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Transition-metal-free approach to synthesis of indolines from *N*-(*ortho*-chloromethyl)aryl amides and iodonium ylides

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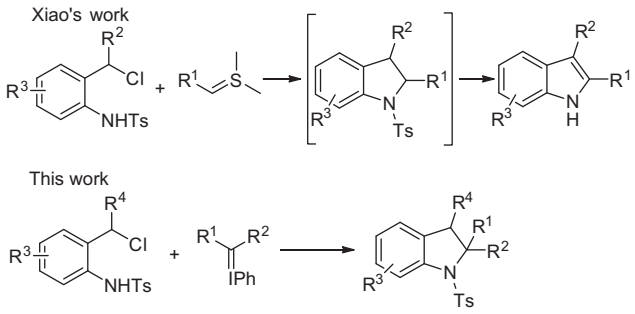
ABSTRACT

A transition-metal-free method for the synthesis of indolines has been developed. In the presence of K_2CO_3, the cyclization reaction of *N*-(*ortho*-chloromethyl)aryl amides and iodonium ylides proceeded smoothly at room temperature in moderate to good yields.

Indolines are important building blocks in a vast number of biologically active natural products[1] and pharmacologically active compounds.[2] The synthesis of this privileged structure has attracted significant interest and numerous synthetic methodologies have been developed for recent years.[3–10] Most of these approaches to construct indolines were focused on transition-metal-catalyzed C–N or C–C bond formation.[4] However, because of the high catalyst loading demand in some of these processes and heavy metal residues in product, the application is restricted to the costly and large workload in purification. Recently, transition-metal-free approaches for the synthesis of indolines have been extensively studied, which include radical-mediated reactions,[5] intramolecular carbolithiation,[6] and phenyliodine(III)-mediated reactions.[7] Moreover, Hao and co-workers reported a cyclization of 2-aminophenethylethanols with common carboxylic acids to form *N*-acyl indolines in the presence of PPh_3, CCl_4, and NEt_3.[8] Stoltz and co-workers reported a coupling reaction of readily available *N*-acyl dehydroamino esters with aryne precursors to produce indolines.[9] Ruano et al. developed an asymmetric tandem reaction to facilitate the one-pot synthesis of optically pure fluorinated indolines from 2-(*p*-tolylsulfinyl)benzylcarbanions and *N*-PMP-fluorinated imines.[10] Although many useful and interesting methods were reported, synthetic methods for the synthesis of indolines, are still in great demand. In addition, diverse starting materials and synthetic strategies are desired to make indoline derivatives more readily accessible.

In 2012, Xiao and co-workers reported the synthesis of indoles from sulfur ylides and *N*-(*ortho*-chloromethyl)aryl amides.[11] The process was initiated by the addition of sulfur ylide to the aza-oquinodimethane intermediate, generated in situ from *N*-(*ortho*-chloromethyl)aryl amide under the basic conditions. This step was followed by cyclization with loss of dimethylsulfide to generate indoline intermediate (Scheme 1). Due to the previous research of iodonium ylides,[12] we envisioned that it would react with *N*-(*ortho*-chloromethyl)aryl amides to construct indolines as sulfur



Scheme 1. Synthesis of indolines by cyclization of *N*-(*ortho*-chloromethyl)aryl amides with iodonium ylides.

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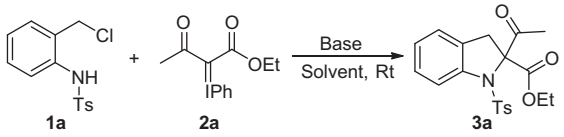
ylides. Here in, we reported a transition-metal-free and mild cyclization of *N*-(*ortho*-chloromethyl)aryl amides with iodonium ylides for the synthesis of indolines.

Initially, the cyclization of *N*-(2-(chloromethyl)phenyl)-4-methylbenzenesulfonamide (**1a**) with methyl 2-phenyliodonio-3-oxobutanoate (**2a**) was selected for optimization of reaction conditions, and the results are summarized in Table 1. Our investigation started by an attempted cyclization of substrate **1a** with **2a** in CH_2Cl_2 at room temperature in the presence of Cs_2CO_3 as base, and the desired product **3a** could be isolated in 44% yields (entry 1). This result encouraged us to develop a transition-metal-free system to synthesize indolines. Then, a variety of solvents, such as toluene, THF, and CH_3CN were screened. Results indicated that solvent (CH_3CN) is the best for this cyclization reaction (entries 1–4). Subsequently, the effects of base (including inorganic base K_2CO_3, KOH, $NaHCO_3$, K_3PO_4, CsOAc, NaOAc, CsF, LiO*t*-Bu, NaOEt and organic base DABCO, NEt_3) (entries 5–15) were examined. K_2CO_3 was found to give the best result. Finally, the amount of base and reaction temperature were evaluated. Relatively low yields were found when the reaction was carried out in 0 and 60 °C (entries 16 and 17), and the yields of **3a** did not lead to an obvious improvement when the amount of K_2CO_3 was increased to 5.0 equiv. Thus, the optimized reaction conditions were as follows: **1a** (0.30 mmol), **2a** (0.36 mmol), K_2CO_3 (2.5 equiv), in CH_3CN (2 mL) at room temperature.

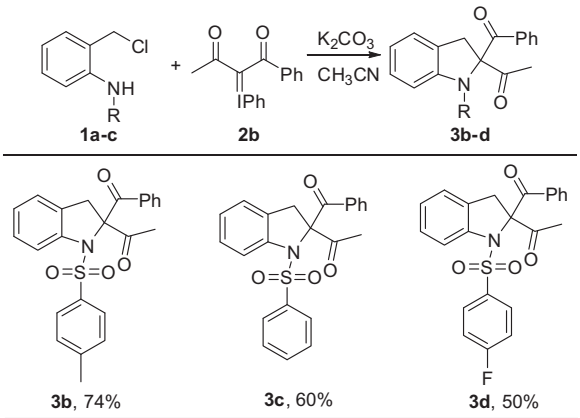
Since such an addition and cyclization process are supposed, we then investigated the effect of 4-methylbenesulfonyl, benesulfonyl, and 4-fluorobenesulfonyl substituents on the *N*-(2-(chloromethyl)phenyl)-sulfonamide (Scheme 2). As expected, 74% yield was obtained when *N*-(2-(chloromethyl)phenyl)-4-methylbenzenesulfonamide was applied. In the reaction of *N*-(2-(chloromethyl)phenyl)-4-fluorobenzenesulfonamide, only 50% yield was observed. A comparison of the reaction yields from *N*-(2-(chloromethyl)phenyl)-sulfonamide indicated a significant sulfonyl dependence in the following order: 4-methylbenesulfonyl > benesulfonyl > 4-fluorobenesulfonyl. We believe this observation supported the formation of indolines via an addition and N-alkylation process.

Table 1
Optimization of reaction conditions[a]



Entry	Base	Solvent	Yield of **3a**[b] (%)
1	Cs_2CO_3	CH_2Cl_2	44
2	Cs_2CO_3	Toluene	33
3	Cs_2CO_3	THF	56
4	Cs_2CO_3	CH_3CN	59
5	K_2CO_3	CH_3CN	68
6	KOH	CH_3CN	20
7	$NaHCO_3$	CH_3CN	20
8	K_3PO_4	CH_3CN	57
9	CsOAc	CH_3CN	56
10	NaOAc	CH_3CN	57
11	CsF	CH_3CN	61
12	LiO*t*-Bu	CH_3CN	31
13	NaOEt	CH_3CN	60
14	DABCO	CH_3CN	0
15	NEt_3	CH_3CN	15
16[c]	K_2CO_3	CH_3CN	65
17[d]	K_2CO_3	CH_3CN	63
18[e]	K_2CO_3	CH_3CN	69

[a] Reaction conditions: **1a** (0.30 mmol), **2a** (0.36 mmol), base (2.5 equiv), solvent (2 mL), 2 h, room temperature.
[b] Isolated yield.
[c] In 0 °C.
[d] In 60 °C.
[e] Base (5 equiv).



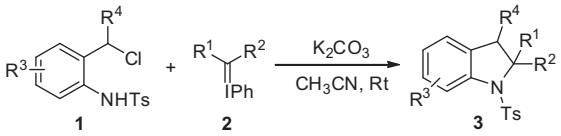
[a] Reaction conditions: **1** (0.3 mmol), **2b** (0.36 mmol), K_2CO_3 (2.5 equiv),solvent (2 mL), 2 h, room temperature. [b] Isolated yield.

Scheme 2. Cyclization of *N*-(2-(chloromethyl)phenyl)-benzenesulfonamides with 2-phenyliodonio-1-phenylbutane-1,3-dione.

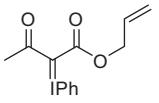
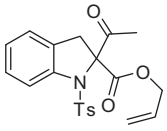
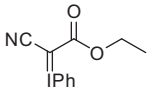
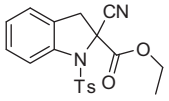
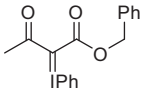
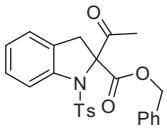
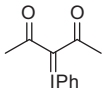
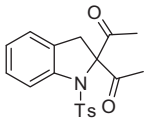
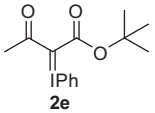
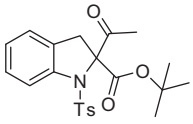
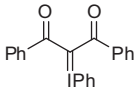
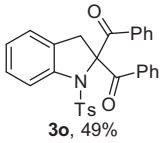
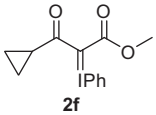
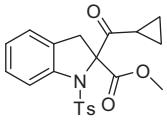
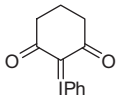
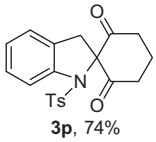
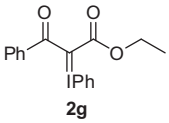
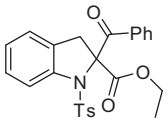
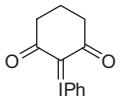
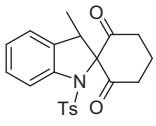
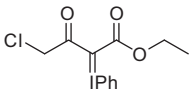
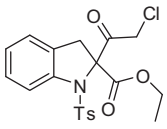
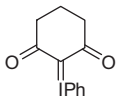
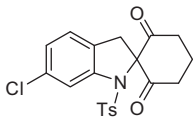
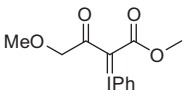
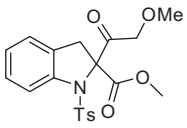
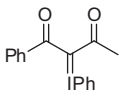
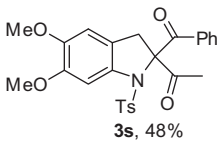
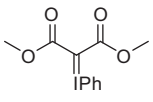
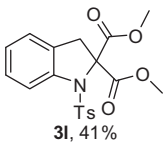
With the standard reaction conditions in hand, the scope of the cyclization of *N*-(2-(chloromethyl)phenyl)-4-methylbenzenesulfonamide with various iodonium ylides were investigated, and the results are summarized in Table 2. The results demonstrated that the yields were affected by the structures of the two reaction partners to some extent. Firstly, a number of 2-phenyliodonio-3-oxobutanoates (**2c**–**2i**) were evaluated, and they all were found to be suitable substrates for the cyclization with *N*-(2-(chloromethyl)phenyl)-4-methylbenzenesulfonamide under the standard conditions (entries 1–7). For instance, when substrate **2c** bearing an allyl group, was treated with *N*-(2-(chloromethyl)phenyl)-4-methylbenzenesulfonamide **1a** and K_2CO_3 in room temperature, indoline **3e** was formed in 61% yield (entry 1). Substrate **2h** and **2i** containing a halo group or methoxyl group was also tolerated well under the same conditions (entries 6 and 7). Subsequently, the reaction of **1a** with the iodonium ylide of dimethyl malonate **2j** was conducted smoothly in 41% yield under the standard conditions (entry 8). Interestingly, the reaction of **1a** with 2-phenyliodonio-3-oxo-3-phenylpropanenitrile (**2k**) was conducted smoothly in 27% yield under the standard conditions (entry 9). We were happy to observe that 2-phenyliodonio-2,4-diones (2l-n) could also react with *N*-(2-(chloromethyl)phenyl)-4-methylbenzenesulfonamide efficiently in moderate yields (entries 10–12). 3-Phenyliodonio-pentane-2,4-dione (**2l**), for example, was treated with **1a** to afford the corresponding products **3n** in 70% yield (entry 10). Importantly, 74% yield of an interesting spiro[cyclohexane-1,2′-indoline]-2,6-dione product **3p** was obtained in the reaction of substrate **1a** with ylide **2n** (entry 12). Finally, the effect of substitutional groups on *N*-(2-(chloromethyl)phenyl)-4-methylbenzenesulfonamide was screened. For example, 1,2-substitutent indoline **3q** was obtained in the yield of 56% when substrate *N*-(2-(1-chloroethyl)phenyl)-4-methylbenzenesulfonamide (**1d**) was applied. *N*-(2-(Chloromethyl)phenyl)-4-methylbenzenesulfonamide bearing electron-withdrawing group such as Cl (**1e**) or electron-donating group such as OMe (**1f**) on benzene ring afforded the corresponding indolines in 40% and 48% yields.

Importantly, the acetyl substituted indolines were found to undergo the elimination and isomerization to afford indoles. For example, the acetyl substituted indulines **3a** and **3n** could be readily converted into corresponding indoles **4** and **5** in

Table 2
Cyclization of N-(2-(chloromethyl)phenyl)- benzenesulfonamides with iodonium ylides[a]



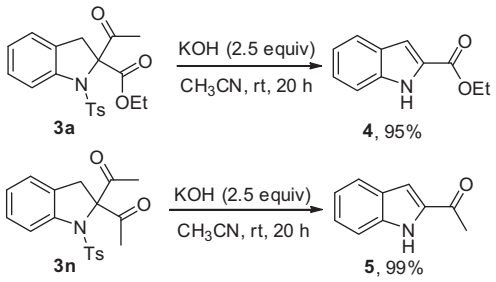
1d: R^3 = H, R^4 = Me; **1e**: R^3 = 3-Cl; R^4 = H; **1f**: R^3 = 3,4-$(OMe)_2$, R^4 = H

Entry	1	Iodonium yield	Indoline[b] (%)	Entry	1	Iodonium yield	Indoline[b] (%)
1	**1a**	 **2c**	 **3e**, 61%	9	**1a**	 **2k**	 **3m**, 27%
2	**1a**	 **2d**	 **3f**, 69%	10	**1a**	 **2l**	 **3n**, 70%
3	**1a**	 **2e**	 **3g**, 40%	11	**1a**	 **2m**	 **3o**, 49%
4	**1a**	 **2f**	 **3h**, 64%	12	**1a**	 **2n**	 **3p**, 74%
5	**1a**	 **2g**	 **3i**, 30%	13	**1a**	 **2n**	 **3q**, 56%
6	**1a**	 **2h**	 **3j**, 68%	14	**1e**	 **2n**	 **3r**, 40%
7	**1a**	 **2i**	 **3k**, 54%	15	**1f**	 **2b**	 **3s**, 48%
8	**1a**	 **2j**	 **3l**, 41%				

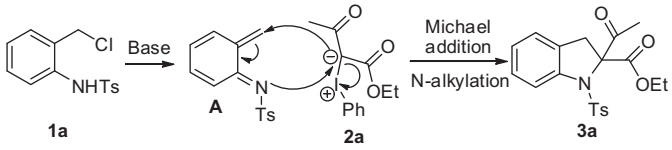
[a] Reaction conditions: **1a** (0.30 mmol), **2** (0.36 mmol), K_2CO_3 (2.5 equiv), solvent (2 mL), 2 h, room temperature.
[b] Isolated yield.

95% and 99% yield under the basic conditions (Scheme 3). Reaction of this type could have been used in the synthesis of 2-substituted indoles.

A working mechanism as outlined in Scheme 4 was proposed for the present reaction on the basis of the previously reported mechanism.[11–13] Firstly, *N*-(2-chlorobenzyl)-4-methylbenzenesulfonamide was converted into the aza-*o*-quinodimethane intermediate A under the basic conditions. Then, aza-*o*-quinodimethane underwent Michael addition and N-alkylation with iodonium ylide to generate product indoline by loss of an iodobenzene.



Scheme 3. Synthesis of 2-substituted indoles by the elimination of the acetyl substituted indolines.



Scheme 4. Proposed reaction pathway for the synthesis of indolines from *N*-(*ortho*-chloromethyl)aryl amides with iodonium ylides.

In summary, we have outlined a transition-metal-free strategy for the preparation of indolines. In the presence of K_2CO_3, *N*-(*ortho*-chloromethyl)aryl amides successfully underwent Michael addition and N-alkylation with iodonium ylide at room temperature to afford the corresponding indolines in moderate to good yields. Further studies of the reaction scope and mechanism are currently underway in our laboratory.

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Supplementary data

Supplementary data (experimental procedures and characterization data for all new compounds and copies of NMR spectra) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.08.096.

References and notes

1. For selected examples, see: (a) Bui, T.; Syed, S.; Barbas, C. F., III *J. Am. Chem. Soc.* **2009**, *131*, 8758; (b) Zhang, H.; Boonsombat, J.; Padwa, A. *Org. Lett.* **2007**, *9*, 279; (c) Iyengar, R.; Schildknegt, K.; Morton, M.; Aube, J. *J. Org. Chem.* **2005**, *70*, 10645; (d) Dounay, A. B.; Overman, L. E.; Wrobleski, A. D. *J. Am. Chem. Soc.* **2005**, *127*, 10186; (e) Kuehne, M. E.; Bornmann, W. G.; Marko, I.; Qin, Y.; Le-Boulluec, K. L.; Frasier, D. A.; Xu, F.; Mulamba, T.; Ensinger, C. L.; Borman, L. S.; Huot, A. E.; Exon, C.; Bizzarro, F. T.; Cheung, J. B.; Bane, S. L. *Org. Biomol. Chem.* **2003**, *1*, 2120; (f) Wang, T.; Xu, Q.; Yu, P.; Liu, X.; Cook, J. M. *Org. Lett.* **2001**, *3*, 345; (g) Sunazuka, T.; Hirose, T.; Shirahata, T.; Harigaya, Y.; Hayashi, M.; Komiyama, K.; Omura, S.; Smith, A. B., III *J. Am. Chem. Soc.* **2000**, *122*, 2122; (h) Boger, D. L.; Boyce, C. W.; Garbaccio, R. M.; Goldberg, J. A. *Chem. Rev.* **1997**, *97*, 787.
2. For selected examples, see: (a) Hobson, L. A.; Nugent, W. A.; Anderson, S. R.; Deshmukh, S. S.; Haley, J. J., III; Liu, P.; Magnus, N. A.; Sheeran, P.; Sherbine, J. P.; Stone, B. R. P.; Zhu, J. *Org. Process Res. Dev.* **2007**, *11*, 985; (b) Bromidge, S. M.; Duckworth, M.; Forbes, I. T.; Ham, P.; King, F. D.; Thewlis, K. M.; Blaney, F. E.; Naylor, C. B.; Blackburn, T. P.; Kennett, G. A.; Wood, M. D.; Clarke, S. E. *J. Med. Chem.* **1997**, *40*, 3494; (c) Rakhit, A.; Hurley, M. E.; Tipnis, V.; Coleman, J.; Rommel, A.; Brunner, H. R. *J. Clin. Pharmacol.* **1986**, *26*, 156; (d) Gruenfeld, N.; Stanton, J. L.; Yuan, A. M.; Ebetino, F. H.; Browne, L. J.; Gude, C.; Huebner, C. F. *J. Med. Chem.* **1983**, *26*, 1277.
3. For reviews, see: (a) Liu, D.; Zhao, G.; Xiang, L. *Eur. J. Org. Chem.* **2010**, 3975; (b) Anas, S.; Kagan, H. B. *Tetrahedron: Asymmetry* **2009**, *20*, 2193.
4. Selected examples for palladium-catalyzed synthesis of indolines, see: (a) Ghorai, M. K.; Nanaji, Y. *J. Org. Chem.* **2013**, *78*, 3867; (b) He, G.; Lu, C.; Zhao, Y.; Nack, W. A.; Chen, G. *Org. Lett.* **2012**, *14*, 2944; (c) Watanabe, T.; Oishi, S.; Fujii, N.; Ohno, H. *Org. Lett.* **2008**, *10*, 1759; (d) Thansandote, P.; Raemy, M.; Rudolph, A.; Lautens, M. *Org. Lett.* **2007**, *9*, 5255; (e) Ganton, M. D.; Kerr, M. A. *Org. Lett.* **2005**, *7*, 4777; (f) Lira, R.; Wolfe, J. P. *J. Am. Chem. Soc.* **2004**, *126*, 13906; (g) Bytschkov, I.; Siebeneicher, H.; Doye, S. *Eur. J. Org. Chem.* **2003**, *15*, 2888; (h) Yang, B. H.; Buchwald, S. L. *Org. Lett.* **1999**, *1*, 35; For copper-catalyzed synthesis of indolines, see: (i) Zhou, F.; Guo, J.; Liu, J.; Ding, K.; Yu, S.; Cai, Q. *J. Am. Chem. Soc.* **2012**, *134*, 14326; (j) Li, S.; Luo, Y.; Wu, J. *Org. Lett.* **2011**, *13*, 3190; (k) Li, J.-J.; Mei, T.-S.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2008**, *47*, 6452; (l) Zabawa, T. P.; Kasi, D.; Chemler, S. R. *J. Am. Chem. Soc.* **2005**, *127*, 11250; (m) Zhang, H.; Cai, Q.; Ma, D. *J. Org. Chem.* **2005**, *70*, 5164; (n) Sherman, E. S.; Chemler, S. R.; Tan, T. B.; Gerlits, O. *Org. Lett.* **2004**, *6*, 1573; (o) Minatti, A.; Buchwald, S. L. *Org. Lett.* **2008**, *10*, 2721; For Ni-catalyzed synthesis of indolines, see: (p) Omar-Amrani, R.; Thomas, A.; Brenner, E.; Schneider, R.; Fort, Y. *Org. Lett.* **2003**, *5*, 2311.
5. (a) Brucelle, F.; Renaud, P. *Org. Lett.* **2012**, *14*, 3048; (b) Viswanathan, R.; Smith, C. R.; Prabhakaran, E. N.; Johnston, J. N. *J. Org. Chem.* **2008**, *73*, 3040; (c) Fuwa, H.; Sasaki, M. *Org. Lett.* **2007**, *9*, 3347; (d) Viswanathan, R.; Prabhakaran, E. N.; Plotkin, M. A.; Johnston, J. N. *J. Am. Chem. Soc.* **2003**, *125*, 163; (e) Leroi, C.; Bertin, D.; Dufils, P. E.; Gigmes, D.; Marque, S.; Tordo, P.; Couturier, J. L.; Guerret, O.; Ciufolini, M. A. *Org. Lett.* **2003**, *5*, 4943; (f) Johnston, J.; Plotkin, M. A.; Viswanathan, R.; Prabhakaran, E. N. *Org. Lett.* **2001**, *3*, 1009.
6. (a) Kang, K. H.; Do, J.; Park, Y. S. *J. Org. Chem.* **2012**, *77*, 808; (b) Bailey, W. F.; Mealy, M. J. *J. Am. Chem. Soc.* **2000**, *122*, 6787; (c) Gil, G. S.; Groth, U. M. *J. Am. Chem. Soc.* **2000**, *122*, 6789; (d) Zhang, D. W.; Liebeskind, L. S. *J. Org. Chem.* **1996**, *61*, 2594; (e) Bailey, W. F.; Jiang, X. L. *J. Org. Chem.* **1996**, *61*, 2596.
7. (a) Landge, K. P.; Jang, K. S.; Lee, S. Y.; Chi, D. Y. *J. Org. Chem.* **2012**, *77*, 5705; (b) Correa, A.; Tellitu, I.; Dominguez, E.; SanMartin, R. *J. Org. Chem.* **2006**, *71*, 8316; (c) Pouysegu, L.; Avenllan, A.-V.; Quideau, S. *J. Org. Chem.* **2002**, *67*, 3425.
8. Wang, Z.; Wan, W.; Jiang, H.; Hao, J. *J. Org. Chem.* **2007**, *72*, 9364.
9. Gilmore, C. D.; Allan, K. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2008**, *130*, 1558.
10. Ruano, J. L. G.; Alemán, J.; Catalán, S.; Marcos, V.; Monteagudo, S.; Parra, A.; Pozo, C. d.; Fustero, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 7941.
11. Yang, Q.-Q.; Xiao, C.; Lu, L.-Q.; An, J.; Tan, F.; Li, B.-J.; Xiao, W.-J. *Angew. Chem., Int. Ed.* **2012**, *51*, 9137.
12. Huang, X.-C.; Liu, Y.-L.; Liang, Y.; Pi, S.-F.; Wang, F.; Li, J.-H. *Org. Lett.* **2008**, *10*, 1525.
13. (a) Robertson, F. J.; Kenimer, B. D.; Wu, J. *Tetrahedron* **2011**, *67*, 4327; (b) Wu, H.-X.; Xue, F.; Xiao, X.; Qin, Y. *J. Am. Chem. Soc.* **2010**, *132*, 14052; (c) Steinhagen, H.; Corey, E. J. *Angew. Chem., Int. Ed.* **1999**, *38*, 1928; (d) Lehmann, H.-G. *Tetrahedron Lett.* **1968**, *9*, 607.