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Iodine-Promoted Construction of Polysubstituted 2,3-Dihydropyrroles from Chalcones and β-Enamine Ketones (Esters)

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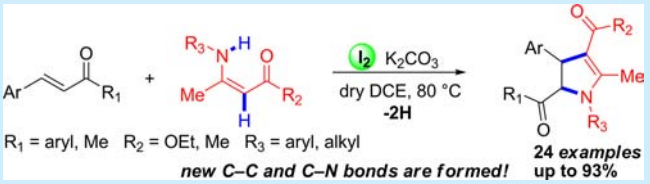
Supporting Information

ABSTRACT: A novel approach for the synthesis of a variety of polysubstituted *trans*-2,3-dihydropyrroles from a wide range of chalcones and β-enamine ketones (esters) via iodine-promoted tandem Michael/cyclization sequence has been developed, affording the desired products in moderate to excellent yields. This methodology is a highly efficient, convenient way to access functionalized 2,3-dihydropyrroles from readily accessible substrates under mild reaction conditions.



Substituted 2,3-dihydropyrroles represent one of the most important classes of five-membered heterocycles. They are found in numerous natural and biologically active compounds[1] such as sibiromycin and anthramycin (Figure 1),[2] which exhibit

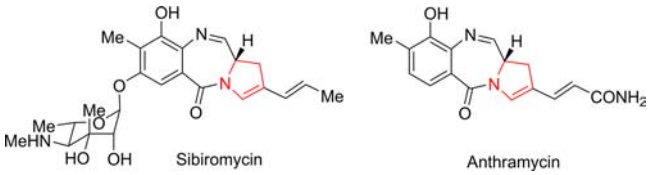


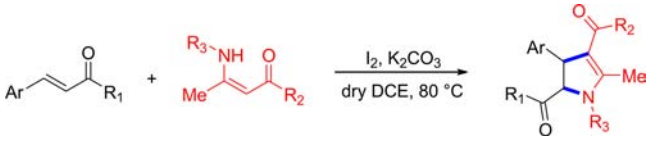
Figure 1. Representative examples of biologically active products.

significant antitumor properties. In addition, 2,3-dihydropyrroles can be used as versatile synthetic intermediates in the preparation of highly functionalized pyrrolidines,[3] pyrroles,[4] and other more complex systems.[5] As a consequence, considerable effort has been devoted to the synthesis of these heterocyclic motifs. Metal-mediated reactions[6] and cycloadditions[7] are some of the commonly used approaches for the synthesis of these systems. However, the development of an efficient and practical strategy for the synthesis of substituted 2,3-dihydropyrroles from readily accessible starting materials is still highly sought after.

Over the past decade, organic reactions promoted by molecular iodine have attracted considerable attention because of their low toxicity, low cost in comparison with transition-metal catalysts, and high tolerance to air and moisture and the abundant availability of iodine.[8,9] Iodine-promoted direct oxidative C−H functionalization is an efficient method for constructing C−C and C−heteroatom bonds, and much attention has been focused on the construction of highly functionalized cyclic rings using this methodology.[10] For example, Wang reported a useful iodine-mediated C−C and C−O bond formation reaction to construct dihydrofurans and cyclopropanes.[11] Subsequently, Yang and co-workers exploited a one-component intramolecular C−C bond-forming reaction which generated cyclopropane rings through iodine-promoted C−H bond functionalization.[12] Recently, a direct method for the synthesis of indolizines by means of iodine-mediated C−N bond formation was developed by Yan.[13]

As part of our continued interest in developing methods for the preparation of nitrogen-containing heterocyclic scaffolds,[14] we herein report a simple, efficient approach for the synthesis of polysubstituted *trans*-2,3-dihydropyrrole derivatives from chalcones and β-enamines promoted by molecular iodine (Scheme 1). To the best of our knowledge, this report

Scheme 1. Tandem Michael/Cyclization Reaction of Chalcones and β-Enamine Ketones (Esters)



represents the first thorough investigation of the tandem cyclization reaction of chalcones with β-enamines for the direct construction of 2,3-dihydropyrroles.

An initial experiment was carried out using 1,3-diphenyl-2-propen-1-one (**1a**, 0.5 mmol), ethyl 3-(phenylamino)but-2-enoate (**2a**, 0.6 mmol), and molecular iodine (0.6 mmol) in dry 1,2-dichloroethane (DCE, 3 mL) at 80 °C for 8 h (Table 1). To our delight, the expected product, ethyl *trans*-5-benzoyl-2-methyl-1,4-diphenyl-4,5-dihydro-1*H*-pyrrole-3-carboxylate (**3a**), was isolated in 59% yield (Table 1, entry 1). The structure of **3a** was confirmed by ^{1}H and 2D-ROESY NMR spectra.[7c,15] Further experiments indicated that iodine was an important promoter in this transformation, as none of the

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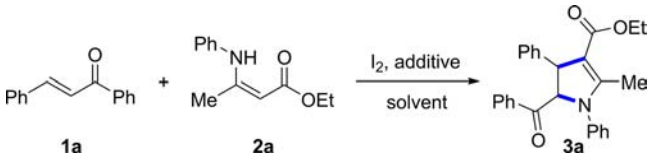
Table 1. Optimization of the Reaction Conditions[a]



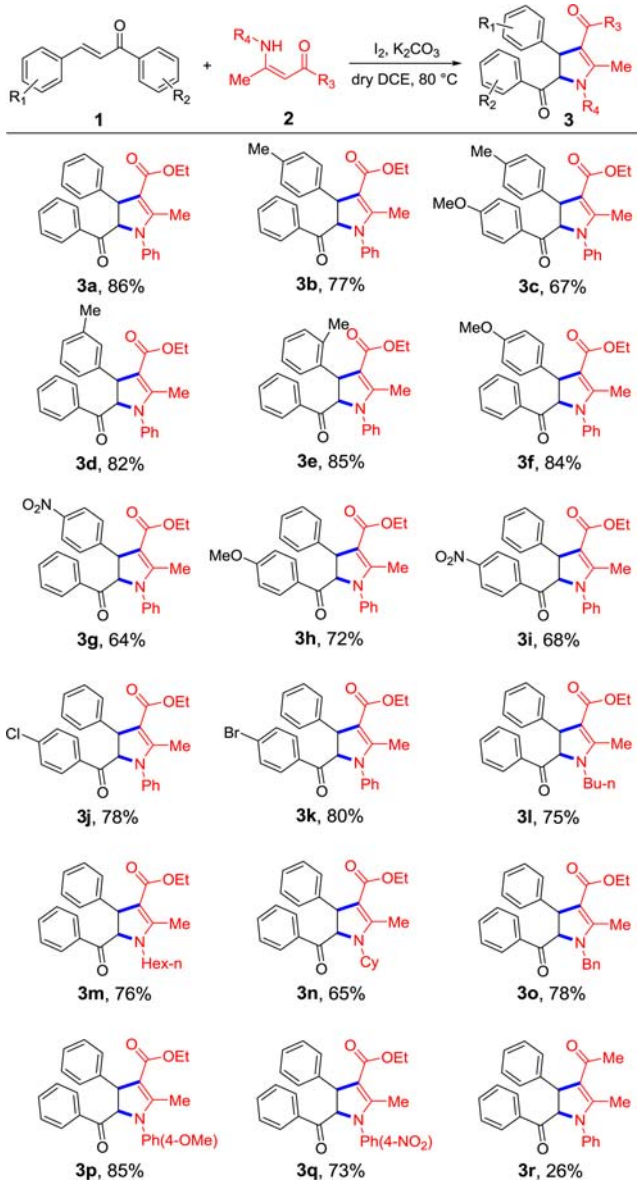
entry	ratio (**1a**/**2a**/I_2)	additive (1 equiv)	solvent	yield[b] (%)
1	1:1.2:1		DCE	59
2	1:1.2:0		DCE	ND[d]
3	1:1.2:0.5		DCE	45
4	1:1.2:1.2		DCE	80
5	1:1.2:1.5		DCE	81
6	1:1.2:1.2		DCE	70[c]
7	1:1.2:1.2	K_2CO_3	DCE	86
8	1:1.2:1.2	Na_2CO_3	DCE	72
9	1:1.2:1.2	NaOH	DCE	78
10	1:1.2:1.2	KF	DCE	77
11	1:1.2:1.2	DBU	DCE	51
12	1:1.2:1.2	DMAP	DCE	60
13	1:1.2:1.2	Et_3N	DCE	56
14	1:1.2:1.2	piperidine	DCE	63
15	1:1.2:1.2	K_2CO_3	EtOH	32
16	1:1.2:1.2	K_2CO_3	THF	26
17	1:1.2:1.2	K_2CO_3	toluene	70
18	1:1.2:1.2	K_2CO_3	MeCN	ND[d]
19	1:1.2:1.2	K_2CO_3	DMF	ND[d]
20	1:1.2:1.2	K_2CO_3	DMSO	ND[d]

[a]Reaction conditions: a mixture of **1a** (0.5 mmol), **2a**, I_2, and additive in dry solvent (3 mL) was stirred for 8 h at 80 °C. [b]Isolated yield based on **1a**. [c]Reacted at 50 °C for 8 h. [d]ND = not detected.

desired product was detected in the absence of iodine (Table 1, entry 2). This result prompted us to explore and optimize the reaction conditions for this transformation. The aim was to develop a new general method to synthesize a variety of polysubstituted 2,3-dihydropyrrole derivatives, potentially providing rapid access to these interesting products in a simple and economical way. The yield of **3a** decreased to 45% when the amount of iodine was lowered to 0.5 equiv (Table 1, entry 3). Conversely, the yield of the target product **3a** significantly improved to 80% when 1.2 equiv of iodine was used (Table 1, entry 4). Interestingly, the yield of **3a** improved to 86% when 1 equiv of K_2CO_3 was added to the reaction mixture (Table 1, entry 7). Encouraged by this result, other bases such as Na_2CO_3, NaOH, KF, 1,8-diazabicycloundec-7-ene (DBU), DMAP, Et_3N, and piperidine were investigated, but none were effective for the formation of the dihydropyrrole (Table 1, entries 8−14). Thus, we chose K_2CO_3 as the additive for this reaction. When the reaction temperature was lowered to 50 °C, the yield of 2,3-dihydropyrrole **3a** decreased to 70% (Table 1, entry 6). Solvent screening then revealed that the use of DCE as the reaction solvent is very important for the reactivity and selectivity of the transformation. Other solvents were inferior with regard to the yield of the desired dihydropyrrole **3a**, for example, toluene (70%), EtOH (32%), and THF (26%) (Table 1, entries 15−17). In addition, none of the desired product **3a** was detected when strongly polar solvents such as MeCN, DMF, and DMSO were used (Table 1, entries 18−20). The optimal reaction conditions were therefore found to be 1 equiv of K_2CO_3 and 1.2 equiv of molecular iodine in dry DCE at 80 °C for 8 h.

With the optimized reaction conditions in hand, we then examined the scope of the reaction for the construction of various *trans*-2,3-dihydropyrroles (Schemes 2 and 3). First,

Scheme 2. Synthesis of Substituted 2,3-Dihydropyrroles from Substituted Chalcones and β-Enamines[a,b]



[a]Reaction conditions: **1** (0.5 mmol), **2** (0.6 mmol), K_2CO_3 (0.5 mmol) and I_2 (0.6 mmol) in dry DCE (3 mL) at 80 °C for 8 h. [b]Isolated yields based on **1**.

various substituted chalcones were reacted with β-enamino ester **2a** under the optimal conditions. Pleasingly, the results indicated that a range of chalcones with different substituents on the aryl ring reacted smoothly with the β-enamino ester to generate the desired products in moderate to good yields (Scheme 2, **3a**−**k**). For some substituted chalcones, the yield of product **3** slightly decreased when the R_1 group of chalcone **1** was *p*-CH_3 or the R_2 group was *p*-OCH_3 or *p*-Cl (Scheme 2, **3b**, **3h**, **3j**). The yield of the product **3** was reduced further when the R_1 and R_2 substituents of the chalcone were nitro groups (Scheme 2, **3g**, **3i**). In addition, we investigated the steric effects of the substituents on the benzene ring on the

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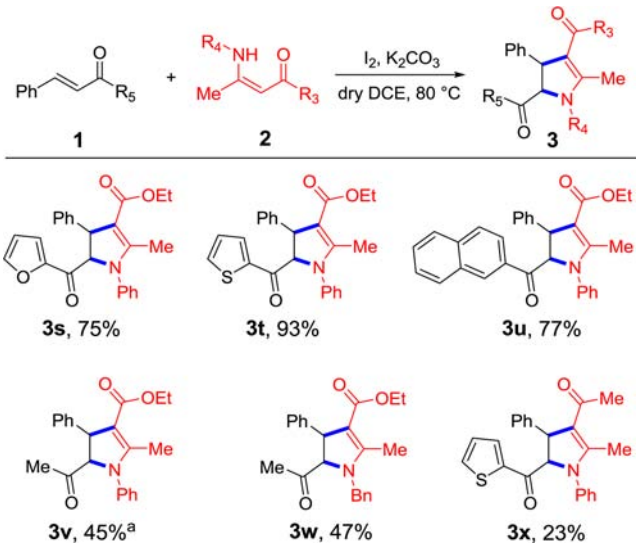
Scheme 3. Synthesis of Substituted 2,3-Dihydropyrroles from Fused Heterocyclic Chalcones/Benzalacetone and β-Enamines[a,b]



[a]Reaction conditions: **1** (0.5 mmol), **2** (0.6 mmol), K_2CO_3 (0.5 mmol) and I_2 (0.6 mmol) in dry DCE (3 mL) at 80 °C for 8 h. [b]Isolated yields based on **1**.

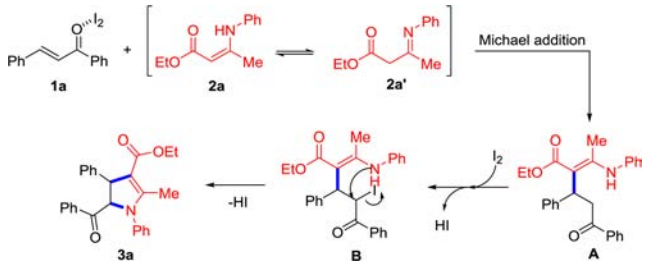
chalcone by varying the position of the R_1 methyl substituent. Reaction with β-enamino ester **2a** indicated that steric hindrance of the substituent on benzene ring does not significantly affect the reaction (Scheme 2, **3d**, **3e**).

To explore the substrate scope further, different β-enamino esters were investigated (Scheme 2, **3l**−**q**). When the derivatives of *N*-aryl β-enamino esters with substituents on the aryl ring were examined, the product dihydropyrroles **3** were obtained in good yields (Scheme 2, **3p**, **3q**). *N*-Alkyl-substituted β-enamino esters were reacted with chalcone **1a** to give good yields of the desired products (Scheme 2, **3l**−**o**). Notably, when β-enaminone 4-(phenylamino)-3-penten-2-one was used in this transformation, the corresponding dihydropyrrole **3r** was obtained in low yield (26%) due to the formation of some unidentified byproducts.

Further experiments involved the evaluation of heteroaryl chalcones and benzalacetone under the optimal reaction conditions (Scheme 3). It was shown that 2-furyl-, 2-thienyl-, and 2-naphthyl-substituted chalcones reacted smoothly with *N*-phenyl-substituted β-enamino esters, and the corresponding dihydropyrroles were obtained in good yields (Scheme 3, **3s**−**u**). In particular, the product **3t** from the reaction of 3-phenyl-1-(2-thienyl)-2-propen-1-one was obtained in excellent yield (93%). When benzalacetone was used in this reaction, the expected products **3v** and **3w** were afforded in lower yields (45 and 47%, respectively) together with a significant amount of unreacted starting material. In the same manner as discussed above, dihydropyrrole **3x** was only obtained in a low yield (23%) when *N*-phenyl β-enaminone was used, due to the formation of unidentified byproducts.

On the basis of the above experimental results and the known literature precedents,[13,16] we proposed a mechanism for this reaction (Scheme 4). First, a Michael addition reaction between 1,3-diphenyl-2-propen-1-one **1a** and ethyl-3-(phenylamino)but-2-enoate **2a** affords intermediate **A**, and then the iodo intermediate **B** is formed via an electrophilic substitution

Scheme 4. Proposed Mechanism



with iodine. Finally, intermediate **B** undergoes intramolecular nucleophilic substitution to give the target product **3a**.

In summary, we have developed a novel protocol for the synthesis of polysubstituted *trans*-2,3-dihydropyrroles via a one-pot, I_2-promoted direct cyclization reaction between chalcones and β-enamines in dry DCE at 80 °C. This reaction provides a novel, rapid, and efficient route for the preparation of a variety of *trans*-2,3-dihydropyrrole derivatives in moderate to excellent yields from readily accessible starting materials. These results will be important for developing new reactions for synthesis of 2,3-dihydropyrroles, which have potential application in construction of building blocks for natural products.

■ ASSOCIATED CONTENT

Supporting Information

Complete experimental procedure and characterization data for the prepared compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01652.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Hurley, L. H. *J. Antibiot.* **1977**, *30*, 349. (b) Hurley, L. H.; Thurston, D. E. *Pharm. Res.* **1984**, *01*, 52. (c) Ye, Z.; Shi, L.; Shao, X.; Xu, X.; Xu, Z.; Li, Z. *J. Agric. Food Chem.* **2013**, *61*, 312. (d) Wiedeman, P. E.; Trevillyan, J. M. *Curr. Opin. Invest. Drugs* **2003**, *4*, 412. (e) Magedov, I. V.; Luchetti, G.; Evdokimov, N. M.; Manpadi, M.; Steelant, W. F. A.; Van Slambrouck, S.; Tongwa, P.; Antipin, M. Y.; Kornienko, A. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1392.

(2) (a) Leber, J. D.; Hoover, J. R. E.; Holden, K. G.; Johnson, R. K.; Hecht, S. M. *J. Am. Chem. Soc.* **1988**, *110*, 2992. (b) Li, W.; Khullar, A.; Chou, S.; Sacramo, A.; Gerratana, B. *Appl. Environ. Microbiol.* **2009**, *75*, 2869.

(3) (a) Stocker, B. L.; Dangerfield, E. M.; Win-Mason, A. L.; Haslett, G. W.; Timmer, M. S. M. *Eur. J. Org. Chem.* **2010**, *2010*, 1615. (b) Mal, D.; Shome, B.; Dinda, B. K. *Heterocycl. Nat. Prod. Synth.* **2012**, *43*, 187. (c) Tejero, T.; Merino, P.; Delso, I.; Sadaba, D. *Targets in Heterocyclic Systems*; RSC Publishing: London, 2011; Vol. *15*, p 164.

DOI: 10.1021/acs.orglett.5b01652
Org. Lett. 2015, 17, 3690−3693

(4) (a) Clive, D. L. J.; Cheng, P. *Tetrahedron* **2013**, *69*, 5067. (b) Young, I. S.; Thornton, P. D.; Thompson, A. *Nat. Prod. Rep.* **2010**, *27*, 1801. (c) Biava, M.; Porretta, G. C.; Poce, G.; Battilocchio, C.; Alfonso, S.; de Logu, A.; Manetti, F.; Botta, M. *ChemMedChem* **2011**, *6*, 593.
(5) (a) Humphrey, J. H.; Liao, Y.; Ali, A.; Rein, T.; Wong, Y. L.; Chen, H. J.; Courtney, A. K.; Martin, S. F. *J. Am. Chem. Soc.* **2002**, *124*, 8584. (b) Marti, C.; Carreira, E. M. *J. Am. Chem. Soc.* **2005**, *127*, 11505. (c) Hadden, M.; Nieuwenhuyzen, M.; Osborne, D.; Stevenson, P. J.; Thompson, N.; Walker, A. D. *Tetrahedron* **2006**, *62*, 3977. (d) Bressy, C.; Menant, C.; Piva, O. *Synlett* **2005**, 577.
(6) Busacca, C. A.; Dong, Y. *Tetrahedron Lett.* **1996**, *37*, 3947. (b) Kinderman, S. S.; Van Maarseveen, J. H.; Schoemaker, H. E.; Hiemstra, H.; Rutjes, F. P. J. T. *Org. Lett.* **2001**, *3*, 2045. (c) Fan, J.; Gao, L.; Wang, Z. *Chem. Commun.* **2009**, 5021. (d) Feng, L.; Gan, Z.; Nie, X.; Sun, P.; Bao, J. *Catal. Commun.* **2010**, *11*, 555. (e) Polindara-García, L. A.; Miranda, L. D. *Org. Lett.* **2012**, *14*, 5408. (f) Miura, T.; Tanaka, T.; Hiraga, K.; Stewart, S. G.; Murakami, M. *J. Am. Chem. Soc.* **2013**, *135*, 13652. (g) Martin, M. C.; Patil, D. V.; France, S. *J. Org. Chem.* **2014**, *79*, 3030.
(7) (a) Wender, P. A.; Strand, D. *J. Am. Chem. Soc.* **2009**, *131*, 7528. (b) Guo, G.; Xue, M.-X.; Zhu, M. K.; Gong, L. Z. *Angew. Chem., Int. Ed.* **2008**, *47*, 3414. (c) Tian, J.; Zhou, R.; Sun, H.; Song, H.; He, Z. *J. Org. Chem.* **2011**, *76*, 2374.
(8) For reviews, see: (a) Ren, Y. M.; Cai, C.; Yang, R. C. *RSC Adv.* **2013**, *3*, 7182. (b) Togo, H.; Iida, S. *Synlett* **2006**, *2006*, 2159.
(9) For recent reactions mediated by iodine, see: (a) Zora, M.; Kivrak, A.; Yazici, C. *J. Org. Chem.* **2011**, *76*, 6726. (b) Verma, A. K.; Shukla, S. P.; Singh, J.; Rustagi, V. *J. Org. Chem.* **2011**, *76*, 5670. (c) He, Z.; Li, H.; Li, Z. *J. Org. Chem.* **2010**, *75*, 4636. (d) Gao, Q.; Wu, X.; Liu, S.; Wu, A. *Org. Lett.* **2014**, *16*, 1732. (e) Ilangovan, A.; Satish, G. *J. Org. Chem.* **2014**, *79*, 4984. (f) Lamani, M.; Prabhu, K. R. *J. Org. Chem.* **2011**, *76*, 7938. (g) Katrun, P.; Mueangkaew, C.; Pohmakotr, M.; Reutrakul, V.; Jaipetch, T.; Soorukram, D.; Kuhakarn, C. *J. Org. Chem.* **2014**, *79*, 1778. (h) Tang, S.; Liu, K.; Long, Y.; Gao, X.; Gao, M.; Lei, A. *Org. Lett.* **2015**, *17*, 2404. (i) Zhu, T. H.; Wang, S. Y.; Tao, Y. Q.; Ji, S. J. *Org. Lett.* **2015**, *17*, 1974. (j) Zhu, Y. P.; Liu, M. C.; Jia, F. C.; Yuan, J. J.; Gao, Q. H.; Lian, M.; Wu, A. X. *Org. Lett.* **2012**, *14*, 3392. (k) Li, Y. X.; Ji, K. G.; Wang, H. X.; Ali, S.; Liang, Y. M. *J. Org. Chem.* **2011**, *76*, 744. (l) Ge, W.; Zhu, X.; Wei, Y. *Adv. Synth. Catal.* **2013**, *355*, 3014. (m) Gao, Q.; Wu, X.; Li, Y.; Liu, S.; Meng, X.; Wu, A. *Adv. Synth. Catal.* **2014**, *356*, 2924. (n) Ding, C. H.; Dai, L. X.; Hou, X. L. *Tetrahedron* **2005**, *61*, 9586. (o) Knight, D. W.; Redfern, A. L.; Gilmore, J. *Chem. Commun.* **1998**, 2207. (p) Knight, D. W.; Redfern, A. L.; Gilmore, J. *J. Chem. Soc., Perkin Trans. 1* **2002**, 622.
(10) (a) Zhao, J.; Huang, H.; Wu, W.; Chen, H.; Jiang, H. *Org. Lett.* **2013**, *15*, 2604. (b) Huang, H.; Ji, X.; Wu, W.; Jiang, H. *Adv. Synth. Catal.* **2013**, *355*, 170. (c) Zhang, X.; Kang, J.; Niu, P.; Wu, J.; Yu, W.; Chang, J. *J. Org. Chem.* **2014**, *79*, 10170.
(11) Wang, G. W.; Gao, J. *Org. Lett.* **2009**, *11*, 2385.
(12) Miao, C. B.; Zhang, M.; Tian, Z. Y.; Xi, H. T.; Sun, X. Q.; Yang, H. T. *J. Org. Chem.* **2011**, *76*, 9809.
(13) Xiang, L.; Yang, Y.; Zhou, X.; Liu, X.; Li, X.; Kang, X.; Yan, R.; Huang, G. *J. Org. Chem.* **2014**, *79*, 10641.
(14) (a) Huang, H. M.; Li, Y. J.; Ye, Q.; Yu, W. B.; Han, L.; Jia, J. H.; Gao, J. R. *J. Org. Chem.* **2014**, *79*, 1084. (b) Xu, H.; Li, Y. J.; Xing, M. M.; Jia, J. H.; Han, L.; Ye, Q.; Gao, J. R. *Chem. Lett.* **2015**, *44*, 574. (c) Li, Y. J.; Huang, H. M.; Dong, H. Q.; Jia, J. H.; Han, L.; Ye, Q.; Gao, J. R. *J. Org. Chem.* **2013**, *78*, 9424. (d) Huang, H. M.; Gao, J. R.; Hou, L. F.; Jia, J. H.; Han, L.; Ye, Q.; Li, Y. J. *Tetrahedron* **2013**, *69*, 9033.
(15) (a) Doyle, M. P.; Yan, M.; Hu, W. H.; Gronenberg, L. S. *J. Am. Chem. Soc.* **2003**, *125*, 4692. (b) Fantauzzi, S.; Gallo, E.; Caselli, A.; Piangiolino, C.; Ragaini, F.; Re, N.; Cenini, S. *Chem. - Eur. J.* **2009**, *15*, 1241.
(16) Mishra, S.; Monir, K.; Mitra, S.; Hajra, A. *Org. Lett.* **2014**, *16*, 6084.

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