DOI: 10.1002/adsc.200900442

Multicatalytic Tandem Reactions of 2-Alkynylbenzaldoximes with Isocyanides

Zhiyuan Chen,[a] Xingxin Yu,[a] Mingchao Su,[a] Xiaodi Yang,[c] and Jie Wu[a,b,*]

[a] Department of Chemistry, Fudan University, 220 Handan Road, Shanghai 200433, People's Republic of China
Fax: (+86)-216-510-2412; e-mail: jie_wu@fudan.edu.cn
[b] State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, People's Republic of China
[c] Laboratory of Advanced Materials, Fudan University, 220 Handan Road, Shanghai 200433, People's Republic of China

Received: June 25, 2009; Revised: September 30, 2009; Published online: October 28, 2009

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.200900442.

Abstract: An efficient tandem reaction of 2-alkynylbenzaldoximes with isocyanides co-catalyzed by silver triflate and bismuth triflate has been developed, which gives rise to the unexpected *N*-(isoquinolin-1-yl)formamides in good to excellent yields. The iodo- and bromo-containing products could be obtained as well by variation of the reaction conditions.

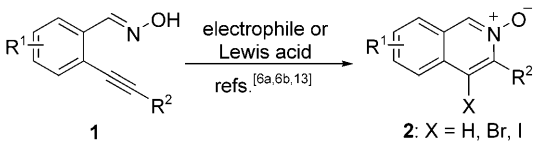
Keywords: 2-alkynylbenzaldoximes; bismuth triflate; isocyanides; *N*-(isoquinolin-1-yl)formamides; silver triflate

Introduction

The chemical genetics approach has created a critical demand to develop practical routes for rapid synthesis of natural product-like molecules.[1] Among the diversity-oriented synthesis strategies, the development of tandem reactions[2] for the efficient construction of small molecules is an important part from the viewpoints of operational simplicity and assembly efficiency. Meanwhile, much attention has been paid to the multicatalytic processes in the field of tandem reactions.[3,4] Usually, in a single flask one or more catalysts promote two or more distinct chemical transformations in a reaction. Recently, we have developed multicatalytic systems for the generation of nitrogen-containing heterocycles.[5] For instance, the combination of silver triflate and proline catalysis shows high efficiency in the multicomponent reactions of 2-alkynylbenzaldehydes, amines, and ketones.[5a] The one-pot reaction of 2-alkynylbenzaldehydes, amines, zinc, and allylic bromide or benzyl bromide could not proceed without the co-catalyst $Mg(ClO_4)_2$ and $Cu(OTf)_2$.[5b] As part of a continuing effort in our laboratory for accessing privileged scaffolds,[6] we have been interested in exploring the new multicatalytic tandem processes to facilitate the preparation of natural product-like compounds.

It is well known that the isoquinoline core exists in many natural products and pharmaceuticals that exhibit remarkable biological activities.[7,8] Moreover, isoquinoline derivatives have found applications as chiral ligands for transition metal catalysts.[9] In addition, their iridium complexes have been demonstrated to be useful in organic light-emitting diodes.[10] Thus, continuous efforts have been made for the development of new methods for the synthesis of isoquinolines.[11,12] Although there are several routes to isoquinolines, the development of efficient methodologies for the synthesis of functionalized isoquinolines under mild conditions is still of high interest. Herein, we disclose an unusual multicatalytic tandem reaction of 2-alkynylbenzaldoximes with isocyanides, which affords the unexpected *N*-(isoquinolin-1-yl)formamide in good to excellent yields.

Recently, 2-alkynylbenzaldoximes have been reported as a versatile building block for the synthesis of nitrogen-containing heterocycles.[6a,b,13] For example, Shin disclosed the gold-catalyzed internal redox/dipolar cycloaddition cascade reactions of 2-alkynylbenzaldoximes.[13a] A tandem electrophilic cyclization-[3+2]cycloaddition-rearrangement reaction of 2-alkynylbenzaldoximes with DMAD in the presence of bromine was developed as well.[6a] We noticed that during the reaction process, the 2-alkynylbenzaldoxime could easily transfer to the isoquinoline *N*-oxide in the presence of suitable Lewis acids or electrophiles (Scheme 1).[6a,b,13] Prompted by these results and the advancement of isocyanide chemistry,[14] we



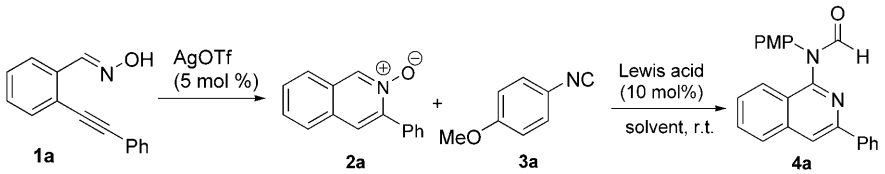
Scheme 1. Electrophile-mediated or Lewis acid-catalyzed cyclization of 2-alkynylbenzaldoxime **1**.

conceived that isocyanides might be a good partner in the tandem reaction of 2-alkynylbenzaldoximes. Thus, we started to explore the possibility of this transformation.

Results and Discussion

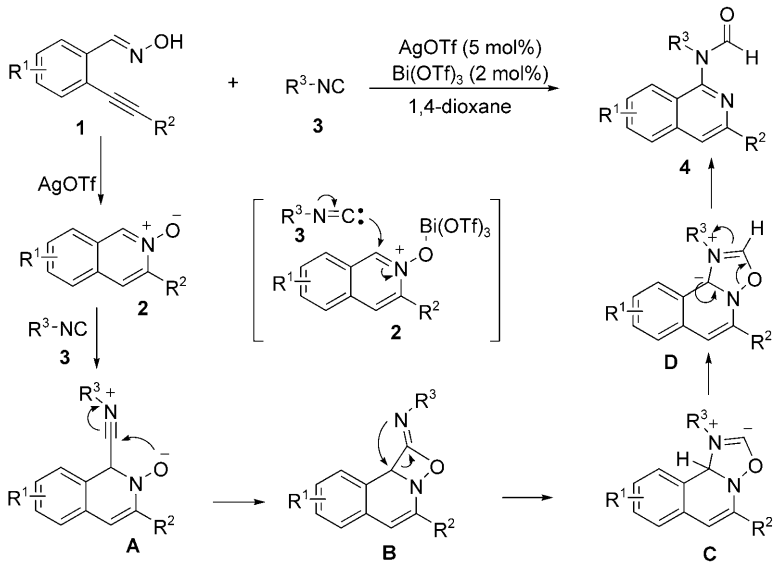
As described above,[13] in the presence of a Lewis acid isoquinoline *N*-oxides could be easily obtained *via* electrophilic cyclization of 2-alkynylbenzaldoximes. In order to simplify the tandem reaction process of 2-alkynylbenzaldoximes with isocyanide, initially the reaction of isoquinoline *N*-oxide **2a** with 4-methoxyphenyl isocyanide **3a** was performed. This reaction occurred in toluene at room temperature to generate an unexpected product in 10% yield (Table 1, entry 1). Structural identification revealed that the compound obtained was the unexpected *N*-(isoquinolin-1-yl)-formamide **4a**. Addition of zinc triflate as catalyst dramatically improved the yield of the product (68% yield, Table 1, entry 2). Further screening of solvents demonstrated that 1,4-dioxane was the best choice for this transformation (72% yield, Table 1, entry 6). Different Lewis acids were examined as catalyst subsequently. The yield increased to 83% when bismuth triflate was utilized in the reaction (Table 1, entry 9). Moreover, the reaction time was shortened to 12 h under these conditions. Inferior results were displayed when other Lewis acids were employed in the reaction. For example, only a 20% yield of product **4a** was isolated when silver triflate was used as catalyst (Table 1, entry 11). Similar yields were afforded when the catalytic amount of bismuth triflate was reduced to 1–5 mol% (Table 1, entries 13–15). Different Brønsted acid catalysts (10 mol%) were examined as well (data not shown in Table 1). No reaction occurred or only a trace amount of product **4a** was detected in the presence of TsOH, TfOH, HOAc, or HCl. The desired product **4a** could be isolated with 31% yield when the reaction was co-catalyzed by TsOH (10 mol%) and $Bi(OTf)_3$ (2 mol%). However, no desired product was generated when the reaction was performed in the presence of $Bi(OTf)_3$ (2 mol%) with other acids (TfOH, HOAc, HCl). With this promising result in hands, we started to investigate the one-pot tandem reaction of 2-alkynylbenzaldox-

Table 1. Screening conditions for the reaction of isoquinoline *N*-oxide **2a** with isocyanide **3a**.



Entry	Lewis acid	Solvent	Time [h]	Yield [%][a]
1	nono	toluene	48	10
2	$Zn(OTf)_2$	toluene	60	68
3	$Zn(OTf)_2$	DCE	60	56
4	$Zn(OTf)_2$	THF	60	NR
5	$Zn(OTf)_2$	DMF	60	NR
6	$Zn(OTf)_2$	1,4-dioxane	60	72
7	$Zn(OTf)_2$	NMP	60	61
8	$Cu(OTf)_2$	1,4-dioxane	60	71
9	$Bi(OTf)_3$	1,4-dioxane	12	83
10	$Sc(OTf)_3$	1,4-dioxane	60	61
11	AgOTf	1,4-dioxane	60	20
12	$Yb(OTf)_3$	1,4-dioxane	60	74
13[b]	$Bi(OTf)_3$	1,4-dioxane	12	84
14[c]	$Bi(OTf)_3$	1,4-dioxane	18	86
15[d]	$Bi(OTf)_3$	1,4-dioxane	24	83

[a] Isolated yield based on isoquinoline *N*-oxide **2a**.
[b] In the presence of 5 mol% of $Bi(OTf)_3$.
[c] In the presence of 2 mol% of $Bi(OTf)_3$.
[d] In the presence of 1 mol% of $Bi(OTf)_3$.



Scheme 2. Possible mechanism for the tandem reactions of 2-alkynylbenzaldoximes **1** with isocyanides **3**.

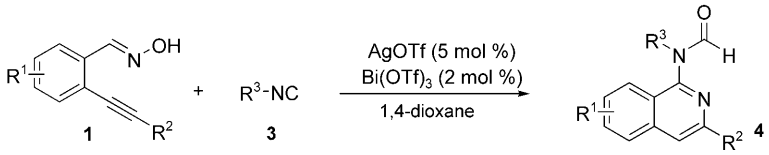
ime **1a** with 4-methoxyphenyl isocyanide **3a**. Since bismuth triflate was not effective for the transformation of 2-alkynylbenzaldoxime **1a** and silver triflate was the best one for the generation of isoquinoline *N*-oxide **2a**, the combination of silver triflate and bismuth triflate was tested in the reaction 2-alkynylbenzaldoxime **1a** with 4-methoxyphenyl isocyanide **3a**. To our delight, a 94% yield of compound **4a** was obtained when the reaction occurred in the presence of silver triflate (5 mol%) and bismuth triflate (2 mol%) in 1,4-dioxane at room temperature. Although the first step of the reaction has already been known,[6b] this tandem reaction *via* a concomitant process provided an efficient way for diversity and complexity generation starting from easily accessible materials. For this tandem reaction, we reasoned that 2-alkynylbenzaldoxime **1** was converted to isoquinoline *N*-oxide **2** firstly. The subsequent nucleophilic addition of isocyanide to isoquinoline *N*-oxide **2** would afford intermediate **A**, which then underwent intramolecular cyclization to generate the intermediate **B**. After rearrangement, *N*-(isoquinolin-1-yl)formamide **4** would be formed (Scheme 2).

The scope of this transformation was then explored under the optimized conditions [silver triflate (5 mol%), bismuth triflate (2 mol%), 1,4-dioxane, room temperature], and the results are summarized in Table 2. For all cases, this multicatalytic tandem reaction proceeded smoothly leading to the corresponding products **4** in good to excellent yields. With respect to 2-alkynylbenzaldoximes, the expected *N*-(isoquinolin-1-yl)formamides resulting from 4-methoxyphenyl isocyanide **3a** were obtained in good yields (Table 1, entries 1–6). For instance, 4-methoxyphenyl isocyanide **3a** reacted with 2-alkynylbenzaldoxime **1b** or **1c** giving rise to the desired product **4b** or **4c** in 65% and 67% yields, respectively (Table 2, entries 2 and 3). The conditions have proven to be useful for other aryl isocyanides as well. For example, an excellent yield was observed in the reaction of 4-methylphenyl isocyanide **3c** with 2-alkynylbenzaldoxime **1a** or **1e** (Table 2, entries 9 and 12). Alkyl isocyanides are also suitable partners in this process. As expected, an almost quantitative yield of compound **4m** was isolated for the reaction of 2-alkynylbenzaldoxime **1a** with *tert*-butyl isocycanide **3d** (Table 2, entry 13). Reaction of cyclohexyl isocyanide **3e** with 2-alkynylbenzaldoxime **1a** or **1e** worked well to generate the desired *N*-(isoquinolin-1-yl)formamide in good yield (Table 2, entries 17 and 18). 2-Alkynylbenzaldoxime **1a** reacted with 1-octyl isocyanide **3f** leading to the desired product **4s** in 82% yield (Table 1, entry 19).

The electrophile involved cascade reactions of 2-alkynylbenzaldoximes **1** with isocyanides **3** were investigated subsequently [Scheme 3, Eq. (1)]. Iodo-containing *N*-(isoquinolin-1-yl)formamide **5a** was isolated in 96% yield in the reaction of 2-alkynylbenzaldoxime **1a** with 4-methoxyphenyl isocyanide **3a**. The structure of **5a** was verified by X-ray diffraction analysis meanwhile (Figure 1). A similar result was obtained when 4-methylphenyl isocyanide **3c** was utilized as a replacement. Fluoro-substituted 2-alkynylbenzaldoxime **1e** with 4-methoxyphenyl isocyanide **3a** gave rise to the expected product **5c** in 93% yield. Bromine also showed efficiency in the reaction of 2-alkynylbenzaldoxime **1a** with 1-octyl isocyanide **3f**, which generated the expected product **5d** in 87% yield [Scheme 3, Eq. (2)]. However, NBS was not a good partner in this transformation (data not shown in Scheme 3).

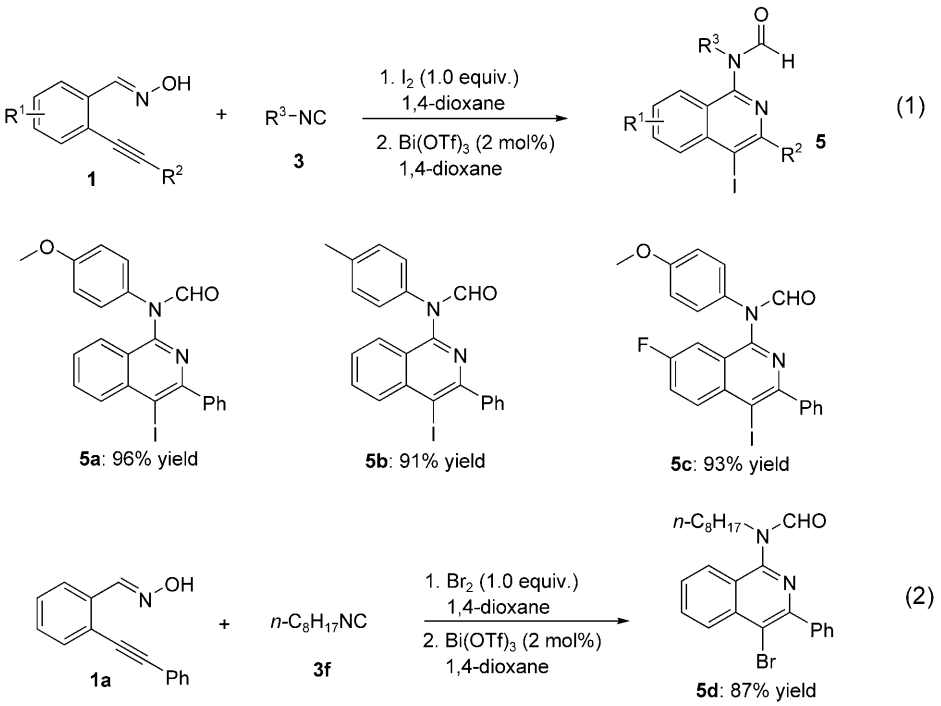
In conclusion, we have described efficient tandem reactions of 2-alkynylbenzaldoximes with isocyanides

Table 2. Tandem reactions of 2-alkynylbenzaldoximes **1** with isocyanides **3** co-catalyzed by silver triflate and bismuth triflate.



Entry	R^1/R^2	R^3	Yield [%][a]
1	H/C_6H_5 (**1a**)	4-$MeOC_6H_4$ (**3a**)	94 (**4a**)
2	5-F/*n*-Bu (**1b**)	4-$MeOC_6H_4$ (**3a**)	65 (**4b**)
3	5-F/cyclopropyl (**1c**)	4-$MeOC_6H_4$ (**3a**)	67 (**4c**)
4	H/cyclopropyl (**1d**)	4-$MeOC_6H_4$ (**3a**)	54 (**4d**)
5	5-F/C_6H_5 (**1e**)	4-$MeOC_6H_4$ (**3a**)	87 (**4e**)
6	5-F/4-$MeOC_6H_5$ (**1f**)	4-$MeOC_6H_4$ (**3a**)	62 (**4f**)
7	H/C_6H_5 (**1a**)	4-$Et_2NC_6H_4$ (**3b**)	83 (**4g**)
8	5-F/C_6H_5 (**1e**)	4-$Et_2NC_6H_4$ (**3b**)	75 (**4h**)
9	H/C_6H_5 (**1a**)	4-MeC_6H_4 (**3c**)	97 (**4i**)
10	5-F/cyclopropyl (**1c**)	4-MeC_6H_4 (**3c**)	75 (**4j**)
11	H/cyclopropyl (**1d**)	4-MeC_6H_4 (**3c**)	50 (**4k**)
12	5-F/C_6H_5 (**1e**)	4-MeC_6H_4 (**3c**)	98 (**4l**)
13	H/C_6H_5 (**1a**)	*t*-Bu (**3d**)	99 (**4m**)
14	5-F/cyclopropyl (**1c**)	*t*-Bu (**3d**)	72 (**4n**)
15	H/cyclopropyl (**1d**)	*t*-Bu (**3d**)	84 (**4o**)
16	5-F/C_6H_5 (**1e**)	*t*-Bu (**3d**)	94 (**4p**)
17	H/C_6H_5 (**1a**)	cyclohexyl (**3e**)	85 (**4q**)
18	5-F/C_6H_5 (**1e**)	cyclohexyl (**3e**)	84 (**4r**)
19	H/C_6H_5 (**1a**)	*n*-octyl (**3f**)	82 (**4s**)

[a] Isolated yield based on 2-alkynylbenzaldoxime **1**.



Scheme 3. Iodine- or bromine-mediated sequential reactions of 2-alkynylbenzaldoximes **1** with isocyanides **3**.

co-catalyzed by silver triflate and bismuth triflate. The *N*-(isoquinolin-1-yl)formamides were generated in good to excellent yields. The iodo- or bromo-containing products could be obtained as well by variation of the reaction conditions, which might undergo further elaboration *via* known palladium chemistry.

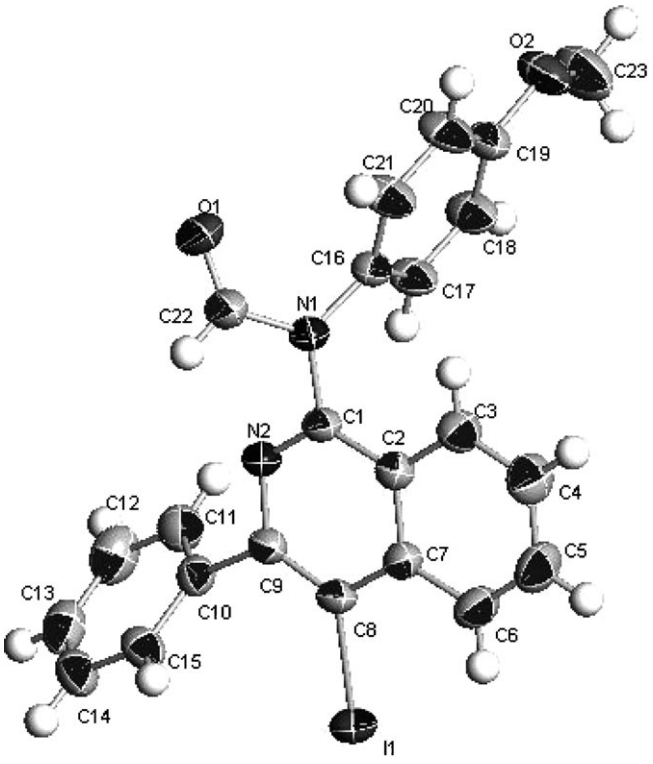


Figure 1. ORTEP drawing of compound **5a** (30% probability ellipsoids).

Small library construction as well as biological screening of these small molecules is ongoing, and the results will be reported in due course.

Experimental Section

General Procedure for Tandem Reactions of 2-Alkynylbenzaldoximes 1 with Isocyanides 3 Co-Catalyzed by Silver Triflate and Bismuth Triflate

A mixture of 2-alkynylbenzaldoxime **1** (0.2 mmol) and silver triflate (5 mol%) in anhydrous 1,4-dioxane (2.0 mL) was heated to 70 °C for 1 hour. Then the solution was cooled to room temperature. Bismuth triflate (2 mol%) and isocyanide **2** (0.3 mmol, 1.5 equiv.) in 1,4-dioxane (0.1 mL) were added subsequently and the mixture was stirred at 30 °C. After completion of the reaction as indicated by TLC, the solvent was removed under reduced pressure and the residue was purified on silica gel provided the corresponding product **4**.

Data of a selected example: *N*-(4-methoxyphenyl)-*N*-(3-phenylisoquinolin-1-yl)formamide (4a): 94% yield; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.77$ (s, 3H), 6.88 (d, $J = 3.2$ Hz, 2H), 7.33–7.55 (m, 6H), 7.58–7.81 (m, 2H), 7.89 (d, $J = 8.24$ Hz, 1H), 8.10–8.16 (m, 3H), 9.05 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 55.4$, 114.4, 116.6, 122.9, 125.0, 126.3, 126.8, 127.6, 127.8, 128.8, 128.9, 130.7, 132.5, 138.1, 139.6, 149.4, 151.4, 157.9, 163.0; HR-MS: $m/z = 355.1436$, calcd. for $C_{23}H_{18}N_2O_2^+$ $[M+H]^+$: 355.1447; elem. anal. calcd. for $C_{23}H_{18}N_2O_2$: C 77.95, H 5.12, N 7.90; found: C 77.91, H 5.36, N 7.78.

General Procedure for Iodine- or Bromine-Mediated Sequential Reactions of 2-Alkynylbenzaldoximes 1 with Isocyanides 3

A mixture of 2-alkynylbenzaldoxime **1** (0.2 mmol) and iodine or bromine (0.2 mmol, 1.0 equiv.) in anhydrous 1,4-dioxane (2.0 mL) was stirred at room temperature under air atmosphere for about 24 h, until 2-alkynylbenzaldoxime **1** was completely consumed. The reaction solution was diluted with ethyl acetate (10 mL), washed with 0.65 M $Na_2S_2O_3$ solution (10 mL × 3). The combined organic layer was washed with saturated brine, dried over Na_2SO_4, and concentrated under vacuum to afford a crude product. Anhydrous 1,4-dioxane (2.0 mL) was added to the crude product subsequently, to which was then added a mixture of bismuth triflate (2 mol%) and isocyanide **3** (0.3 mmol, 1.5 equiv.) in 1,4-dioxane (0.1 mL) at 30 °C. After completion of the reaction as indicated by TLC, the solvent was removed under reduced pressure and the residue was purified on silica gel provided the corresponding product **5**.

Data of a selected example: *N*-(4-iodo-3-phenylisoquinolin-1-yl)-*N*-(4-methoxyphenyl)formamide (5a): 96% yield; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.78$ (s, 3H), 6.86–6.90 (m, 2H), 7.30 (d, $J = 8.7$ Hz, 2H), 7.42–7.52 (m, 4H), 7.61–7.86 (m, 4H), 8.30 (d, $J = 8.2$ Hz, 1H), 8.94 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 56.0$, 115.1, 126.0, 126.7, 126.8, 126.9, 128.5, 129.1, 129.2, 129.4, 129.5, 130.6, 133.0, 133.7, 141.5, 143.2, 152.1, 158.6, 163.2; HR-MS: $m/z = 481.0422$, calcd. for $C_{23}H_{17}IN_2O_2^+$ $[M+H]^+$: 481.0413; elem. anal. calcd. for $C_{23}H_{17}IN_2O_2$: C 57.52, H 3.57, N 5.83; found: C 57.39, H 3.66, N 5.71 (for details, please see Supporting Information)

CCDC 745747 contains the supplementary crystallographic data for compound **5a** of this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif or on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax.: (internat.) + 44 1223/336–033; e-mail: deposit@ccdc.cam.ac.uk].

Acknowledgements

Financial support from National Natural Science Foundation of China (20772018), the Science and Technology Commission of Shanghai Municipality (09JC14049), and Program for New Century Excellent Talents in University (NCET-07-0208) is gratefully acknowledged.

References

[1] a) D. P. Walsh, Y.-T. Chang, *Chem. Rev.* **2006**, *106*, 2476; b) P. Arya, D. T. H. Chou, M.-G. Baek, *Angew. Chem.* **2001**, *113*, 351; *Angew. Chem. Int. Ed.* **2001**, *40*, 339; c) S. L. Schreiber, *Science* **2000**, *287*, 1964.

[2] For reviews, see: a) J. Montgomery, *Angew. Chem.* **2004**, *116*, 3980; *Angew. Chem. Int. Ed.* **2004**, *43*, 3890; b) E. Negishi, C. Copéret, S. Ma, S. Y. Liou, F. Liu,

Chem. Rev. **1996**, *96*, 365; c) L. F. Tietze, *Chem. Rev.* **1996**, *96*, 115; d) R. Grigg; V. Sridharan, *J. Organomet. Chem.* **1999**, *576*, 65; e) T. Miura, M. Murakami, *Chem. Commun.* **2007**, 217. For recent examples, see: f) K. Agapiou, D. F. Cauble, M. J. Krische, *J. Am. Chem. Soc.* **2004**, *126*, 4528; g) K. Subburaj, J. Montgomery, *J. Am. Chem. Soc.* **2003**, *125*, 11210; h) H.-C. Guo, J.-A. Ma, *Angew. Chem.* **2006**, *118*, 362; *Angew. Chem. Int. Ed.* **2006**, *45*, 354.

[3] For selected recent reviews on multicatalysis, see: a) A. Ajamian, J. L. Gleason, *Angew. Chem.* **2004**, *116*, 3842; *Angew. Chem. Int. Ed.* **2004**, *43*, 3754; b) J. M. Lee, Y. Na, H. Han, S. Chang, *Chem. Soc. Rev.* **2004**, *33*, 302; c) J. C. Wasilke, O S. J. Brey, R. T. Baker, G. C. Bazan, *Chem. Rev.* **2005**, *105*, 1001; d) D. Enders, C. Grondal, M. R. Huttl, *Angew. Chem.* **2007**, *119*, 1590; *Angew. Chem. Int. Ed.* **2007**, *46*, 1570; e) C. J. Chapman, C. G. Frost, *Synthesis* **2007**, 1; f) A. M. Walji, D. W. C. MacMillan, *Synlett* **2007**, 1477; g) C. Wang, Z. Xi, *Chem. Soc. Rev.* **2007**, *36*, 1395.

[4] For recent selected examples, see: a) T. A. Cernak, T. H. Lambert, *J. Am. Chem. Soc.* **2009**, *131*, 3124, and references cited therein; b) B. D. Kelly, J. M. Allen, R. E. Tundel, T. H. Lambert, *Org. Lett.* **2009**, *11*, 1381; c) L.-Q. Lu, Y.-J. Cao, X.-P. Liu, J. An, C.-J. Yao, Z.-H. Ming, W.-J. Xiao, *J. Am. Chem. Soc.* **2008**, *130*, 6946.

[5] a) Q. Ding, J. Wu, *Org. Lett.* **2007**, *9*, 4959; b) K. Gao, J. Wu, *J. Org. Chem.* **2007**, *72*, 8611; c) Q. Ding, X. Yu, J. Wu, *Tetrahedron Lett.* **2008**, *49*, 2752; d) Q. Ding, Z. Wang, J. Wu, *Tetrahedron Lett.* **2009**, *50*, 198.

[6] a) Q. Ding, Z. Wang, J. Wu, *J. Org. Chem.* **2009**, *74*, 921; b) Q. Ding, J. Wu, *Adv. Synth. Catal.* **2008**, *350*, 1850; c) K. Gao, J. Wu, *Org. Lett.* **2008**, *10*, 2251; d) Q. Ding, J. Wu, *J. Comb. Chem.* **2008**, *10*, 541; e) L. Zhang, J. Wu, *Adv. Synth. Catal.* **2007**, *349*, 1047; f) Z. Wang, R. Fan, J. Wu, *Adv. Synth. Catal.* **2007**, *349*, 1943; g) Q. Ding, Y. Ye, R. Fan, J. Wu, *J. Org. Chem.* **2007**, *72*, 5439; h) L. Zhang, T. Meng, R. Fan, J. Wu, *J. Org. Chem.* **2007**, *72*, 7279; i) Z. Wang, B. Wang, J. Wu, *J. Comb. Chem.* **2007**, *9*, 811.

[7] For selected examples, see: a) K. W. Bentley, *The Isoquinoline Alkaloids*, Harwood Academic, Australia, **1998**, Vol. 1; b) B. W. Trotter, K. K. Nanda, N. R. Kett, C. P. Regan, J. J. Lynch, G. L. Stump, L. Kiss, J. Wang, R. H. Spencer, S. A. Kane, R. B. White, R. Zhang, K. D. Anderson, N. J. Liverton, C. J. McIntyre, D. C. Eshore, G. D. Hartman, C. J. Dinsmore, *J. Med. Chem.* **2006**, *49*, 6954; c) P. Ramesh, N. S. Reddy, Y. Venkateswarlu, *J. Nat. Prod.* **1999**, *62*, 780; d) S. Oi, K. Ikedou, K. Takeuchi, M. Ogino, Y. Banno, H. Tawada, T. Yamane, *PCT Int. Appl.* WO 2002062764 A1, **2002**; e) T. Kaneda, Y. Takeuchi, H. Matsui, K. Shimizu, N. Urakawa, S. Nakajyo, *J. Pharmacol. Sci.* **2005**, *98*, 275; f) Y. Mikami, K. Yokoyama, H. Tabeta, K. Nakagaki, T. Arai, *J. Pharm. Dyn.* **1981**, *4*, 282; g) C. Marchand, S. Antony, K. W. Kohn, M. Cushman, I A. Oanoviciu, B. L. Staker, A. B. Burgin, L. Stewart, Y. Pommier, *Mol. Cancer Ther.* **2006**, *5*, 287; h) G. R. Pettit, V. Gaddamidi, D. L. Herald, S. B. Singh, G. M. Cragg, J. M. Schmidt, F. E. Boettner, M. Williams, Y. Sagawa, *J. Nat. Prod.* **1986**, *49*, 995.

[8] a) D. Kletsas, W. Li, Z. Han, V. Papadopoulos, *Biochem. Pharmacol.* **2004**, *67*, 1927; b) U. R. Mach, A. E. Hackling, S. Perachon, S. Ferry, C. G. Wermuth, J.-C. Schwartz, P. Sokoloff, H. Stark, *ChemBioChem* **2004**, *5*, 508; c) D. E. Muscarella, K. A. O'Brian, A. T. Lemley, S. E. Bloom, *Toxicol. Sci.* **2003**, *74*, 66; d) F. Dzierszinski, A. Coppin, M. Mortuaire, E. Dewally, C. Slomianny, J.-C. Ameisen, F. Debels, S. Tomavo, *Antimicrob. Agents Chemother.* **2002**, *46*, 3197.

[9] For selected examples, see: a) F. Durola, J.-P. Sauvage, O. S. Wenger, *Chem. Commun.* **2006**, 171; b) B. A. Sweetman, H. Müller-Bunz, P. J. Guiry, *Tetrahedron Lett.* **2005**, *46*, 4643; c) C. W. Lim, O. Tissot, A. Mattison, M. W. Hooper, J. M. Brown, A. R. Cowley, D. I. Hulmes, A. J. Blacker, *Org. Process Res. Dev.* **2003**, *7*, 379; d) N. W. Alcock, J. M. Brown, G. I. Hulmes, *Tetrahedron: Asymmetry* **1993**, *4*, 743.

[10] For selected examples, see: a) K.-H. Fang, L.-L. Wu, Y.-T. Huang, C.-H. Yang, I.-W. Sun, *Inorg. Chim. Acta* **2006**, *359*, 441; b) S.-J. Liu, Q. Zhao, R.-F. Chen, Y. Deng, Q.-L. Fan, F.-Y. Li, L.-H. Wang, C.-H. Huang, W. Huang, *Chem. Eur. J.* **2006**, *12*, 4351; c) Q. Zhao, S. Liu, M. Shi, C. Wang, M. Yu, L. Li, F. Li, T. Yi, C. Huang, *Inorg. Chem.* **2006**, *45*, 6152; d) A. Tsuboyama, H. Iwawaki, M. Furugori, T. Mukaide, J. Kamatani, S. Igawa, T. Moriyama, S. Miura, T. Takiguchi, S. Okada, M. Hoshino, K. Ueno, *J. Am. Chem. Soc.* **2003**, *125*, 12971.

[11] a) Q. Huang, R. C. Larock, *J. Org. Chem.* **2003**, *68*, 980; b) G. Dai, R. C. Larock, *J. Org. Chem.* **2003**, *68*, 920; c) G. Dai, R. C. Larock, *J. Org. Chem.* **2002**, *67*, 7042; d) Q. Huang, J. A. Hunter, R. C. Larock, *J. Org. Chem.* **2002**, *67*, 3437; e) K. R. Roesch, R. C. Larock, *J. Org. Chem.* **2002**, *67*, 86; f) K. R. Roesch, H. Zhang, R. C. Larock, *J. Org. Chem.* **2001**, *66*, 8042; g) K. R. Roesch, R. C. Larock, *Org. Lett.* **1999**, *1*, 553.

[12] For selected examples, see: a) M. Balasubramanian, J. G. Keay, *Isoquinoline Synthesis*, in: *Comprehensive Heterocyclic Chemistry II*, (Eds.: A. E. McKillop, A. R. Katrizky, C. W. Rees, E. F. V. Scrivem), Elsevier, Oxford, **1996**, 5, p 245; b) For a review on the synthesis of isoquinoline alkaloid, see: M. Chrzanowska, M. D. Rozwadowska, *Chem. Rev.* **2004**, *104*, 3341; c) Y.-N. Niu, Z.-Y. Yan, G.-L. Gao, H.-L. Wang, X.-Z. Shu, K. G. Ji, Y.-M. Liang *J. Org. Chem.* **2009**, *74*, 2893; d) Y.-Y. Yang, W.-G. Shou, Z.-B. Chen, D. Hong, Y.-G. Wang, *J. Org. Chem.* **2008**, *73*, 3928; e) D. Fischer, H. Tomeba, N. K. Pahadi, N. T. Patil, Z. Huo, Y. Yamamoto, *J. Am. Chem. Soc.* **2008**, *130*, 15720; f) M. Movassaghi, M. D. Hill, *Org. Lett.* **2008**, *10*, 3485; g) T. Blackburn, Y. K. Ramtohul, *Synlett* **2008**, 1159; h) G. Pandey, M. Balakrishnan, *J. Org. Chem.* **2008**, *73*, 8128; i) S. Su, J. A. Porco, *Org. Lett.* **2007**, *9*, 4983; j) M. Mori, H. Wakamatsu, K. Tonogaki, R. Fujita, T. Kitamura, Y. Sato, *J. Org. Chem.* **2005**, *70*, 1066; k) Z. Xiang, T. Luo, K. Lu, J. Cui, X. Shi, R. Fathi, J. Chen, Z. Yang, *Org. Lett.* **2004**, *6*, 3155; l) B. K. Ghorai, S. Duan, D. Jiang, J. W. Herndon, *Synthesis* **2006**, 3661; m) F. Palacios, C. Alonso, M. Rodríguez, de E. M. Marigorta, G. Rubiales, *Eur. J. Org. Chem.* **2005**, 1795; n) F. Palacios, C. Alonso, G. Rubiales, M. Villegas, *Tetrahedron* **2005**, *61*, 2779; o) T. K. Sarkar, N. Panda, S. Basak, *J. Org.*

Chem. **2003**, *68*, 6919; p) P. R. Carly, T. C. Govaerts, S. L. Cappelle, F. Compernolle, G. J. Hoornaert, *Tetrahedron* **2001**, *57*, 4203; q) T. K. Sarkar, S. K. Ghosh, T. J. Chow, *J. Org. Chem.* **2000**, *65*, 3111; r) P. R. Carly, S. L. Cappelle, F. Compernolle, G. J. Hoornaert, *Tetrahedron* **1996**, *52*, 11889; s) J. A. R. Rodrigues, G. C. Leiva, J. D. F. de Sousa, *Tetrahedron Lett.* **1995**, *36*, 59.

[13] a) H.-S. Yeom, J.-E. Lee, S. Shin, *Angew. Chem.* **2008**, *120*, 7148; *Angew. Chem. Int. Ed.* **2008**, *47*, 7040; b) H.-S. Yeom, S. Kim, S. Shin, *Synlett* **2008**, 924; c) Z. Huo, H. Tomeba, Y. Yamamoto, *Tetrahedron Lett.* **2008**, *49*, 5531; d) Q. Ding, Z. Wang, J. Wu, *Tetrahedron Lett.* **2009**, *50*, 198.

[14] For recent reviews, see: a) L. El Kaim, L. Grimaud, *Tetrahedron* **2009**, *65*, 2153; b) I. Akritopoulou-Zanze, *Curr. Opin. Chem. Biol.* **2008**, *12*, 324; c) A. Dömling, *Chem. Rev.* **2006**, *106*, 17; d) A. Dömling, I. Ugi, *Angew. Chem.* **2000**, *112*, 3300; *Angew. Chem. Int. Ed.* **2000**, *39*, 3168. For recent selected examples, see: e) J.-M. Grassot, G. Masson, J.-P. Zhu, *Angew. Chem.* **2008**, *120*, 961; *Angew. Chem. Int. Ed.* **2008**, *47*, 947; f) T. Yue, M.-X. Wang, D.-X. Wang, J. Zhu, *Angew. Chem.* **2008**, *120*, 9596; *Angew. Chem. Int. Ed.* **2008**, *47*, 9454; g) V. V. Tumanov, A. A. Tishkov, H. Mayr, *Angew. Chem.* **2007**, *119*, 3633; *Angew. Chem. Int. Ed.* **2007**, *46*, 3563.

