ORGANIC LETTERS

2011
Vol. 13, No. 13
3458–3461

Regiodivergent Annulation of Alkynyl Indoles To Construct Spiro-pseudoindoxyl and Tetrahydro-β-carbolines

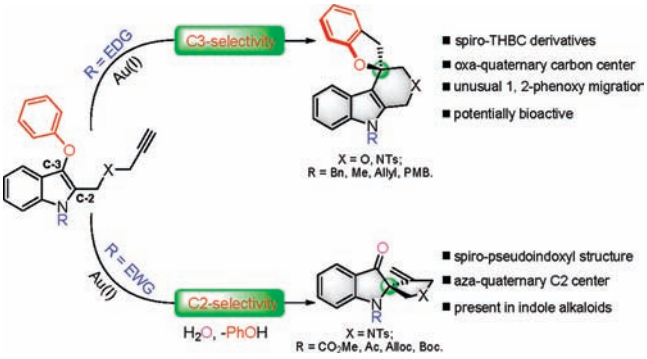
Yong-Qiang Zhang, Dao-Yong Zhu, Zhi-Wei Jiao, Bao-Sheng Li, Fu-Min Zhang, Yong-Qiang Tu,* and Zhigang Bi

State Key Laboratory of Applied Organic Chemistry and Department of Chemistry, Lanzhou University, Lanzhou 730000, P. R. China

tuyq@lzu.edu.cn

Received May 5, 2011

ABSTRACT



Regiodivergent annulations of 3-phenoxy alkynyl indoles have been developed and tuned by protective groups through gold catalysis. With electron-donating protective groups, the substrate followed a C3-selective annulation and gave structurally interesting tetrahydro-β-carboline derivatives possessing potential bioactivity. Using electron-withdrawing protective groups, the substrate underwent a C2-selective annulation and afforded the structurally useful spiro-pseudoindoxyl found in natural indole alkaloids. Notably, an interesting and unusual 1, 2-migration of the phenoxy group was found in the C3-selective process.

As an important indole derivative, pseudoindoxyl[1] represents a common feature of some indole alkaloids. As shown in Figure 1, the pesudoindoxyl structure, especially those containing a spiro quaternary C2 carbon center, represents the core skeleton of indole alkaloids such as fluorocurine,[2] diketopiperazine,[3] brevianamide B,[4] and rauniticine pseudoindoxyl.[5] The primary method to construct this structural unit is limited to oxidative rearrangement of the corresponding indole compounds.[6] Thus, there is a need for the development of mild and efficient alternative synthetic routes to the spiro-pseudoindoxyl structure. A second well-known indole derivative, tetrahydro-β-carboline (THBC),[7] is a pharmacophore existing in a wide array of natural and synthetic products that have important medicinal activities.[8] Owing to their biological relevance, molecularly diverse THBCs are required and have been traditionally prepared by Pictet–Spengler condensation of tryptophan with aliphatic or aromatic aldehydes.[7,9]

(1) Hans-Jurg, B. *Curr. Org. Chem.* **2005**, *9*, 1465.
(2) Schmid, H.; Karrer, P. *Helv. Chim. Acta* **1947**, *30*, 2081.
(3) Wang, F.; Fang, Y.; Zhu, T.; Zhang, M.; Lin, A.; Gu, Q.; Zhu, W. *Tetrahedron* **2008**, *64*, 7986.
(4) Birch, A. J.; Wright, J. J. *Tetrahedron* **1970**, *26*, 2329.
(5) Phillipson, J. D.; Supavita, N. *Phytochemistry* **1983**, *22*, 1809.
(6) (a) Finch, N.; Gemenden, C. W.; Hsu, I. H.-C.; Kerr, A.; Sim, G. A.; Taylor, W. I. *J. Am. Chem. Soc.* **1965**, *87*, 2229. (b) O'Rell, D. D.; Lee, F. G. H.; Boekelheide, V. *J. Am. Chem. Soc.* **1972**, *94*, 3205. (c) Bennasar, M.-L.; Zulaica, E.; Jiménez, J.-M.; Bosch, J. *J. Org. Chem.* **1993**, *58*, 7756. (d) Reto, S.; Hans-Juerg, B. *Helv. Chim. Acta* **1994**, *77*, 1331. (e) Karadeolian, A.; Kerr, M. A. *J. Org. Chem.* **2010**, *75*, 6830. (f) Frebault, F. C.; Simpkins, N. S. *Tetrahedron* **2010**, *66*, 6585. (g) Lee, J.; Panek, J. S. *Org. Lett.* **2011**, *13*, 502.
(7) Cox, E. D.; Cook, J. M. *Chem. Rev.* **1995**, *95*, 1797.
(8) (a) *Introduction to Alkaloids: A Biosynthetic Approach*; Cordell, G. A., Ed.; Wiley: New York, 1981. (b) Rabindran, S. K.; He, H.; Singh, M.; Collins, E.; Annable, K. I.; Greberger, L. M. *Cancer Res.* **1998**, *58*, 5850. (c) Li, X.; Zhang, L.; Zhang, W.; Hall, S. E.; Tam, J. P. *Org. Lett.* **2000**, *2*, 3075. (d) Ulven, T.; Kostenis, E. *J. Med. Chem.* **2005**, *48*, 897.
(9) (a) Pictet, A.; Spengler, T. *Ber. Dtsch. Chem. Ges.* **1911**, *44*, 2030. (b) Taylor, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 10558. (c) Seayad, J.; Seayad, A. M.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 1086. (d) Raheem, I. T.; Thiara, P. S.; Peterson, E. A.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2007**, *129*, 13404.

10.1021/ol201194n
Published on Web 06/07/2011

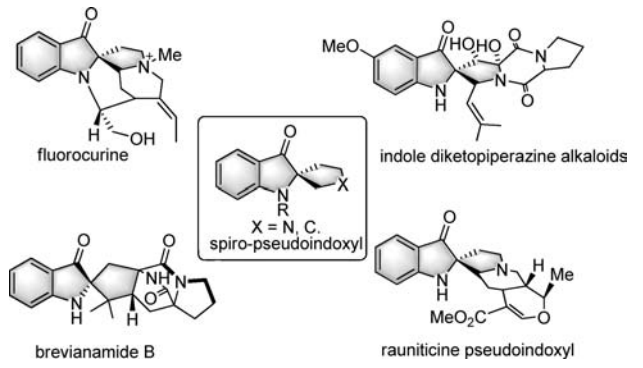
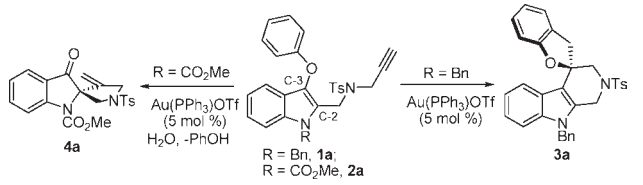


Figure 1. Representative indole alkaloids with spiro-pseudoindoxyl structure.

However, the direct elaboration of substituted THBCs remains a challenge.[10]

During our efforts examining the reactivity of alkynyl indoles catalyzed by gold,[11] we have developed an efficient divergent strategy to construct both the spiro-pseudoindoxyl structure and THBC derivatives from 3-aryloxy alkynyl indoles. In particular, this gold-catalyzed regiodivergent annulation can be tuned by protective groups on the indoles. As shown in Scheme 1, in the presence of a gold(I) catalytic system, a 3-phenoxy alkynyl indole model substrate with an electron-donating group (benzyl (Bn), **1a**) followed a C3-site selective annulation to afford the spiro-THBC derivative **3a**,

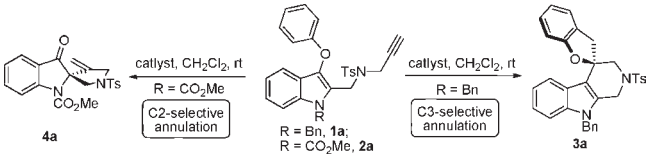
Scheme 1. Gold-Catalyzed Regiodivergent Annulations of **1a**, **2a**



which contains a benzo[*b*]dihydrofuran subunit and an oxa-quaternary carbon center embedded in the core. Notably, an interesting 1,2-migration of the phenoxy group took place in this C3-selective process. While the protective group was CO_2Me as the electron-withdrawing group, the substrate **2a** underwent a C2-site selective annulation, affording the synthetically useful spiro-pseudoindoxyl derivative **4a** and the release of phenol.

To optimize the reaction conditions, a series of gold and platinum catalysts were screened. We found that the use of $Au(PPh_3)Cl/AgOTf$ (5 mol %) in CH_2Cl_2 (used as purchased without further purification, containing about 0.05% H_2O), at room temperature within 30 min, gave the best results for either the N-Bn substrate (**1a**) or the N-CO_2Me substrate (**2a**), with high yields and short reaction times (Table 1, entry 1). In contrast, using $Au(PPh_3)Cl/AgSbF_6$ or $Au(PPh_3)Cl/AgBF_4$ as a catalyst gave low yields of **4a**, and the former catalyst was completely ineffective for catalyzing the formation of **3a** (Table 1, entries 2 and 3).

Table 1. Optimization of Reaction Conditions[a]



entry	yield (%)[b]/**4a**	catalyst	time	yield (%)[b]/**3a**
1	95	$Au(PPh_3)Cl/AgOTf$	0.5 h	80
2	41	$Au(PPh_3)Cl/AgSbF_6$	10 h	–
3	65	$Au(PPh_3)Cl/AgBF_4$	0.5 h	65
4	12[c]	$AuCl_3$	10 h	10[d]
5[e]	–	$PtCl_2$	10 h	–
6[e]	–	PTSA[f]	10 h	–

[a] Reaction conditions: substrate **1a** or **2a** (0.1 mmol), catalyst (5 mmol %), and CH_2Cl_2 (2 mL, used as purchased without further purification, containing about 0.05% H_2O) at rt under an Ar atmosphere. [b] Isolated yield. [c] 55% of starting material was recovered. [d] 50% of starting material was recovered. [e] No reaction. [f] PTSA = *p*-toluenesulfonic acid.

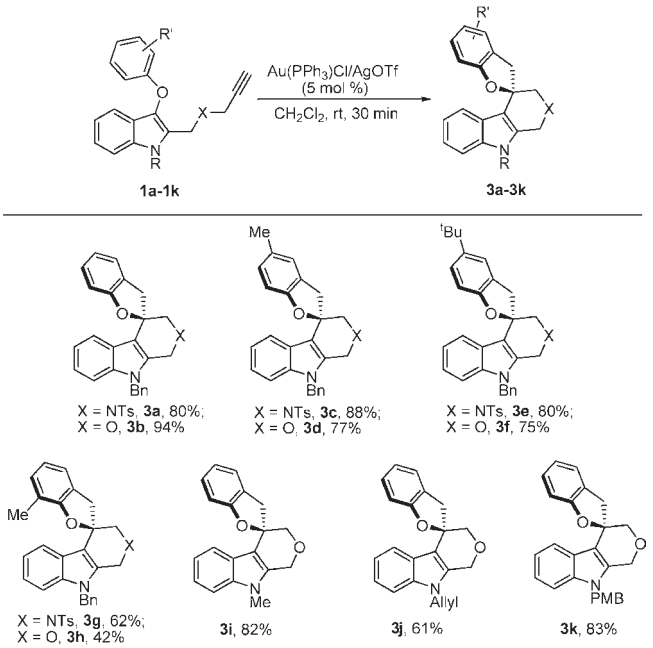
$AuCl_3$ in CH_2Cl_2 gave the products **3a** and **4a** in very low yields and required long reaction times (Table 1, entry 4). Employment of nongold catalyst $PtCl_2$ in CH_2Cl_2 resulted in no reaction for both substrate **1a** and **2a** (Table 1, entry 5). PTSA was used as a protic acid to catalyze the C2- and C3-selective reaction, but none of the expected products could be isolated (Table 1, entry 6).

Intrigued by the mild standard reaction conditions described above, we then examined the generality of this gold-catalyzed regiodivergent annulation. Various indole substrates bearing different alkyl substituents on the aryloxy group (**1b**–**1h**) were subjected to the C3-selective reaction. Scheme 2 shows that all examples reacted smoothly within 30 min to afford the desired products in moderate to high yields (42–94%). It should be noted that the yields of the current reactions were dependent, to some degree, on the position of the substituents on the aryloxy group. For example, when

(10) (a) Agnusdei, M.; Bandini, M.; Melloni, A.; Umani-Ronchi, A. *J. Org. Chem.* **2003**, *68*, 7126. (b) Bandini, M.; Alfonso, A.; Piccinelli, F.; Sinisi, R.; Tommasi, S.; Umani-Ronchi, A. *J. Am. Chem. Soc.* **2003**, *128*, 1424. (c) Li, C.-F.; Liu, H.; Liao, J.; Cao, Y.-J.; Liu, X.-P.; Xiao, W.-J. *Org. Lett.* **2007**, *9*, 1847. (d) Rannoux, C.; Roussi, F.; Retailleau, P.; Guéritte, F. *Org. Lett.* **2010**, *12*, 1240.

(11) For gold catalysis in indole chemistry, see: (a) Li, Z.; Shi, Z.; He, C. *J. Organomet. Chem.* **2005**, *690*, 5049. (b) Zhang, L. *J. Am. Chem. Soc.* **2005**, *127*, 16804. (c) Ferrer, C.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 1105. (d) Ferrer, C.; Amijs, C. H. M.; Echavarren, A. M. *Chem.—Eur. J.* **2007**, *13*, 1358. (e) Yang, T.; Campbell, L.; Dixon, D. J. *J. Am. Chem. Soc.* **2007**, *129*, 12070. (f) England, D. B.; Padwa, A. *Org. Lett.* **2008**, *10*, 3631. (g) Zhang, G.; Huang, X.; Li, G.; Zhang, L. *J. Am. Chem. Soc.* **2008**, *130*, 1814. (h) Barluenga, J.; Fernandez, A.; Rodriguez, F.; Fananas, J. *J. Organomet. Chem.* **2009**, *694*, 546. (i) Ferrer, C.; Escribano-Cuesta, A.; Echavarren, A. M. *Tetrahedron* **2009**, *65*, 9015. (j) Li, G.; Liu, Y. *J. Org. Chem.* **2010**, *75*, 3526. (k) Lu, Y.; Du, X.; Jia, X.; Liu, Y. *Adv. Synth. Catal.* **2009**, *351*, 1517. (l) Liu, Y.; Xu, W.; Wang, X. *Org. Lett.* **2010**, *12*, 1448. (m) Verniest, G.; England, D.; Kimpe, N. D.; Padawa, A. *Tetrahedron* **2010**, *66*, 1496.

Scheme 2. Scope of the C3-Selective Annulations[a]

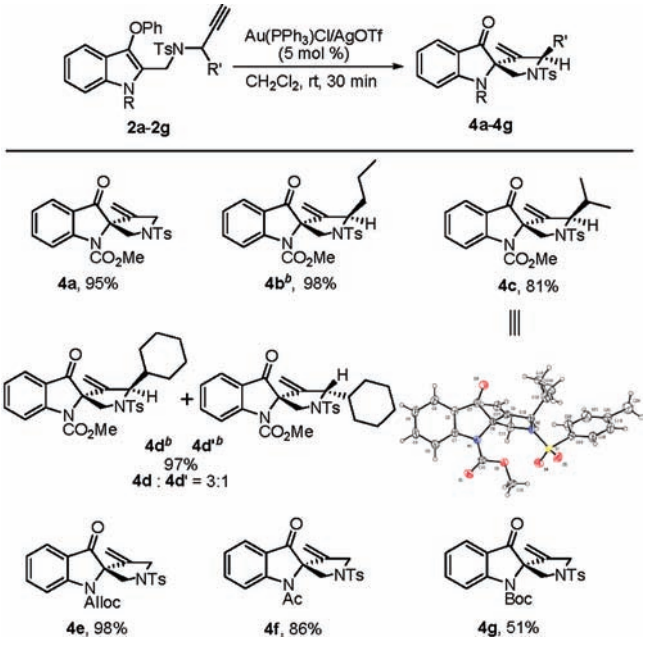


[a] Isolated yield throughout.

substrates bearing an alkyl group at the para-position of the aryloxy (**1c**−**1f**) were employed, the reaction proceeded smoothly to give the expected products (**3c**−**3f**) in good to high yields. In contrast, when an alkyl was substituted at the ortho-position (**1g**, **1h**), the reaction gave relatively lower yields. Additionally, when the "NTs" group in the substituent of the substrate was replaced by "O" (**1b**, **1d**, **1f**, **1h**), the substrates were still effective in this process. To examine the tolerance of the reaction for other protective groups, substrates with electron-donating protective groups, such as methyl (Me, **1i**), allyl (**1j**), and *p*-methoxybenzyl (PMB, **1k**), were used under the same conditions and afforded the expected products (**3i**−**3k**).

We focused our attention on the diversity of the side chain at C2 to expand the scope of C2-selective annulation. As summarized in Scheme 3, indole substrates substituted with Pr (propyl), *i*-Pr (iso- propyl), and Cy (cyclohexyl) at the alkyne-containing chain (**2b**−**2d**) worked well in this C2-selective reaction, and these indoles were efficiently converted to the desired spiro products (**4b**−**4d**) in good to excellent yields. Remarkably, when the substituent was Pr or *i*-Pr, the annulation proceeded in a fully stereoselective manner and afforded the products **4b** and **4c**, respectively, as single diastereomers. The relative configuration of product **4c** was determined by X-ray analysis. We reasoned that this stereoselectivity was a result of repulsion between the alkyl substituent and the protective group (CO_2Me) in the transition state.[12] However, treatment of substrate **2d** containing a Cy substituent afforded spiro-compounds **4d** as an inseparable 3:1 mixture of diastereomers. To make this protocol more applicable in natural product synthesis, we also changed the protective group on the basis of various deprotection methods. As we anticipated, substrates with electron-withdrawing groups such as allyl carbamate (Alloc, **2e**), acetyl (Ac, **2f**), and *tert*-butyl carbamate (Boc, **2g**) worked well in the transformation and gave the expected products (**4e**−**4g**).

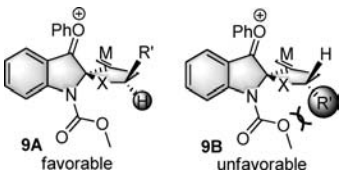
Scheme 3. Scope of the C2-Selective Annulations[a]



[a] Isolated yield throughout. [b] The relative configurations of **4b** and **4d** were confirmed by comparison of ^{1}H NMR data with **4c**.

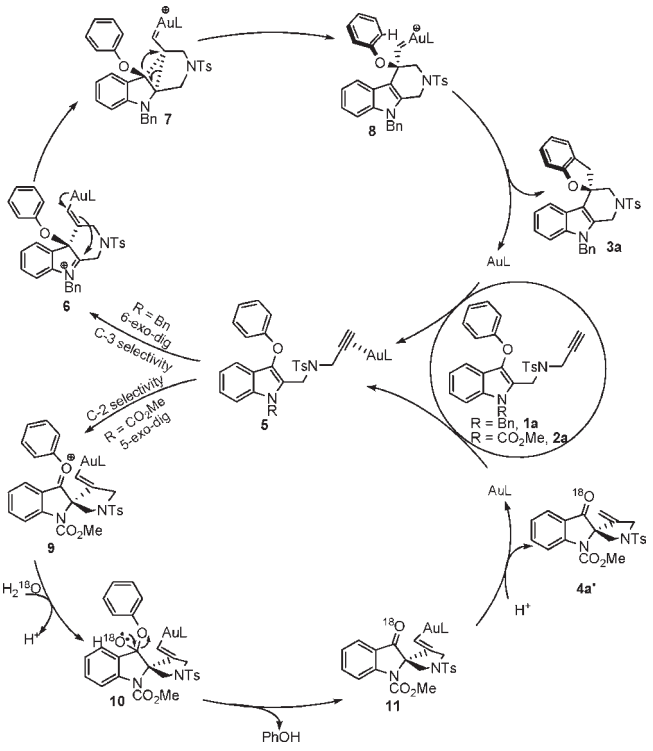
On the basis of the above experimental results, a possible mechanism for this regiodivergent annulation is proposed in Scheme 4. The two different pathways start from the common activated intermediate **5**, which has enamine and enol functionalities. When R was Bn as an electron-donating group, the more reactive C3-center underwent nucleophilic addition to a triple bond by a 6-exo-dig cyclization pathway, resulting in Friedel−Crafts alkenylation of the indole nucleus to give the intermediate **6**. Next, the alkenyl gold species in **6** underwent an intramolecular nucleophilic attack on the iminium cation to generate the gold cyclopropyl carbene intermediate **7**.[13] Subsequent rearomatization

(12) It is assumed that the intemediate **9A** in C2-selective reaction is more favorable than **9B** as a result of the hindrance between R′ and CO_2Me:



(13) (a) Benitez, D.; Shapiro, N. D.; Tkatchouk, E.; Wang, Y.; Gdddard, W. A.; Toste, F. D. *Nat. Chem.* **2009**, *1*, 482. (b) Ye, L.; Cui, L.; Zhang, G.; Zhang, L. *J. Am. Chem. Soc.* **2010**, *132*, 3258. (c) Péréz-Galán, P.; Herrero-Gómez, E.; Hog, D. T.; Martin, N. J. A.; Maseras, F.; Echavarren, A. M. *Chem. Sci.* **2011**, *2*, 141.

Scheme 4. Proposed Catalytic Cycle



via an unusual 1,2-migration of a phenoxy group along with the opening of the cyclopropyl ring afforded intermediate **8**. Finally, **8** underwent a Friedel–Crafts reaction to give the product **3a** and the release of AuL for the next catalytic cycle.[14] Importantly, very few papers have reported this unusual 1,2-migration of an aryloxy group in the opening of the cyclopropyl rings.[15] Thus, a new tandem process involving cyclopropanation/1,2-phenoxy migration/Friedel–Crafts annulation has been described here.

In contrast, using CO_2Me as an electron-withdrawing group to reduce C3 reactivity, along with the efficiency of the installed phenoxy group at the C3-site to enhance C2 reactivity, the nucleophilic addition of **5** took place at the C2 center to give a spirocyclic intermediate **9** with an oxacarbonium at the C3-site.[16] **9** was quenched by water in the reaction system to form hemiketal **10**. Subsequently, **10** lost a molecule of phenol and afforded the pseudoindoxyl intermediate **11**. Finally, protodemetalation of **11** delivered the product **4a** and the reformation of the catalyst AuL. The participation of H_2O in this 5-exo-dig cyclization process was confirmed by an isotopic labeling experiment. Compound **2a** was treated with $Au(PPh_3)Cl/AgOTf$ (5 mol %) in ultradry CH_2Cl_2 saturated by $H_2{}^{18}O$ and afforded product **4a′** labeled by ^{18}O, which was determined by MS (ESI) and HRMS.

In conclusion, we have developed a gold-catalyzed regiodivergent annulation of alkynyl indoles tuned by a protective group on the indoles. With an electron-donating protective group, C3-selective annulation took place and gave structurally interesting spiro-THBC derivatives possessing potential bioactivity. In particular, an interesting and unusual 1,2-phenoxy migration was found in this process. In contrast, with electron-withdrawing protective groups, C2-selective annulations occurred and afforded a synthetically useful spiro-pseudoindoxyl structure, which is present in natural indole alkaloids. Further studies aimed at application of this synthetic protocol to natural product synthesis are currently underway.

Acknowledgment. This work was supported by the NSFC (Nos. 20621091, 20672048, 20732002, and 20972059), "973" program of 2010CB833200, "111" program of MOE, and the fundamental research funds for the central universities (lzujbky-2010-k09, lzujbky-2009-76, lzujbky-2009-158).

Supporting Information Available. Representative experimental procedures, X-ray crystallographic data of **3a**, **4a**, **4c**, and NMR spectra of substrates and products. This material is available free of charge via the Internet at http://pubs.acs.org.

(14) (a) Prasad, B. A. B.; Yoshimoto, F. K.; Sarpong, R. *J. Am. Chem. Soc.* **2005**, *127*, 12468. (b) Horino, Y.; Yamamoto, T.; Ueda, K.; Kuroda, S.; Toste, F. D. *J. Am. Chem. Soc.* **2009**, *131*, 2809.

(15) (a) Sanz, R.; Miguel, D.; Rodriguez, F. *Angew. Chem., Int. Ed.* **2008**, *47*, 7354. (b) Peng, L.; Zhang, X.; Zhang, S.; Wang, J. *J. Org. Chem.* **2007**, *72*, 1192.

(16) (a) Staben, S. T.; Kennedy-Smith, J. J.; Huang, D.; Corkey, B. K.; Lalonde, R. L.; Toste, F. D. *Angew. Chem., Int. Ed.* **2006**, *45*, 5991. (b) Linghu, X.; Kennedy-Smith, J. J.; Toste, F. D. *Angew. Chem., Int. Ed.* **2007**, *46*, 7671.