ACES Asian Chemical Editorial Society

DOI: 10.1002/ajoc.201900289

ASIAN JOURNAL OF ORGANIC CHEMISTRY Communication

Special Issue

A Condensation/Reductive Alkylation/Hydrogenation Cascade for Facile Synthesis of Chiral 2,3-Disubstituted Indolines

Chang-Bin Yu,*[a] Xiang Li,[a] and Yong-Gui Zhou*[a, b]

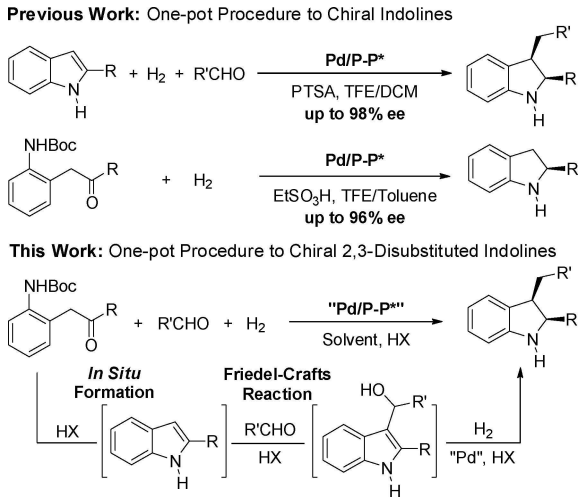
Abstract: A divergent and enantioselective procedure for synthesis of 2,3-disubstituted indolines was developed through Brønsted acid/palladium-complex promoted condensation/reductive alkylation/ hydrogenation cascade reactions from simple amino ketones and aldehydes in one operation. Five Brønsted acid-promoted steps and two Pd-catalyzed hydrogenation steps were involved in this process. This strategy provides facile synthesis of structurally diverse multi-substituted chiral indolines.

Chiral 2,3-disubstituted indolines are significant building blocks in natural products and pharmaceutically compounds.[1] Previous syntheses of chiral 2,3-disubstituted indolines mainly focused on multiple step reactions[2] or metal catalyzed tandem reactions,[3] *et al.*,[4] which caused tremendous low atom economy and environmental problems. To satisfy the demand for optically pure indolines, the development of efficient methods for their synthesis has attracted increasing attention. One of the straightforward and efficient ways to access chiral indolines may be the asymmetric reduction of substituted indole derivatives. Thus, a few of metal[5–8] or organic catalyst[9] systems have been successfully developed. Despite these contributions, the tedious procedure for the preparation of indoles limits its synthetic applications.

Tandem reactions have become a powerful tool due to their ability to construct multiple stereogenic centers in a single operation.[10] These processes represent a new entry for the preparation of complex molecules in a more cost-efficient and environmentally friendly manner. Given the importance of chiral indolines, the development of facile tandem reactions to prepare chiral 2,3-disubstituted indoline derivatives remains indispensable. In 2011, our group reported a tandem reaction for the synthesis of chiral 2,3-disubstituted indolines from 2-substituted indoles and aldehydes (or *N*-sulfonylimines) in the presence of Brønsted acid/palladium complex.[7c,d] Recently, we reported a one-pot synthesis of chiral 2-substituted indolines through palladium-catalyzed asymmetric hydrogenation of indoles generated in situ (Scheme 1).[11] We envisioned that 2,3-disubstituted indolines should be also synthesized through 3-component reaction from the readily available aminoketones, aldehydes and hydrogen gas through 2-substituted indole synthesis, 2,3-disubstituted indole synthesis and asymmetric hydrogenation cascade. The detailed reaction pathway was shown in Scheme 1.

First, the Brønsted acid could promote aminoketone to 2-substituted indole and following Friedel-Crafts reaction with aldehyde to afford the intermediate 3-(*a*-hydroxyalkyl)indole. Then, this intermediate proceeds Brønsted acid-catalyzed dehydration and palladium-catalyzed hydrogenation to give the 2,3-disubstituted indole, followed by palladium-catalyzed asymmetric hydrogenation to give the chiral 2,3-disubstituted indoline in the presence of Brønsted acid. For the above process, several issues should be addressed. Firstly, aldehyde and 2-substituted indole might be directly hydrogenated (Scheme 2a and b). Secondly, the rate of the condensation to 2-substituted indole and reductive alkylation (Friedel-Crafts/dehydration/ reduction) of 2-substituted indoles and aldehydes should be fast (Scheme 2c and d). In our previous work, we found that indole synthesis[11] and the Friedel-Crafts reaction between 2-methylindole and benzaldehyde[7c] were very fast.

To verify the hypothesis of this process, we began the reaction with aminoketone **1a** and *p*-tolualdehyde **2a** as model substrates, $EtSO_3H$ and chiral palladium/SegPhos complex[12]



Scheme 1. Strategies for Synthesis of Chiral 2,3-Disubstituted Indolines.

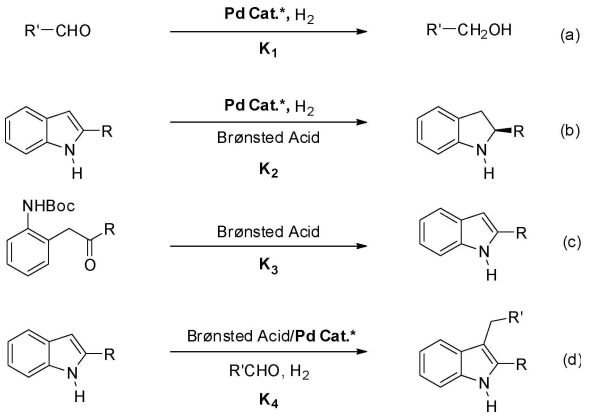
[a] *Dr. C.-B. Yu, X. Li, Dr. Y.-G. Zhou*
State Key Laboratory of Catalysis
Dalian Institute of Chemical Physics
Chinese Academy of Sciences
Dalian 116023, P. R. China
E-mail: cbyu@dicp.ac.cn
ygzhou@dicp.ac.cn
Homepage: http://www.lac.dicp.ac.cn/

[b] *Dr. Y.-G. Zhou*
Collaborative Innovation Centre of Chemical Science and Engineering
Tianjin 300071, P. R. China

Supporting information for this article is available on the WWW under https://doi.org/10.1002/ajoc.201900289

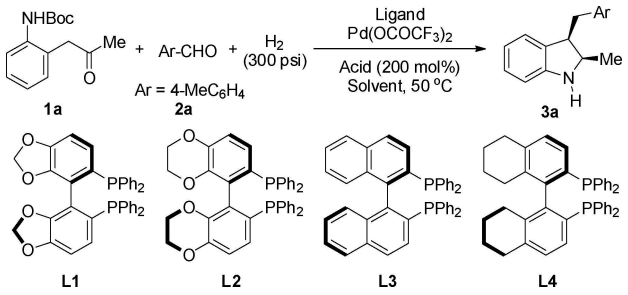
This manuscript is part of a special issue on Heterocyclic Chemistry. For the joint special collection with the European Journal of Organic Chemistry on the same topic, please click here.

© 2019 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim



Scheme 2. Possible Intermediates and Side Products.

Table 1. The Evaluation of Reaction Parameters[a].



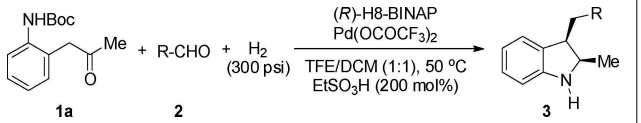
Entry	Solvent	L*	Additive	Conv. [%][b]	Ee[c]
1	TFE	**L1**	$EtSO_3H$	>95	81
2	TFE	**L1**	$TsOH{\cdot}H_2O$	>95	74
3	Toluene	**L1**	$EtSO_3H$	>95	72
4	DCM	**L1**	$EtSO_3H$	81	87
5	TFE/DCM (1:1)	**L1**	$EtSO_3H$	>95	88
6	TFE/DCM (1:2)	**L1**	$EtSO_3H$	>95	88
7	TFE/DCM (1:1)	**L2**	$EtSO_3H$	>95	87
8	TFE/DCM (1:1)	**L3**	$EtSO_3H$	>95	87
9	TFE/DCM (1:1)	**L4**	$EtSO_3H$	>95(94)[d]	91

[a] Conditions: 1a (0.1 mmol), 2a (0.12 mmol), $Pd(OCOCF_3)$/L* (2.5 mol%), additive (0.20 mmol), solvent (2 mL), 50 °C, H_2 (300 psi), 24 h. [b] Determined by ^1H NMR. [c] Determined by chiral HPLC. [d] Isolated yields. DCM = Dichloromethane, TFE = trifluoroethanol, $TsOH{\cdot}H_2O$ = *p*-toluenesulfonic acid monohydrate

were employed as Brønsted acid catalyst and hydrogenation catalyst, respectively. Fortunately, the desirable product 2,3-disubstituted indoline **3a** was obtained with 81% ee and full conversion (Table 1, entry 1). The results showed that the hypothesis was feasible.

Encouraged by the above result, we next optimized the reaction conditions to further improve the enantioselectivity. Next, Brønsted acid was evaluated (entry 2), and slightly lower enantioselectivity was obtained with $TsOH{\cdot}H_2O$. Solvent played a crucial role in the transformation, moderate ee was observed in toluene (entry 3). The highest ee was obtained in DCM albeit with moderate conversion (entry 4). Fortunately, the mixed solvent of trifluoroethanol and dichloromethane (TFE/DCM = 1:1) provided full conversion and the identical enantioselectivity (entries 5–6). Finally, several commercially available chiral

Table 2. Substrate Scope: the Variant of Aryl Aldehydes[a].



Entry	R	Yield [%][b]	Ee [%]
1	4-MeC_6H_4	94 (**3a**)	91
2	3-MeC_6H_4	91 (**3b**)	90
3	2-MeC_6H_4	94 (**3c**)	93
4	Ph	93 (**3d**)	90
5	1-naphthyl	92 (**3e**)	93
6	2,4-$Cl_2C_6H_3$	85 (**3f**)	93
7	4-FC_6H_4	91 (**3g**)	91
8	4-ClC_6H_4	93 (**3h**)	91
9	4-BrC_6H_4	91 (**3i**)	89
10	4-$MeOC_6H_4$	93 (**3j**)	90
11	2-$MeOC_6H_4$	90 (**3k**)	96
12	*n*-Pentyl	96 (**3l**)	92
13	isobutyl	91 (**3m**)	93
14	isopropyl	83 (**3n**)	94

[a] Conditions: **1** (0.25 mmol), **2** (0.30 mmol), $Pd(OCOCF_3)$/(*R*)-H8-BINAP(**L4**) (2.5 mol%), $EtSO_3H$ (0.50 mmol), TFE/DCM (2 mL/2 mL), 50 °C, H_2 (300 psi), 24 h. [b] Isolated yields.

bisphosphine ligands were investigated (entries 7–9); (*R*)-H8-BINAP was superior to other ligands (91% *ee* in Table 1, entry 9). Therefore, the optimal conditions were: $Pd(OCOCF_3)_2$/(*R*)-**L4**/$EtSO_3H$/TFE-DCM (1:1)/H_2 (300 psi)/50 °C.

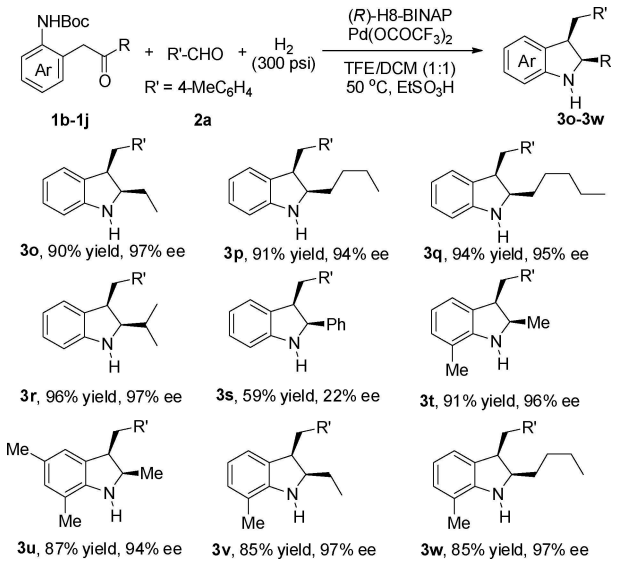
With the optimal condition in hand, the substrate scope was explored. The results were summarized in Table 2. Gratifyingly, various aromatic aldehydes performed very well under the standard reaction conditions, giving the desirable products with 89–96% ee regardless of steric hindrance and electronic properties (Table 2, entries 1–11). For aliphatic aldehydes such as hexanal, isobutyraldehyde and isovaleraldehyde, the reaction proceeded smoothly, providing the desirable chiral 2,3-disubstituted indolines with 92–94% of enantioselectivities (entries 12–14).

Then, various N-Boc aminoketones **1** were also investigated with *p*-tolualdehyde **2a** under the standard conditions. The results are summarized in Scheme 3. Full conversion and excellent enantioselectivities (94–97%) were achieved with alkyl ketones (Scheme 3, **3o**–**3r**). Phenyl ketone **1f** also was tested, and 22% of ee and 59% yield were obtained (**3s**). As for the substitutent on the benzene ring of aminoketones, the reaction also proceeded smoothly, providing the desirable indolines with 94–97% ee (**3t**–**3w**).

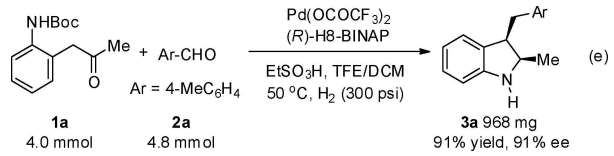
A scale-up experiment was carried out on a 4.0 mmol scale to check the practicality of this protocol (Scheme 4). To our delight, the desired chiral 2,3-disubstituted indoline **3a** was obtained without loss of activity and/or enantioselectivity (91% yield, 91% ee).

To explore the reaction pathway of this cascade reaction, control experiments were conducted. Firstly, **1a** was subjected to ethanesulfonic acid in TFE/DCM at 0 °C for 5 minutes, *N*-Boc protected indole **4** was obtained with 73% yield (Scheme 5f). Then **4** was conducted with ethanesulfonic acid at 50 °C for one hour, it transformed into 2-methylindole **5** with 96% yield

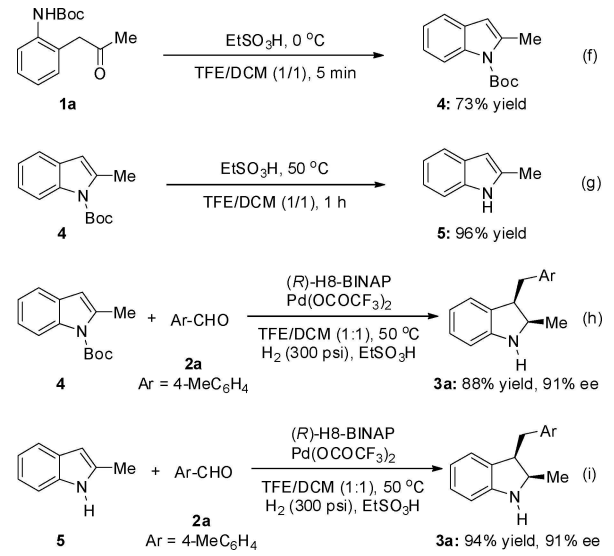
© 2019 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim



Scheme 3. Substrate Scope: Aminoketones.

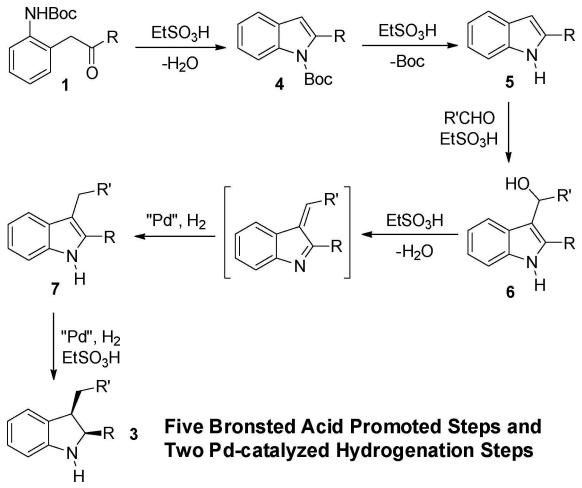


Scheme 4. The Scale-up Experiment..



Scheme 5. The Mechanism Investigation.

(Scheme 5g). The above experimental results demonstrated that the formation of indole is very fast with Brønsted acid. When *N*-Boc protected indole **4** or 2-methyl-indole **5** with toluadehyde **2a** were subjected to the optimized reaction conditions, chiral 2,3-disubstituted indoline **3a** was observed with identical reactivity and enantioselectivity (Scheme 5h and i). These experimental results indicated that the *N*-Boc protected indole **4** or 2-methylindole **5** should be the key intermediates.



Scheme 6. Proposed Reaction Pathway.

Based on the above experimental results, a detailed reaction pathway was proposed in Scheme 6. Firstly, aminoketone **1a** proceeded Brønsted acid-catalyzed condensation to give the *N*-Boc protected indole **4**. Next, Brønsted acid-catalyzed deprotection and Friedel-Crafts reaction afforded the active intermediate **6**, followed by Brønsted acid-catalyzed dehydration and palladium-catalyzed hydrogenation to give 2,3-disubstituted indole **7**. Finally, the chiral product 2,3-disubstituted indolines were obtained through Pd-catalyzed asymmetric hydrogenation in the presence of Brønsted acid.

In summary, a facile and enantioselective procedure for the synthesis of chiral 2,3-disubstituted indolines was successfully developed through a indole synthesis/reductive alkylation/hydro-genation cascade in a one-pot process. Excellent yields and up to 97% ee could be obtained. Easily available substituted amino ketones and aldehydes, and simple operation make this method very useful for the rapid and divergent synthesis of the chiral 2,3-disubstituted indolines. A detailed reaction pathway was proposed based on some control experiments.

Experimental Section

The One-Pot Procedure for Synthesis of Chiral Indolines

In a dried Schlenk tube under nitrogen was added Ligand (*R*)-H8-BINAP (4.8 mg, 0.0076 mmol), Pd(OCOCF$_3$)$_2$ (2.1 mg, 0.0063 mmol), and degassed anhydrous acetone. The mixture was then stirred at room temperature for one hour. The solvent was removed under vacuum to give the catalyst. This catalyst was taken into a glove box and dissolved in 2,2,2-trifluoroethanol (1 mL). In a glovebox, ethanesulfonic acid (0.50 mmol) and **1a** (0.25 mmol) were stirred in TFE (1 mL) at room temperature for 10 min. Subsequently, **2a** (0.30 mmol) and the above chiral catalyst solution together with dichloromethane (2 mL) were added to the reaction mixture. The mixture was transferred to an autoclave, which was charged hydrogen gas (300 psi). The hydrogenation was stirred at 50 °C for

© 2019 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

24 h. After careful release of the hydrogen, the autoclave was opened, and the solvent was evaporated. Then, saturated sodium bicarbonate (10 mL) and dichloromethane (6 mL) were added. After stirring for 10 min, the mixture was extracted with dichloromethane, and the combined organic layer was dried over sodium sulfate and concentrated in vacuo. The residue was purified by flash chromatography using hexanes/ethyl acetate (10:1) as the eluent to give the chiral product **3 a** as colorless oil (56 mg, 94% yield, 91% *ee*). Enantiomeric excess was determined by HPLC: OD-H, eluent: *n*-Hexane/*i*-PrOH = 99/1, detector: 254 nm, 30 °C, flow rate: 1.0 mL/min, retention time 16.3 min and 23.1 min (major).

Acknowledgements

We are grateful for the financial support from National Natural Science Foundation of China (21871255, 21532006) and the Strategic Priority Program of the Chinese Academy of Sciences (XDB17020300).

Conflict of Interest

The authors declare no conflict of interest.

Keywords: palladium · asymmetric hydrogenation · tandem reactions · indoles · 2,3-disubstituted indolines

[1] a) F. M. Miloserdov, M. S. Kirillova, M. E. Muratore, A. M. Echavarren, *J. Am. Chem. Soc.* **2018**, *140*, 5393; b) H.-C. Lin, T. C. McMahon, A. Patel, M. Corsello, A. Simon, W. Xu, M. Zhao, K. N. Houk, N. K. Garg, Y. Tang, *J. Am. Chem. Soc.* **2016**, *138*, 4002; c) X.-X. Zhu, Y.-Y. Fan, L. Xu, Q.-F. Liu, J.-P. Wu, J.-Y. Li, J. Li, K. Gao, J.-M. Yue, *Org. Lett.* **2019**, *21*, 1471; d) M. Tayu, Y. -Hui, S. Takeda, K. Higuchi, N. Saito, T. Kawasaki, *Org. Lett.* **2017**, *19*, 6582; e) T. Yamada, T. Ideguchi-Matsushita, T. Hirose, T. Shirahata, R. Hokari, A Ishiyama, M. Iwatsuki, A. Sugawara, Y. Kobayashi, K. Otoguro, S. Ōmura, T. Sunazuka, *Chem. Eur. J.* **2015**, *21*, 11855.

[2] a) F. O. Arp, G. C. Fu, *J. Am. Chem. Soc.* **2006**, *128*, 14264; b) X. L. Hou, B. H. Zheng, *Org. Lett.* **2009**, *11*, 1789; c) J. l. Murray, N. J. Flodén, A. Bauer, N. D. Fessner, D. L. Dunklemann, O. Bob-Egbe, H. S. Rzepa, T. Bürgi, J. Richardson, A. C. Spivey, *Angew. Chem. Int. Ed.* **2017**, *56*, 5760; d) M. López-Iglesias, E. Busto, V. Gotor, V. Gotor-Fernández, *J. Org. Chem.* **2012**, *77*, 8049.

[3] a) K.-T. Yip, M. Yang, K.-L. Law, N.-Y. Zhu, D. Yang, *J. Am. Chem. Soc.* **2006**, *128*, 3130; b) G. Zhang, V. J. Catalano, L. Zhang, *J. Am. Chem. Soc.* **2007**, *129*, 11358; c) L. Zhang, *J. Am. Chem. Soc.* **2005**, *127*, 16804; d) T. Noji, H. Fujiwara, K. Okano, H. Tokuyama, *Org. Lett.* **2013**, *15*, 1946; e) J. E. Hill, Q. Lefebvre, L. A. Fraser, J. Clayden, *Org. Lett.* **2018**, *20*, 5770; f) L.-Y. Mei, Y. Wei, X.-Y. Tang, M. Shi, *J. Am. Chem. Soc.* **2015**, *137*, 8131; g) X. Zhang, W.-B. Liu, H.-F. Tu, S.-L. You, *Chem. Sci.* **2015**, *6*, 4525.

[4] a) K. H. Kang, J. Do, Y. S. Park, *J. Org. Chem.* **2012**, *77*, 808; b) L. Chen, J.-J. Shen, Q. Gao, S. Xu, *Chem. Sci.* **2018**, *9*, 5855; c) Y. Yang, Y. Bai, S. Sun, M. Dai, *Org. Lett.* **2014**, *16*, 6216; d) M.-C. Tong, X. Chen, J. Li, R. Huang, H. Tao, C.-J. Wang, *Angew. Chem. Int. Ed.* **2014**, *53*, 4680; e) R. Viswanathan, E. N. Prabhakaran, M. A. Plotkin, J. N. Johnston, *J. Am. Chem. Soc.* **2003**, *125*, 163; f) M. Zhu, C. Zheng, X. Zhang, S.-L. You, *J. Am. Chem. Soc.* **2019**, *141*, 2636.

[5] a) T. Touge, T. Arai, *J. Am. Chem. Soc.* **2016**, *138*, 11299; b) Z. Yang, F. Chen, Y. He, N. Yang, Q.-H. Fan, *Angew. Chem. Int. Ed.* **2016**, *55*, 13863.

[6] a) S. E. Lyubimov, D. V. Ozolin, V. A. Davankov, *Tetrahedron Lett.* **2014**, *55*, 3613; b) J. L. Núñez-Rico, H. Fernández-Pérez, A. Vidal-Ferran, *Green Chem.* **2014**, *16*, 1153.

[7] a) D.-S. Wang, Q.-A. Chen, W. Li, C.-B. Yu, Y.-G. Zhou, X. Zhang, *J. Am. Chem. Soc.* **2010**, *132*, 8909; b) D.-S. Wang, J. Tang, Y.-G. Zhou, M.-W. Chen, C.-B. Yu, Y. Duan, G.-F. Jiang, *Chem. Sci.* **2011**, *2*, 803; c) Y. Duan, M.-W. Chen, Z.-S. Ye, D.-S. Wang, Q.-A. Chen, Y.-G. Zhou, *Chem. Eur. J.* **2011**, *17*, 7193; d) Y. Duan, M.-W. Chen, Q.-A. Chen, C.-B. Yu, Y.-G. Zhou, *Org. Biomol. Chem.* **2012**, *10*, 1235; e) C. Li, J. Chen, G. Fu, D. Liu, Y. Liu, W. Zhang, *Tetrahedron* **2013**, *69*, 6839.

[8] a) R. Kuwano, M. Kashiwabara, *Org. Lett.* **2006**, *8*, 2653; b) J. Wen, X. Fan, R. Tan, H.-C. Chien, Q. Zhou, L. W. Chung, X. Zhang, *Org. Lett.* **2018**, *20*, 2143.

[9] a) K. Saito, Y. Shibata, M. Yamanaka, T. Akiyama, *J. Am. Chem. Soc.* **2013**, *135*, 11740; b) L. Chen, C. Wang, L. Zhou, J. Sun, *Adv. Synth. Catal.* **2014**, *356*, 2224; c) Y.-C. Xiao, C. Wang, Y. Yao, J. Sun, Y.-C. Chen, *Angew. Chem. Int. Ed.* **2011**, *50*, 10661.

[10] a) P. Kalck, M. Urrutigoïty, *Chem. Rev.* **2018**, *118*, 3833; b) P. Eilbracht, L. Bärfacker, C. Buss, C. Hollmann, B. E. Kitsos-Rzychon, C. L. Kranemann, T. Rische, R. Roggenbuck, A. Schmid, *Chem. Rev.* **1999**, *99*, 3329; c) S. E. Denmark, A. Thorarense, *Chem. Rev.* **1996**, *96*, 137; d) S. Panda, J. M. Ready, *J. Am. Chem. Soc.* **2018**, *140*, 13242; e) J. Chen, X. Han, X. Lu, *Org. Lett.* **2018**, *20*, 7470; f) P. Chen, Z.-C. Chen, Y. Li, Q. Ouyang, W. Du, Y.-C. Chen, *Angew. Chem. Int. Ed.* **2019**, *58*, 4036.

[11] C.-B. Yu, J. Wang, Y.-G. Zhou, *Org. Chem. Front.* **2018**, *5*, 2805.

[12] a) Q.-A. Chen, Z.-S. Ye, Y. Duan, Y.-G. Zhou, *Chem. Soc. Rev.* **2013**, *42*, 497; b) Y. Duan, L. Li, M.-W. Chen, C.-B. Yu, H.-J. Fan, Y.-G. Zhou, *J. Am. Chem. Soc.* **2014**, *136*, 7688.

Manuscript received: May 9, 2019
Revised manuscript received: May 21, 2019
Version of record online: June 13, 2019

© 2019 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim