne, 1-phenyl-1-propyne (**2b**), occurred regioselectively to provide 4-methyl-3-phenylisoquinoline **3ab** as a sole product (entry 1). Similarly, 3-phenyl-2-propyn-1-ol (**2c**) afforded isoquinoline **3ac** with high regioselectivity albeit in moderate yield that was improved by protection of a hydroxy group with TBS (entries 2 and 3). The reactions with dialkyl-substituted alkynes also proceeded smoothly (entries 4 and 5). As substituents on the benzene ring of acetophenone *O*-acetyloxime **1**, both electron-donating and -withdrawing groups could be introduced. This process could keep a C−Br bond intact (entries 8, 11, and 12). In the case of *meta*-substituted substrates, regioisomeric mixtures were obtained where the sterically less hindered C−H bond was preferentially cleaved (marked in blue) (entries 12 and 13). This method allowed construction of a thieno[2,3-*c*]pyridine structure (entry 14). At the C(1) position of isoquinolines **3**, phenyl and alkenyl groups as well as a methoxycarbonyl moiety could be installed (entries 15−17). α-Tetralone *O*-acetyloxime (**1n**) was successfully applied for preparing tricyclic isoquinoline **3na** (entry 18).

To obtain detailed mechanistic information of the present catalytic process, several reactions were performed as shown in Scheme 1. When *O*-acetyloxime **1a** was treated in MeOD in the absence of alkynes, deuteration of the *ortho*-positions was observed with deacetylation (Scheme 1a). On the contrary, the reaction in MeOD in the presence of alkyne **2a** afforded isoquinoline **3aa-*d*** without deuterium incorporation at the C(8) position (Scheme 1b). These results could suggest that the C−H rhodation initiates the catalytic cycle and is most likely the rate-determining step. It was rather interesting that deuterium was incorporated into the methyl group of isoquinoline **3aa-*d*** (Scheme 1b), whereas it was confirmed that treatment of isoquinoline **3aa** under the present catalytic conditions in MeOD did not result in deuteration of the methyl group. These observations indicated that deuterium incorporation into the methyl group of isoquinoline **3aa** might have occurred during the catalytic ring formation process.[13]

Based on these results, a potential mechanistic possibility was outlined in Scheme 2. It commences with *ortho*-C−H activation of aryl ketone *O*-acetyloximes **1** with the aid of the oxime sp^2 nitrogen to give arylrhodium intermediate **A**,

(6) For recent reports on *ortho*-metallation of aryloxime derivatives, see: (a) Sun, C.-L.; Liu, N.; Li, B.-J.; Yu, D.-G.; Wang, Y.; Shi, Z.-J. *Org. Lett.* **2010**, *12*, 184. (b) Thirunavukkarasu, V. S.; Parthasarathy, K.; Cheng, C.-H. *Angew. Chem., Int. Ed.* **2008**, *47*, 9462. (c) Yu, W.-Y.; Sit, W. N.; Lai, K.-M.; Zhou, Z.; Chan, A. S. C. *J. Am. Chem. Soc.* **2008**, *130*, 3304. (d) Thu, H.-Y.; Yu, W.-Y.; Che, C.-M. *J. Am. Chem. Soc.* **2006**, *126*, 9048. (e) Desai, L. V.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 9542.

(7) For reports on Rh(III)-catalyzed oxidative C-H bond functionalization−C-N bond formation sequence triggered by amido and indole N-H bonds, see: (a) Hyster, T. K.; Rovis, T. *J. Am. Chem. Soc.* **2010**, *132*, 10565. (b) Rakshit, S.; Patureau, F. W.; Glorius, F. *J. Am. Chem. Soc.* **2010**, *132*, 9585. (c) Morimoto, K.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2010**, *12*, 2068. (d) Mochida, S.; Umeda, N.; Hirano, K.; Satoh, T.; Miura, M. *Chem. Lett.* **2010**, *39*, 744. (e) Stuart, D. R.; Bertrand-Laperle, M.; Burgess, K. M. N.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 16474.

(8) For a report on Rh(III)-catalyzed redox-neutral synthesis of isoquinolones from benzhydroxamic acid derivatives and alkynes, see: Guimond, N.; Gouliaras, C.; Fagnou, K. *J. Am. Chem. Soc.* **2010**, *132*, 6908.

(9) For reports on Pd-catalyzed redox-neutral intramolecular aromatic C−H amination processes of *O*-acyloximes for the synthesis of indoles, see: (a) Tan, Y.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 3676. (b) Chiba, S.; Zhang, L.; Sanjaya, S.; Ang, G. Y. *Tetrahedron* **2010**, *66*, 5692.

(10) Rh(I) catalysts such as $RhCl(PPh_3)_3$ did not work at all for the present process.

(11) (a) Li, L.; Brennessel, W. W.; Jones, W. D. *Organometallics* **2009**, *28*, 3492. (b) Davies, D. L.; Al-Duaij, O.; Fawcett, J.; Giardiello, M.; Hilton, S. T.; Russell, D. R. *Dalton Trans.* **2003**, 4132.

(12) All *O*-acetyloximes **1** in Table 2 were prepared from the corresponding ketones by treatment with hydroxylamine followed by acetylation of the resulting oximes. These processes could provide the desired *anti* stereochemistry as a sole/major isomer (see Supporting Information).

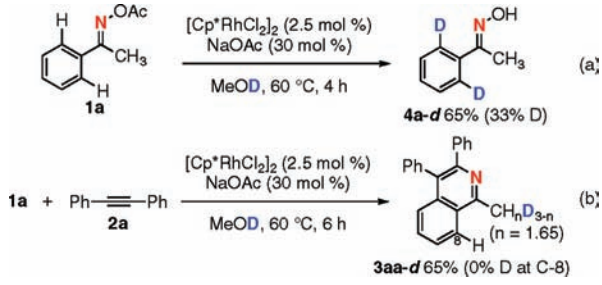
(13) 6π-Electrocyclization was most likely ruled out from the possible reaction pathways by the reactions of *ortho*-alkenyloxime; see Supporting Information.

Table 2. Synthesis of Isoquinolines from Aryl Ketone *O*-Acetyloximes and Alkynes[a]

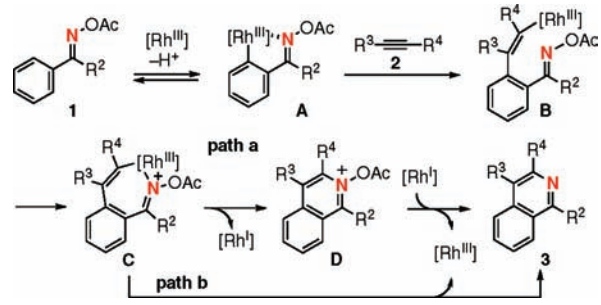
entry	oximes **1**	alkynes **2**	isoquinolines **3** / yield[b]
1	**1a**	**2b** (R^3 = Me, R^4 = Ph)	**3ab:** 72%
2	**1a**	**2c** (R^3 = CH_2OH, R^4 = Ph)	**3ac:** 42% (9:1)[c]
3	**1a**	**2d** (R^3 = CH_2OTBS, R^4 = Ph)	**3ad:** 65% (14:1)[c]
4	**1a**	**2e** (R^3 = *n*-Pr, R^4 = *n*-Pr)	**3ae:** 87%
5	**1a**	**2f** (R^3 = CH_2OTBS, R^4 = CH_2OTBS)	**3af :** 73%
6	**1b**	**2a**	**3ba:** 87%
7	**1c**	**2a**	**3ca:** 92%
8	**1d**	**2a**	**3da:** 94%
9	**1e**	**2a**	**3ea:** 89%
10	**1f**	**2a**	**3fa:** 89%
11	**1g**	**2a**	**3ga:** 82%
12	**1h**	**2a**	**3ha:** 67%; **3ha'**: 25%
13	**1i**	**2a**	**3ia:** 58%; **3ia'**: 31%
14	**1j**	**2a**	**3ja:** 69%
15	**1k**	**2a**	**3ka:** 98%
16	**1l**	**2a**	**3la:** 95%
17	**1m**	**2a**	**3ma:** 91%
18	**1n**	**2a**	**3na:** 76%

[a] The reactions were carried out by treatment of a mixture of oxime **1** (0.5 mmol) and alkyne **2** (1.2 equiv) with $[Cp^*RhCl_2]_2$ (2.5 mol %) and NaOAc (30 mol %) in MeOH (0.2 M) at 60 °C under a N_2 atmosphere for 4−10 h. [b] Isolated yields. [c] Regioselectivity determined by ^1H NMR. The strucutre of the major isomer was described.

Scheme 1. Investigation of the Reaction Mechanism



Scheme 2. Proposed Mechanistic Possibility

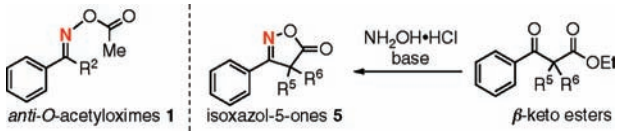


which undergoes insertion to alkynes **2** to afford vinyl rhodium species **B**. Formation of seven-membered ring rhodacyclic iminium cation intermediate **C** followed by C−N reductive elimination would provide *N*-acetoxyisoquinolinium cation **D**,[14] the reduction of which by the resulting Rh(I) species could form isoquinolines **3** along with regeneration of the Rh(III) catalyst (path a). Alternatively, direct formation of isoquinolines **3** and Rh(III) species from rhodacycle **C** via a concerted redox process could also be proposed (path b). Deuterium incorporation into the methyl

moiety of isoquinoline **3aa** in MeOD (see Scheme 1b) strongly supported the presence of the iminium cation **C** or isoquinolinium cation **D** bearing acidic α-protons (R^2 = Me) in the reaction course.[15]

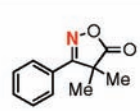
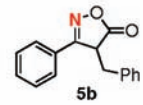
Although aryl ketone *O*-acetyloximes **1** were found to be promising precursors for the present Rh(III)-catalyzed isoquinoline formation with internal alkynes, the stereochemical requirement of oximes **1** (i.e., the N−O bond of oximes should be *anti* to the aryl moiety)[16] might be a hurdle for the process especially in the case of the substrates bearing a bulky substituent as R^2.[17] Isoxazol-5-one derivatives **5** are easily accessible from the corresponding *β*-keto esters by the reaction with hydroxylamine, where even two alkyl groups (R^5 and R^6) could easily be introduced at the C(4) position of isoxazol-5-ones (Scheme 3).[18] Stimulated by the structural analogy of isoxazol-5-ones **5** with *anti*-*O*-acetyloximes **1**, we turned our attention to investigating the chemical reactivity of several 3-phenylisoxazol-5-ones **5** with alkynes **2**.

Scheme 3. *O*-Acetyloximes **1** and Isoxazol-5-ones **5**



It was found that the reaction of 4,4-dimethyl-3-phenylisoxazol-5(4*H*)-one (**5a**) with diphenylacetylene (**2a**) proceeded smoothly under the present reaction conditions (2.5 mol % $[Cp^*RhCl_2]_2$, 30 mol % NaOAc, MeOH, 60 °C), providing 1-isopropylisoquinoline **6aa** via decarboxylation in 91% yield (Table 3, entry 1). Deuteration of the methine carbon of the isopropyl moiety was observed when the reaction was conducted in MeOD (entry 2). Unsymmetrical

Table 3. Synthesis of Isoquinolines from 3-Phenylisoxazol-5-ones and Alkynes[a]

entry	isoxazolones **5**	alkynes **2**	isoquinolines **6** / yield[b]
		 **2**	
1	**5a**	**2a** (R^3 = Ph, R^4 = Ph)	**6aa:** 91%
2[c]	**5a**	**2a** (R^3 = Ph, R^4 = Ph)	**6aa-*d*:** 94% (93% D)
3	**5a**	**2b** (R^3 = Me, R^4 = Ph)	**6ab:** 56%[d,e]
4	**5a**	**2e** (R^3 = *n*-Pr, R^4 = *n*-Pr)	**6ac:** 82%
5	 **5b**	**2a**	 **6ba:** 69%
6	 **5c**	**2a**	 **6ca**(= **3aa**): 72%

[a] Unless otherwise noted, the reactions were carried out by treatment of a mixture of isoxazol-5-one **5** (0.5 mmol) and alkyne **2** (1.0 equiv) with $[Cp^*RhCl_2]_2$ (2.5 mol %) and NaOAc (30 mol %) in MeOH (0.2 M) at 60 °C under a N_2 atmosphere for 4−6 h. [b] Isolated yields. [c] The reaction was performed in MeOD. [d] **5a** was recovered in 38% yield. [e] The reaction time was 28 h.

alkyne **2b** and dialkyl-substituted alkyne **2e** could also be coupled with **5a** in good yields albeit in relatively longer reaction times (entries 3 and 4). 3-Phenylisoxazol-5-ones **5** bearing a monosubstituent and no substituent at C(4) could be utilized for this transformation (entries 5 and 6).

Further investigation of the detailed mechanism, reaction scope, and synthetic application of these reactions for the preparation of a variety of azaheterocycles is currently underway and will be reported in due course.

Acknowledgment. This work was supported by funding from the Nanyang Technological University, Singapore Ministry of Education, and Science & Engineering Research Council (A*STAR Grant No. 082 101 0019).

Supporting Information Available: Experimental procedures, characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL102504B

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(15) Traynelis, V. J.; Pacini, P. L. *J. Am. Chem. Soc.* **1964**, *86*, 4917.
(16) For example, the reaction of *Z*-isomer of **1l** provided only deacetylated oxime without formation of isoquinoline **3la**; see Supporting Information.
(17) For example, the reaction of isobutyrophenone with hydroxylamine provided an *E*,*Z*-mixture of oxime in an almost 1:1 ratio; see: Zhao, H.; Vandenbossche, C. P.; Koenig, S. G.; Singh, S. P.; Bakale, R. P. *Org. Lett.* **2008**, *10*, 505.
(18) Canonne, P.; Thibeault, D.; Fytas, G. *Tetrahedron* **1986**, *42*, 4203.