DOI: 10.1002/adsc.201300327

Silver Triflate-Palladium Chloride Cooperative Catalysis in a Tandem Reaction for the Synthesis of *H*-Pyrazolo[5,1-*a*]isoquinolines

Qing Xiao,[a] Jie Sheng,[b] Qiuping Ding,[a,*] and Jie Wu[b,c,*]

[a] Key Laboratory of Functional Small Organic Molecules, Ministry of Education and College of Chemistry & Chemical Engineering, Jiangxi Normal University, Nanchang, Jiangxi 330022, People's Republic of China
E-mail: dqpjxnu@gmail.com
[b] Department of Chemistry, Fudan University, 220 Handan Road, Shanghai 200433, People's Republic of China
Fax: (+86)-216-564-1740; e-mail: jie_wu@fudan.edu.cn
[c] Key Laboratory of Organic Synthesis of Jiangsu Province,College of Chemistry, Chemical Engineering and Materials Science, Soochow University, Suzhou, 215123, People's Republic of China

Received: April 18, 2013; Revised: June 6, 2013; Published online: ■■ ■■, 0000

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201300327.

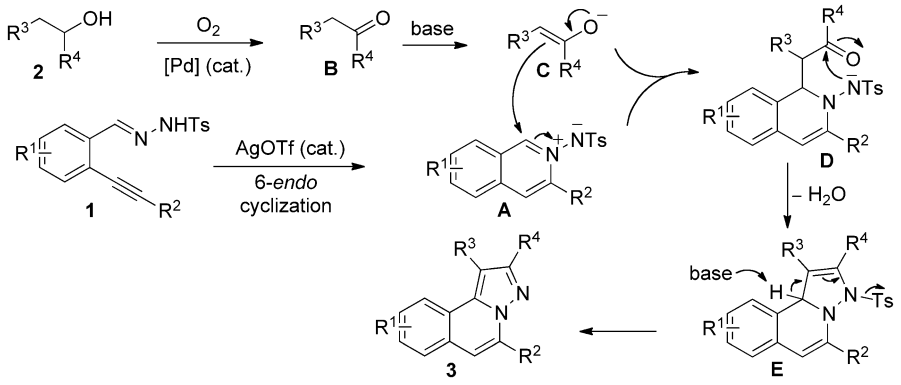
Abstract: A tandem reaction of *N*′-(2-alkynylbenzylidene)hydrazone with alcohol in the presence of oxygen co-catalyzed by silver triflate and palladium chloride under mild conditions is reported, providing *H*-pyrazolo[5,1-*a*]isoquinolines in good yields. During the transformation, isoquinolinium-2-yl amide was the key intermediate *via* a silver(I)-catalyzed 6-*endo* cyclization of *N*′-(2-alkynylbenzylidene)hydrazone. The presence of a palladium catalyst and molecular oxygen promoted the oxidation of the alcohol to the aldehyde or ketone. Subsequent nucleophilic attack of the *in situ* generated enolate to isoquinolinium-2-yl amide, intramolecular condensation, and aromatization afforded the *H*-pyrazolo[5,1-*a*]isoquinolines. The easily available starting materials, good substrate generality, mild reaction conditions, and experimental ease should make this method attractive for further library construction.

Keywords: alcohols; hydrazones; oxygen; palladium; pyrazolo[5,1-*a*]isoquinolines; silver

Introduction

The power of cooperative catalysis has been demonstrated in organic synthesis.[1] Usually, two or more catalysts are combined in a one pot process, which would enable activation of both reactants. The transformation could not be fulfilled by one activation mechanism alone. For instance, Hu and co-workers described several sequential reaction cascades under cooperative catalysis that provided stereo-controlled access to useful structural motifs.[2] In connection with our interest in the generation of natural product-like compounds for the studies of chemical genetics,[3] we were attracted by the power of cooperative catalysis and the efficiency of tandem reactions. These processes would lead to a rapid build-up of molecular complexity and diversity with the formation of multibonds.

Among the N-heterocycles, the *H*-pyrazolo[5,1-*a*]isoquinoline structure has been recognized as a privileged scaffold with remarkable biological activities. For example, *H*-pyrazolo[5,1-*a*]isoquinoline derivatives have been reported for inhibitory activity against PTP1B (protein tyrosine phosphatase 1 B) and CDC25B.[4] It would be attractive if this architectural complexity could be constructed from easily available starting materials *via* a cascade process. Recently, the *N*′-(2-alkynylbenzylidene)hydrazone moiety has been employed as a useful building block for the synthesis of N-heterocycles.[5] During the transformation, an isoquinolinium-2-yl amide was demonstrated as the key intermediate formed *via* a silver(I)-catalyzed 6-*endo* cyclization of *N*′-(2-alkynylbenzylidene)hydrazone. For example, *H*-pyrazolo[5,1-*a*]isoquinolines could be generated *via* a silver triflate-catalyzed three-component reaction of 2-alkynylbenzaldehyde, sulfonohydrazide, and ketone or aldehyde.[5c] Amine could also be utilized as a partner in the reaction of *N*′-(2-alkynylbenzylidene)hydrazone under palladium-catalyzed oxidative conditions *via* C–H bond activation.[5g] The enamine was believed to be the key intermediate during the process. Since the aldehyde or



Scheme 1. A proposed synthetic route to *H*-pyrazolo[5,1-*a*]isoquinolines

ketone could be afforded *in situ* from alcohol, we conceived that the scaffold of *H*-pyrazolo[5,1-*a*]isoquinoline would be constructed as well *via* a cascade reaction of *N*′-(2-alkynylbenzylidene)hydrazone with alcohol in the presence of oxygen under cooperative catalysis.

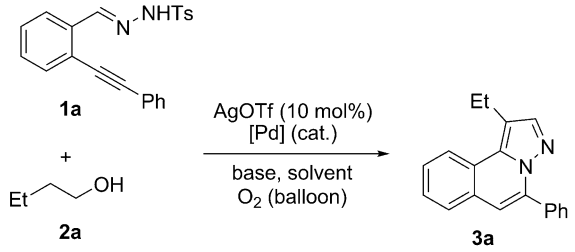
The proposed synthetic route is shown in Scheme 1. We envisaged that the presence of silver and palladium catalysts would enable the activation of both substrates, which would promote the transformation smoothly. As mentioned above, a silver(I)-catalyzed 6-*endo* cyclization of *N*′-(2-alkynylbenzylidene)hydrazone **1** would occur to form isoquinolinium-2-yl amide **A**. Meanwhile, the alcohol **2** would be oxidized to aldehyde or ketone **B** in the presence of a palladium catalyst and molecular oxygen.[6] Subsequently, an enolate **C** would be formed if there was a base in the reaction system. Therefore, a nucleophilic attack of enolate **C** to the isoquinolinium-2-yl amide **A** would be expected, leading to the intermediate **D**. An intramolecular condensation with a loss of a molecule of water would produce compound **E**, which would then undergo aromatization to generate compound **3**. This one-step tandem transformation[7] reveals a complex structure formed with exquisite control of three new bonds and an array of exploitable functionality. During the process, the presence of cooperative catalysis would play an important role if the cascade process were feasible. Otherwise, the efficiency and success would be hampered.

Results and Discussion

To identify suitable conditions for the proposed silver triflate-palladium chloride cooperative catalysis in a tandem reaction for the synthesis of *H*-pyrazolo[5,1-*a*]isoquinolines, we started to explore the possibility of this protocol as presented in Scheme 1. The model reaction of *N*′-(2-alkynylbenzylidene)hydrazone **1a** and *n*-butanol **2a** was selected for reaction development. At the outset, silver triflate (10 mol%) and palladium acetate (5 mol%) were used as the co-catalysts. To our delight, the desired *H*-pyrazolo[5,1-*a*]isoquinoline **3a** was isolated and obtained in 47% yield when the reaction was run in the presence of potassium carbonate as a base in toluene under air (Table 1, entry 1). As expected, the reaction failed when the transformation was performed under a nitrogen atmosphere. (Table 1, entry 2). The yield was improved to 61% when the reaction proceeded using a balloon of oxygen (Table 1, entry 3). Subsequently, a range of solvents was surveyed (Table 1, entries 4–8). However, no better results were observed when other solvents were employed in the reaction, and toluene was demonstrated as the best choice. We further screened the reaction with different bases (Table 1, entries 9–14). Again, the results were inferior. We next shifted our focus to other palladium catalysts (Table 1, entries 15–18). A similar outcome was obtained when $Pd(TFA)_2$ was used in the reaction (Table 1, entry 15). Interestingly, the yield was increased to 75% when $Pd(PPh_3)_3Cl_2$ or $PdCl_2$ was utilized as a replacement (Table 1, entries 16 and 17). A control experiment without the addition of palladium catalyst failed to give the corresponding product (Table 1, entry 19). The yield was lower when the reaction occurred in the presence of 2 mol% of palladium chloride (Table 1, entry 20). No improvement was observed when the catalytic amount of palladium chloride was increased to 10 mol% (Table 1, entry 21).

Using the optimized reaction conditions as shown in Table 1, a range of *N*′-(2-alkynylbenzylidene)hydrazones **1** reacted with selected alcohols leading to diverse *H*-pyrazolo[5,1-*a*]isoquinolines **3** in good yields (Table 2). This silver(I) and palladium(II) co-catalyzed *H*-pyrazolo[5,1-*a*]isoquinoline formation was found to be workable with various alcohols. The alcohols bearing pyridinyl and indolyl functionality were all compatible under the standard conditions. The substrate *N*′-(2-alkynylbenzylidene)hydrazones **1** with electron-withdrawing and electron-donating substituents on the aromatic backbone were also investigated to provide the *H*-pyrazolo[5,1-*a*]isoquinoline core

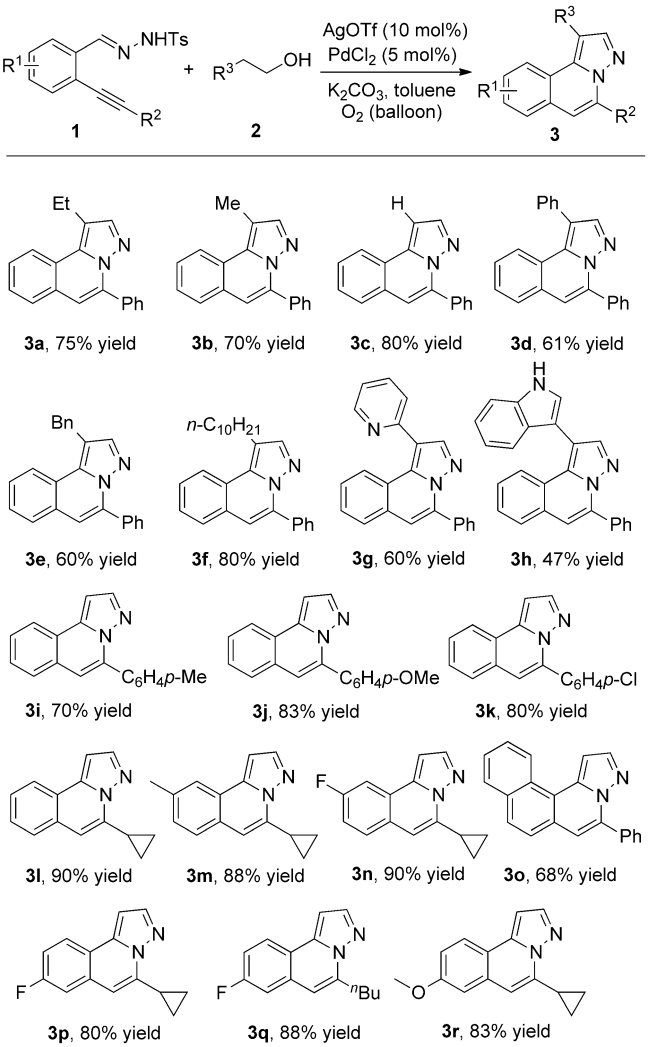
Table 1. Initial studies on the reaction of *N*′-(2-alkynylbenzylidene)hydrazone **1a** with *n*-butanol **2a**.



Entry	[Pd]	Solvent	Base	Yield [%][a]
1[b]	$Pd(OAc)_2$	toluene	K_2CO_3	47
2[c]	$Pd(OAc)_2$	toluene	K_2CO_3	trace
3	$Pd(OAc)_2$	toluene	K_2CO_3	61
4	$Pd(OAc)_2$	DMF	K_2CO_3	39
5	$Pd(OAc)_2$	dioxane	K_2CO_3	37
6	$Pd(OAc)_2$	THF	K_2CO_3	30
7	$Pd(OAc)_2$	MeCN	K_2CO_3	52
8	$Pd(OAc)_2$	DCE	K_2CO_3	51
9	$Pd(OAc)_2$	toluene	Na_2CO_3	23
10	$Pd(OAc)_2$	toluene	K_3PO_4	52
11	$Pd(OAc)_2$	toluene	Cs_2CO_3	24
12	$Pd(OAc)_2$	toluene	KOAc	19
13	$Pd(OAc)_2$	toluene	$KHCO_3$	15
14	$Pd(OAc)_2$	toluene	*t*BuOk	17
15	$Pd(TFA)_2$	toluene	K_2CO_3	61
16	$PdCl_2(PPh_3)_2$	toluene	K_2CO_3	75
17	$PdCl_2$	toluene	K_2CO_3	75
18	$PdBr_2$	toluene	K_2CO_3	68
19	–	toluene	K_2CO_3	trace
20[d]	$PdCl_2$	toluene	K_2CO_3	40
21[e]	$PdCl_2$	toluene	K_2CO_3	73

[a] Isolated yield based on *N*′-(2-alkynylbenzylidene)hydrazone **1a**.
[b] The reaction was carried out under air.
[c] The reaction was performed under a nitrogen atmosphere.
[d] In the presence of 2 mol% of $PdCl_2$.
[e] In the presence of 10 mol% of $PdCl_2$.

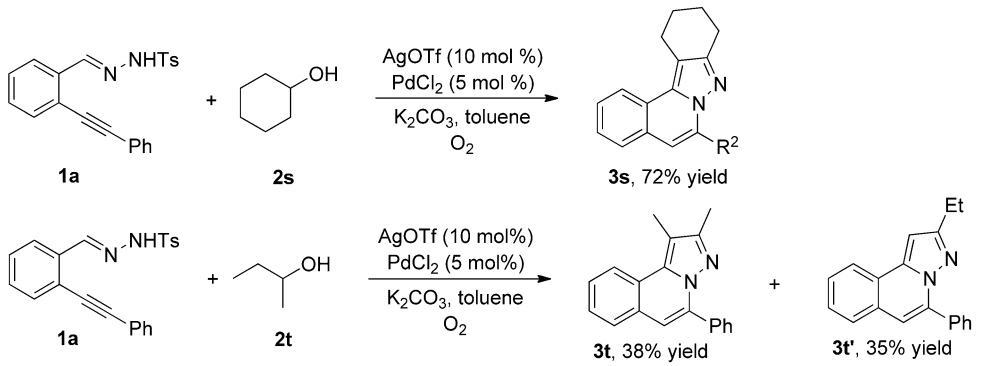
Table 2. Synthesis of *H*-pyrazolo[5,1-*a*]isoquinolines through reaction of *N*′-(2-alkynylbenzylidene)hydrazones with alcohols in the presence of a cooperative catalysis.[a]



[a] Isolated yield based on *N*′-(2-alkynylbenzylidene)hydrazone **1**.

structure. Additionally, it seemed that the substituents on the triple bond of *N*′-(2-alkynylbenzylidene)hydrazone **1** did not affect the final outcome.

Reactions of *N*′-(2-alkynylbenzylidene)hydrazones **1** with secondary alcohols were explored as well (Scheme 2). For instance, *N*′-(2-alkynylbenzylidene)-



Scheme 2. Reactions of *N*′-(2-alkynylbenzylidene)hydrazone **1a** with secondary alcohols.

hydrazone **1a** reacted with cyclohexanol leading to the desired product **3s** in 72% yield. When 1-methyl-1-propanol was employed in the reaction of *N*′-(2-alkynylbenzylidene)hydrazone **1a** under the cooperative catalysis conditions, a mixed product was isolated although the regioselectivity is reasonable.

Conclusions

In conclusion, we have reported a tandem reaction of *N*′-(2-alkynylbenzylidene)hydrazones with alcohols in the presence of oxygen co-catalyzed by silver triflate and palladium chloride under mild conditions. Diverse *H*-pyrazolo[5,1-*a*]isoquinolines were generated under the cooperative catalysis conditions. Application of the cooperative catalysis system for the formation of other N-heterocycles is currently under investigation in our laboratory.

Experimental Section

General Experimental Procedure for the Synthesis of *H*-Pyrazolo[5,1-*a*]isoquinolines through Reaction of N′-(2-Alkynylbenzylidene)hydrazones with Alcohol in the Presence of a Cooperative Catalysis

N′-(2-Alkynylbenzylidene)hydrazone **1** (0.3 mmol) was added to a solution of AgOTf (10 mol%) in toluene (2.0 mL) under air. After stirring of the mixture at 65 °C for one hour, $PdCl_2$ (2 or 10 mol%), alcohol **2** (1.5 mmol), and K_2CO_3 (0.9 mmol) were added. The mixture was stirred at 80 °C. After completion of the reaction as indicated by TLC (~16 h), the mixture was purified directly by flash column chromatograph (EtOAc/*n*-hexane, 1:50) to give the desired product **3**.

1-Ethyl-5-phenylpyrazolo[5,1-*a*]isoquinoline (3a):[8] ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.29$ (d, $J = 8.0$ Hz, 1H), 7.90–7.88 (m, 3H), 7.76 (d, $J = 8.4$ Hz, 1H), 7.63–7.52 (m, 5H), 7.01 (s, 1H), 3.19–3.13 (m, 2H), 1.50 (t, $J = 7.6$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 140.4$, 138.7, 134.5, 134.1, 129.4, 129.2, 128.4, 127.2, 127.17, 127.11, 117.1, 112.4, 19.5, 14.1.

1-Methyl-5-phenylpyrazolo[5,1-*a*]isoquinoline (3b):[8] ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.30$ (d, $J = 8.0$ Hz, 1H), 7.88 (d, $J = 7.2$ Hz, 2H), 7.84 (s, 1H), 7.27 (d, $J = 8.0$ Hz, 1H), 7.57–7.51 (m, 5H), 6.32 (d, $J = 8.0$ Hz, 1H), 6.98 (s, 1H), 2.68 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 142.1$, 138.6, 135.2, 134.1, 129.4, 129.2, 128.4, 127.1, 125.7, 123.2, 112.4, 110.1, 11.9.

5-Phenylpyrazolo[5,1-*a*]isoquinoline (3c):[8] ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.14$–8.12 (m 1H), 8.03 (d, $J = 2.0$ Hz, 1H), 7.92–7.90 (m, 2H), 7.76–73.7 (m, 1H), 7.60–7.49 (m, 5H), 7.10 (d, $J = 2.0$ Hz, 1H), 7.06 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 140.9$, 139.4, 138.6, 133.9, 129.5, 129.3, 129.2, 128.4, 128.0, 127.4, 127.2, 124.1, 123.6, 112.6, 97.9.

1,5-Diphenylpyrazolo[5,1-*a*]isoquinoline (3d): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.08$ (d, $J = 8.0$ Hz, 1H), 7.97 (s, 1H), 7.92 (d, $J = 7.2$ Hz, 2H), 7.73 (d, $J = 8.0$ Hz, 1H), 7.62 (d, $J = 7.2$ Hz, 2H), 7.58–7.52 (m, 5H), 7.50–7.45 (m, 2H), 7.34 (t, $J = 7.2$ Hz, 1H), 7.07 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 144.7$, 138.6, 134.6, 134.1, 134.0, 130.1, 129.8, 129.5, 129.4, 128.8, 128.5, 127.9, 127.5, 127.3, 127.0, 124.7, 123.3, 117.1, 113.0; HR-MS (ACPI); $m/z = 321.1392$, calcd. for $C_{23}H_{17}N_2^+$ [M + H$^+$]: 321.1386.

1-Benzyl-5-phenylpyrazolo[5,1-*a*]isoquinoline (3e): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.12$ (d, $J = 7.6$ Hz, 1H), 7.90 (d, $J = 6.8$ Hz, 2H), 7.82 (s, 1H), 7.74 (d, $J = 7.2$ Hz, 1H), 7.58–7.47 (m, 5H), 7.33–7.32 (m, 4H), 7.26–7.23 (m, 1H), 7.04 (s, 1H), 4.50 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 142.5$, 139.6, 138.7, 135.4, 134.0, 129.7, 129.5, 129.3, 128.7, 128.5, 127.4, 127.3, 127.2, 126.4, 125.0, 123.5, 113.2, 112.8, 32.0; HR-MS (ACPI): $m/z = 335.1551$, calcd. for $C_{24}H_{19}N_2^+$ [M + H$^+$]: 335.1543.

1-Decyl-5-phenylpyrazolo[5,1-*a*]isoquinoline (3f): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.26$ (d, $J = 8.0$ Hz, 1H), 7.78–7.85 (m, 3H), 7.74 (d, $J = 7.6$ Hz, 1H), 7.59 (t, $J = 7.2$ Hz, 1H), 7.56–7.49 (m, 4H), 6.97 (s, 1H), 3.08 (d, $J = 7.6$ Hz, 2H), 1.88–1.81 (m, 2H), 1.67–1.48 (m, 4H), 1.45–1.28 (m, 10H), 0.90 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 141.1$, 138.7, 134.6, 134.1, 129.6, 129.4, 129.2, 128.4, 127.3, 127.1, 123.2, 115.7, 112.4, 31.9, 29.7, 29.6, 29.4, 26.2, 22.7, 14.2; HR-MS (ACPI): $m/z = 385.2664$, calcd. for $C_{27}H_{33}N_2^+$ [M + H$^+$]: 385.2638.

5-Phenyl-1-(pyridin-2-yl)pyrazolo[5,1-*a*]isoquinoline (3g): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.81$ (d, $J = 4.0$ Hz, 1H), 8.59 (d, $J = 8.4$ Hz, 1H), 8.13 (s, 1H), 7.91–7.71 (d, $J = 6.8$ Hz, 2H), 7.82 (t, $J = 8.0$ Hz, 1H), 7.74 (d, $J = 8.4$ Hz, 1H), 7.65 (d, $J = 6.80$ Hz, 1H), 7.58–7.49 (m, 4H), 7.45–7.41 (m, 1H), 7.32 (t, $J = 7.2$ Hz, 1H), 7.11 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 153.9$, 149.7, 142.1, 136.8, 134.0, 130.1, 129.6, 129.3, 128.4, 127.2, 127.0, 124.6, 124.5, 124.3, 121.9, 117.0, 113.7; HR-MS (ACPI): $m/z = 322.1372$, calcd. for $C_{22}H_{16}N_3^+$ [M + H$^+$]: 322.1339.

1-(Indol-3-yl)-5-phenylpyrazolo[5,1-*a*]isoquinoline (3h): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.02$ (d, $J = 8.0$ Hz, 2H), 7.95 (d, $J = 6.8$ Hz, 2H), 7.72 (d, $J = 8.0$ Hz, 1H), 7.58 (t, $J = 6.8$ Hz, 2H), 7.54–7.49 (m, 2H), 7.45 (t, $J = 7.6$ Hz, 2H), 7.36 (d, $J = 2.0$ Hz, 1H), 7.29 (t, $J = 8.0$ Hz, 1H), 7.24–7.21 (m, 1H), 7.12 (t, $J = 8.0$ Hz, 1H), 7.09 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 142.9$, 138.7, 136.3, 135.8, 134.1, 129.7, 129.6, 129.3, 128.5, 127.7, 127.6, 127.0, 126.9, 125.0, 123.8, 123.6, 122.5, 120.4, 120.2, 112.9, 111.1, 109.2, 108.5; HR-MS (ACPI): $m/z = 360.1498$, calcd. for $C_{25}H_{18}N_3^+$ [M + H$^+$]: 360.1495.

5-(*p*-Tolyl)pyrazolo[5,1-*a*]isoquinoline (3i): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.14$–8.12 (m, 1H), 8.00 (d, $J = 2.0$ Hz, 1H), 7.78 (d, $J = 8.0$ Hz, 2H), 7.75–7.73 (m, 1H), 7.59–7.52 (m, 2H), 7.35 (d, $J = 8.0$ Hz, 2H), 7.09 (d, $J = 2.0$ Hz, 1H), 7.04 (s, 1H), 2.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 140.3$, 139.3, 131.0, 129.3, 129.1, 127.9, 127.2, 127.1, 123.6, 112.2, 97.8, 21.5; HR-MS (ACPI): $m/z = 259.1230$, calcd. for $C_{18}H_{15}N_2^+$ [M + H$^+$]: 259.1235.

5-(4-Methoxyphenyl)pyrazolo[5,1-*a*]isoquinoline (3j): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.12$–8.10 (m, 1H), 8.02 (s, 1H), 7.86 (d, $J = 8.8$ Hz, 1H), 7.74–7.72 (m, 1H), 7.57–7.52 (m, 2H), 7.09–7.08 (m, 2H), 7.06 (s, 1H), 7.02 (s, 1H), 3.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 160.4$, 140.8, 139.4, 138.3, 130.8, 129.3, 127.9, 127.1, 127.0, 126.2, 123.9, 123.5,

113.7, 111.7, 97.8, 55.4; HR-MS (ACPI): m/z=275.1185, calcd. for $C_{18}H_{15}N_2O^+$ [M+H$^+$]: 275.1179.

5-(4-Chlorophenyl)pyrazolo[5,1-*a*]isoquinoline (3k): ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.12 (d, J=6.8 Hz, 1H), 8.00 (d, J=2.0 Hz, 1H), 7.85 (d, J=8.0 Hz, 2H), 7.75–7.73 (m, 1H), 7.60–7.55 (m, 2H), 7.51 (d, J=8.0 Hz, 2H), 7.09 (d, J=2.0 Hz, 1H), 7.03 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=140.9, 139.4, 137.3, 135.3, 132.2, 130.8, 129.0, 128.7, 128.1, 127.6, 127.2, 124.2, 123.6, 112.7, 98.0; HR-MS (ACPI): m/z=279.0679, calcd. for $C_{17}H_{12}N_2Cl^+$ [M+H$^+$]: 279.0684.

5-Cyclopropylpyrazolo[5,1-*a*]isoquinoline (3l): ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.06 (d, J=2.0 Hz, 2H), 7.62 (d, J=2.8 Hz, 1H), 7.50–7.47 (m, 2H), 7.05 (d, J=1.6 Hz, 1H), 6.65 (m, 1H), 2.73–2.66 (m, 1H), 1.23 −1.18 (m, 2H), 0.95–0.91 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=140.7, 138.8, 129.1, 127.7, 126.6, 126.5, 123.4, 106.9, 97.8, 11.5, 7.0; HR-MS (ACPI): m/z=209.1080, calcd. for $C_{14}H_{13}N_2^+$ [M+H$^+$]: 209.1073.

5-Cyclopropyl-9-methylpyrazolo[5,1-*a*]isoquinoline (3m): ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.04 (d, J=2.0 Hz, 1H), 7.85 (s, 1H), 7.51 (d, J=8.0 Hz, 1H), 7.31–7.29 (m, 1H), 7.02 (d, J=2.0 Hz, 1H), 6.62 (s, 1H), 2.71–2.64 (m, 1H), 2.51 (s, 3H), 1.21–1.16 (m, 2H), 0.93–0.89 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=140.5, 139.9, 138.7, 136.6, 129.3, 126.9, 126.4, 123.4, 123.2, 106.8, 97.6, 21.7, 11.4, 6.9; HR-MS (ACPI): m/z=223.1255, calcd. for $C_{15}H_{15}N_2^+$ [M+H$^+$]: 223.1230.

5-Cyclopropyl-9-fluoropyrazolo[5,1-*a*]isoquinoline (3n): ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.04 (d, J=2.4 Hz, 1H), 7.66 (dd, J=9.2 Hz, 1H), 7.58 (dd, J=8.8 Hz, 1H), 7.20 (t, J=8.8 Hz, 1H), 6.98 (d, J=2.0 Hz, 1H), 6.60 (s, 1H), 2.69–2.62 (m, 1H), 121–1.16 (m, 2H), 0.92–0.87 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=161.1(d, $J_{C,F}$=245.4 Hz), 140.7, 140.1, 138.1, 128.7 (d, $J_{C,F}$=8.6 Hz), 125.7, 124.5 (d, $J_{C,F}$=9.3 Hz), 116.4 (d, $J_{C,F}$=23.5 Hz), 108.6 (d, $J_{C,F}$=22.7 Hz), 106.3, 98.3, 11.3, 6.9; HR-MS (ACPI); m/z=227.0997, calcd. for $C_{14}H_{12}FN_2^+$ [M+H$^+$]: 227.0979.

5-Phenylbenzo[*h*]pyrazolo[5,1-*a*]isoquinoline (3o): ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.99 (d, J=8.4 Hz, 1H), 8.20 (d, J=2.0 Hz, 1H), 8.00 (d, J=8.00 Hz, 1H), 7.97–7.92 (m, 3H), 7.80 (t, J=8.0 Hz, 1H), 7.74 (d, J=8.4 Hz, 1H), 7.67 (t, J=7.6 Hz, 1H), 7.63 (d, J=2.2 Hz, 1H), 7.60–7.52 (m, 3H), 7.23 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=141.7, 140.5, 139.9, 139.2, 138.7, 138.3, 136.6, 134.1, 132.9, 129.5, 129.4, 129.3, 129.2, 129.1, 129.0, 128.5, 127.5, 126.9, 126.4, 126.3, 125.7, 124.9, 123.4, 123.2, 120.3, 113.5, 106.8, 101.2, 97.6; HR-MS (ACPI): m/z=295.1242, calcd. for $C_{21}H_{15}N_2^+$ [M+H$^+$]: 295.1230.

5-Cyclopropyl-8-fluoropyrazolo[5,1-*a*]isoquinoline (3p): ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.05 (d, J=8.0 Hz, 2H), 7.30–7.20 (m, 2H), 7.00 (s, 1H), 6.58 (s, 1H), 2.75–2.68 (m, 1H), 1.25–1.20 (m, 2H), 0.96–0.92 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=161.9 (d, $J_{C,F}$=245.8 Hz), 140.9, 125.7 (d, $J_{C,F}$=9.1 Hz), 115.2 (d, $J_{C,F}$=23.8 Hz), 111.3 (d, $J_{C,F}$=21.6 Hz), 106.03, 106.00, 97.5, 11.4, 7.2; HR-MS (ACPI): m/z=227.1007, calcd. For $C_{14}H_{12}FN_2^+$ [M+H$^+$]: 227.0979.

5-*n*-Butyl-8-fluoropyrazolo[5,1-*a*]isoquinoline (3q): ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.03–7.99 (m, 2H), 7.28 (d, J=9.6 Hz, 1H), 7.21 (t, J=8.4 Hz, 1H), 6.95(s, 1H), 6.73 (s, 1H), 3.18–3.14 (m, 2H), 1.90–1.82 (m, 2H), 1.56–1.47 (m, 2H), 1.02–0.99 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=161.9 (d, $J_{C,F}$=245.7 Hz), 140.7, 138.4, 130.8 (d, $J_{C,F}$=9.1 Hz), 125.6 (d, $J_{C,F}$=8.9 Hz), 120.2, 115.2 (d, $J_{C,F}$=23.8 Hz), 111.2 (d, $J_{C,F}$=21.6 Hz), 108.7, 97.4, 30.7, 28.9, 22.6, 14.0; HR-MS (ACPI): m/z=243.1296, calcd. for $C_{15}H_{16}FN_2^+$ [M+H$^+$]: 243.1292.

5-Cyclopropyl-8-methoxypyrazolo[5,1-*a*]isoquinoline (3r): ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.01 (d, J=2.0 Hz, 1H), 7.96 (d, J=8.8 Hz, 1H), 7.10 (d, J=8.8 Hz, 1H), 7.02 (d, J=1.6 Hz, 1H), 6.92 (d, J=2.0 Hz, 1H), 6.58 (s, 1H), 3.89 (s, 3H), 2.73–2.66 (m, 1H), 1.22–1.17 (m, 2H), 0.94–0.90 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=159.2, 141.3, 140.8, 138.9, 130.8, 125.0, 117.6, 116.4, 107.5, 106.5, 96.6, 55.4, 11.4, 7.1; HR-MS (ACPI): m/z=239.1206, calcd. for $C_{15}H_{15}N_2O^+$ [M+H$^+$]: 239.1179.

6-Phenyl-9,10,11,12-tetrahydroindazolo[3,2-*a*]isoquinoline (3s):[5c] ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.18 (d, J=7.6 Hz, 1H), 7.91 (d, J=6.8 Hz, 2H), 7.71 (d, J=7.6 Hz, 1H), 7.54–7.48 (m, 5H), 6.92 (s, 1H), 3.15 (t, J=6.0 Hz, 2H), 2.94 (d, J=6.0 Hz, 2H), 1.98–1.94 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=151.1, 138.5, 134.8, 134.3, 129.6, 129.4, 129.2, 128.3, 126.9, 126.8, 125.4, 123.3, 111.5, 109.9, 24.3, 23.6, 23.1, 23.0.

1,2-Dimethyl-5-phenylpyrazolo[5,1-*a*]isoquinoline (3t): ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.30 (d, J=8.0 Hz, 1H), 7.91 (d, J=6.4 Hz, 2H), 7.71 (d, J=7.2 Hz, 1H), 7.57–7.45 (m, 5H), 6.90 (s, 1H), 2.59 (s, 3H), 2.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=149.5, 138.3, 134.2, 129.7, 129.5, 129.1, 128.3, 127.0, 126.9, 126.8, 125.4, 123.0, 111.4, 12.3, 10.8; HR-MS (ACPI): m/z=273.1394, calcd. for $C_{19}H_{17}N_2^+$ [M+H$^+$]: 273.1386.

2-Ethyl-5-phenylpyrazolo[5,1-*a*]isoquinoline (3t′): ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.08 (d, J=8.4 Hz, 1H), 7.96 (d, J=6.4 Hz, 2H), 7.73–7.71 (m, 1H), 7.55–7.50 (m, 5H), 6.98 (s, 1H), 6.93 (s, 1H), 2.94–2.88 (m, 2H), 1.39 (t, J=7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=156.6, 140.1, 138.3, 134.0, 129.5, 129.2, 128.3, 127.7, 127.1, 123.8, 123.4, 111.7, 95.9, 22.0, 14.1; HR-MS (ACPI): m/z=273.1375, calcd. for $C_{19}H_{17}N_2^+$ [M+H$^+$]: 273.1386.

Acknowledgements

Financial support from the National Natural Science Foundation of China (Nos. 21032007, 21172038) is gratefully acknowledged. We thank Dr. Jason Wong for English review.

References

[1] For selected recent reviews on cooperative catalysts, see: a) A. Ajamian, J. L. Gleason, *Angew. Chem.* **2004**, *116*, 3842–3848; *Angew. Chem. Int. Ed.* **2004**, *43*, 3754–3760; b) J. M. Lee, Y. Na, H. Han, S. Chang, *Chem. Soc. Rev.* **2004**, *33*, 302–312; c) J. C. Wasilke, O. S. J. Brey, R. T. Baker, G. C. Bazan, *Chem. Rev.* **2005**, *105*, 1001–1020; d) D. Enders, C. Grondal, M. R. Huttl, *Angew. Chem.* **2007**, *119*, 1590–1601; *Angew. Chem. Int. Ed.* **2007**, *46*, 1570–1581; e) C. J. Chapman, C. G. Frost, *Synthesis* **2007**, 1–21; f) A. M. Walji, D. W. C. MacMillan, *Synlett* **2007**, 1477–1489; g) C. Wang, Z. Xi, *Chem. Soc. Rev.* **2007**, *36*, 1395–1406; h) Z. Shao, H. Zhang, *Chem. Soc. Rev.* **2009**,

38, 2745–2755; i) C. Zhong, X. Shi, *Eur. J. Org. Chem.* **2010**, 2999–3025.

[2] For selected examples, see: a) J. Ji, X. Zhang, Y. Zhu, Y. Qian, J. Zhou, L. Yang, W. Hu, *J. Org. Chem.* **2011**, *76*, 5821–5824; b) X. Xu, Y. Qian, L. Yang, W. Hu, *Chem. Commun.* **2011**, *47*, 797–799; c) Y. Qian, X. Xu, L. Jiang, D. Prajapati, W. Hu, *J. Org. Chem.* **2010**, *75*, 7483–7486; d) Z. Guo, M. Cai, J. Jiang, L. Yang, W. Hu, *Org. Lett.* **2010**, *12*, 652–655; e) X. Xu, J. Zhou, L. Yang, W. Hu, *Chem. Commun.* **2008**, 6564–6566; f) W. Hu, X. Xu, J. Zhou, W.-J. Liu, H. Huang, J. Hu, L. Yang, L.-Z. Gong, *J. Am. Chem. Soc.* **2008**, *130*, 7782–7783.

[3] a) D. P. Walsh, Y.-T. Chang, *Chem. Rev.* **2006**, *106*, 2476–2530; b) P. Arya, D. T. H. Chou, M.-G. Baek, *Angew. Chem.* **2001**, *113*, 351–358; *Angew. Chem. Int. Ed.* **2001**, *40*, 339–346; c) S. L. Schreiber, *Science* **2000**, *287*, 1964–1969; d) M. D. Burke, S. L. Schreiber, *Angew. Chem.* **2004**, *116*, 48–60; *Angew. Chem. Int. Ed.* **2004**, *43*, 46–58; e) S. L. Schreiber, *Nature* **2009**, *457*, 153–154; f) D. S. Tan, *Nat. Chem. Biol.* **2005**, *1*, 74–84; g) C. Cordier, D. Morton, S. Murrison, A. Nelson, C. O'Leary-Steele, *Nat. Prod. Rep.* **2008**, *25*, 719–737.

[4] Z. Chen, J. Wu, *Org. Lett.* **2010**, *12*, 4856–4859.

[5] For selected examples, see: a) S. Li, Y. Luo, J. Wu, *Org. Lett.* **2011**, *13*, 4312–4315; b) S. Ye, X. Yang, J. Wu, *Chem. Commun.* **2010**, *46*, 5238–5240; c) X. Yu, S. Ye, J. Wu, *Adv. Synth. Catal.* **2010**, *352*, 2050–2056; d) X. Yu, Z. Chen, X. Yang, J. Wu, *J. Comb. Chem.* **2010**, *12*, 374–378; e) Z. Chen, X. Yang, J. Wu, *Chem. Commun.* **2009**, 3469–3471; f) Z. Chen, Q. Ding, X. Yu, J. Wu, *Adv. Synth. Catal.* **2009**, *351*, 1692–1698; g) J. Sheng, Y. Guo, J. Wu, *Tetrahedron* **2013**, *69*, doi: 10.1016/j.tet.2013.05.066.

[6] For selected examples, see: a) T. Nishimura, T. Onoue, K. Ohe, S. Uemura, *J. Org. Chem.* **1999**, *64*, 6750–6755; b) B. A. Steinhoff, S. S. Stahl, *Org. Lett.* **2002**, *4*, 4179–4181; c) T. Nishimura, H. Araki, Y. Maeda, S. Uemura, *Org. Lett.* **2003**, *5*, 2997–2999; d) M. Yang, K. Yip, J. Pan, Y. Chen, N. Zhu, D. Yang, *Synlett* **2006**, 3057–3060; e) B. Frederic, B. Emmanuel, K. Youssef, F. Fabienne, *Synlett* **2007**, 1869–1872; f) D. C. Ebner, J. T. Bagdanoff, E. M. Ferreira, R. M. McFadden, D. D. Caspi, R. M. Trend, B. M. Stoltz, *Chem. Eur. J.* **2009**, *15*, 12978–12992; g) D. Barats, R. Neumanna, *Adv. Synth. Catal.* **2010**, *352*, 293–298; h) C. Liu, J. Wang, L. Meng, Y. Deng, Y. Li, A. Lei, *Angew. Chem.* **2011**, *123*, 5250–5254; *Angew. Chem. Int. Ed.* **2011**, *50*, 5144–5148; i) W. Wu, H. Jiang, Y. Gao, H. Huang, W. Zeng, D. Cao, *Chem. Commun.* **2012**, *48*, 10340–10342; j) J. Soulé, H. Miyamura, S. Kobayashi, *Chem. Commun.* **2013**, *49*, 355–357.

[7] For reviews, see: a) J. Montgomery, *Angew. Chem.* **2004**, *116*, 3980–3998; *Angew. Chem. Int. Ed.* **2004**, *43*, 3890–3908; b) J. Panteleev, L. Zhang, M. Lautens, *Angew. Chem.* **2011**, *123*, 9255–9258; *Angew. Chem. Int. Ed.* **2011**, *50*, 9089–9092; c) S. H. Kim, S. H. Park, J. H. Choi, S. Chang, *Chem. Asian J.* **2011**, *6*, 2618–2634; d) P. Lu, Y. Wang, *Chem. Soc. Rev.* **2012**, *41*, 5687–5705; e) T. Miura, M. Murakami, *Chem. Commun.* **2007**, 217–224; f) M. Malacria, *Chem. Rev.* **1996**, *96*, 289–306; g) K. C. Nicolaou, T. Montagnon, S. A. Snyder, *Chem. Commun.* **2003**, 551–564; h) K. C. Nicolaou, D. J. Edmonds, P. G. Bulger, *Angew. Chem.* **2006**, *118*, 7292–7344; *Angew. Chem. Int. Ed.* **2006**, *45*, 7134–7186; i) D. Enders, C. Grondal, M. R. M. Hüttl, *Angew. Chem.* **2007**, *119*, 1590–1601; *Angew. Chem. Int. Ed.* **2007**, *46*, 1570–1581; j) L. F. Tietze, G. Brasche, K. Gericke, *Domino Reactions in Organic Synthesis*, Wiley-VCH, Weinheim, **2006**; k) L. F. Tietze, M. A. Düfert, T. Hungerland, K. Oum, T. Lenzer, *Chem. Eur. J.* **2011**, *17*, 8452–8461.

[8] S. Li, J. Wu, *Org. Lett.* **2011**, *13*, 712–715.

