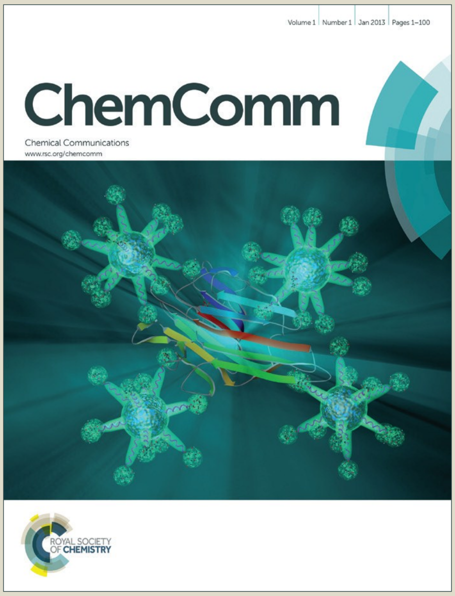

Volume 1 | Number 1 | Jan 2013 | Pages 1–100
ChemComm
Chemical Communications
www.rsc.org/chemcomm
ROYAL SOCIETY OF CHEMISTRY

Journal Name

ChemComm

Dynamic Article Links▶

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

**ARTICLE TYPE**

# Synthesis of Unsymmetric Tertiary Amines via Alcohol Amination

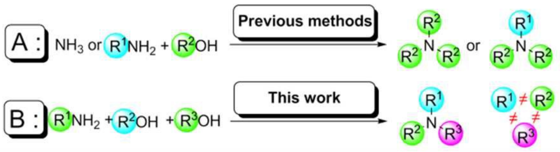
**Shaofeng Pang,[a,b] Youquan Deng[a] and Feng Shi*[a]**

*Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX*

**DOI: 10.1039/b000000x**

**The first one-pot selective-synthesis of unsymmetric tertiary amine is reported by the amination of two types of alcohols with primary amine via the development of a simple CuAlOx-HT catalyst and enables the synthesis of unsymmetric amines in a wide variety of primary amines and alcohols.**

The development of alcohol amination reaction that allow the fast and environmentally compatible generation of secondary amine or tertiary amine as products directly from simple and readily available starting materials is at the forefront of fine chemical synthesis,and it entails a strong potential for industrial developments. In this context, great progress has been made in the search for efficient catalytic processes for the reactions of various amines with primary and even secondary alcohols in the past decade, with state-of-the-art systems reported by the research groups of Williams, Beller, Fujita, Kempe, Crabtree, Peris, Martín-Matute, andothers.[1-8] Among these methods, the amination of alcohols by the use of borrowing hydrogen methodology[9] (also known asthe hydrogen auto transfer process) has long been recognized as a highly atom economical and green method for the production of amines. In the above reports, widely researches and attentions have been focused on the direct synthesis of tertiary aminefrom alcohols via a hydrogen borrowing mechanism. However, the tertiary amines are often derived from one alcohol, and therefore, the amine substituents are with the same structure (Scheme 1, A).[10] The direct transformation of primary amine into unsymmetric tertiary amine is still a challenging reaction (Scheme 1, B).



**Scheme 1.** Symmetric (A) and unsymmetric tertiary amine (B) synthesis.

Generally, the benzylic alcohols are more easily to be activated comparing with aliphatic alcohols.[9] These results inspire us a catalyst for unsymmetric amine synthesis might be developed if it can catalyze the amination of benzylic alcohol in short time, and following further reaction occurred with aliphatic alcohol. In our former report, we had found that the combination of nickel and copper can generate an active catalyst for the amination reaction of both aromatic and aliphatic alcohols.[11] It was less active for the amination reaction of aliphatic alcohol but active enough for aromatic alcohol amination. Therefore, it might a suitable catalyst for the one-pot synthesis of unsymmetric amine with primary amine, and an aromatic and an aliphatic alcohol.

Based on our continuing study in alcohol amination reactions through borrowing-hydrogen methodology,[11,12] here we present our new results of selective synthesis of unsymmetric tertiary amine via the development of a simple CuAlOx-HT catalyst for the one-pot synthsis of unsymmetric tertiary amines (Fig. 1). Unsymmetric tertiary amines with versatile structures can be synthesized with up to 98% yields.

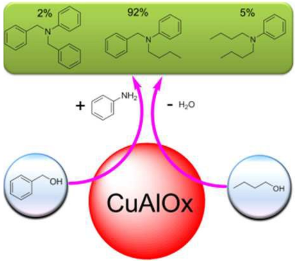
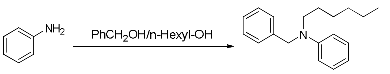


**Figure 1.** An illustration of the CuAlOx-HT catalyst and the alcohol amination reaction for unsymmetric tertiary amine synthesis

The CuAlOx-HT catalysts were prepared by a modified hydro-thermal method using $Al(NO_3)_3$and $Cu(NO_3)_2$ as precursors, and urea as precipitant. After being hydrothermal treated at 120 °C for 24 h, the solid sample was washed by deionized water, dried at 100°C in air and reduced under hydrogen flow at 370 °C. A series of CuAlOx-HT catalysts were obtained and denoted as $Cu_mAl_nOx$-HT (m : n = the molar ratios between Cu and Al). As a catalyst for control reaction, $Cu_2Al_3Ox$-CP was prepared with co-precipitation method. Further on, the CuAlOx-HT catalysts were characterized by XPS, BET, XRD and TEM to explore their structures. The $Cu_{2p}$ spectra suggested that metallic copper formed on all the catalyst surfaces (Table 1 and Fig. S2). In addition, the copper species were entrapped inside the AlOx. The surface Cu : Al ratio of $Cu_2Al_3Ox$-HT was 1 : 16 while the Cu : Al ratio in the bulk catalyst was 1.82 : 3. XRD characterization confirmed the formation of metallic copper but small amount of $Cu_2O$ was observable in catalysts $Cu_2Al_3Ox$-HT and $Cu_1Al_2Ox$-HT (Fig. S3). Nitrogen adsorption-desorption analysis suggested that the addition of AlOx into CuOx results in higher BET surface area (Table 1 and Fig. S4). The BET surface area of CuOx was 7 $m^2$/g while it reached 226 $m^2$/g when the Cu : Alratio was 1 : 5 ($Cu_1Al_5Ox$-HT). Next, the CuAlOx-HT catalysts were characterized using TEM (Fig. 2). The TEM images and line-scan EDS analysis of different catalysts indicated that the copper species were well mixed with the AlOx phase.

**Table 1.** Results of catalyst screening.[a]



| Entry | Catalyst | A[b] | B[c] | C[d] | Con./% [e] | Y. /%[f] |
|---|---|---|---|---|---|---|
| 1 | AlOx-HT | ---- | ---- | 231 | <1 | ---- |
| 2 | $Cu_1Al_5Ox$-HT | 0.54:5 | 1:18 | 226 | 84 | 47 |
| 3 | $Cu_1Al_3Ox$-HT | 0.71:1 | 1:25 | 192 | 90 | 63 |
| 4 | $Cu_1Al_2Ox$-HT | 0.94:2 | 1:24 | 148 | 94 | 80 |
| 5 | $Cu_2Al_3Ox$-HT | 1.82:3 | 1:16 | 120 | 99/96[g] | 88/82[g] |
| 6 | $Cu_2Al_1Ox$-HT | 1.44:1 | 1:20 | 78 | 69 | 23 |
| 7 | $Cu_5Al_1Ox$-HT | 3.35:1 | 1:18 | 37 | 27 | ---- |
| 8 | CuOx-HT | ---- | ---- | 7 | <1 | ---- |
| 9 | $Cu_2Al_3Ox$-CP | 1.8:3 | 1:6 | 145 | 99 | 20 |
| 10 | NiCuFeOx | ---- | ---- | 124 | 89 | 34 |

[a] aniline (0.5 mmol), benzyl alcohol (0.55 mmol), 1-hexanol (0.55 mmol), toluene (1 mL), catalyst (35 mg), 160 ºC (reaction temperature), 24h, Ar. [b] the ratios of copper and aluminium in the bulk catalyst determined by ICP-AES. [c] the ratios copper and aluminium on the catalyst surface determined by XPS. [d] BET surface area ($m^2$/g). [e] conversion of aniline determined by GC-MS. [f] isolated yield of N-benzyl-N-hexyl aniline. [g] the catalyst was reused at the 2nd run.

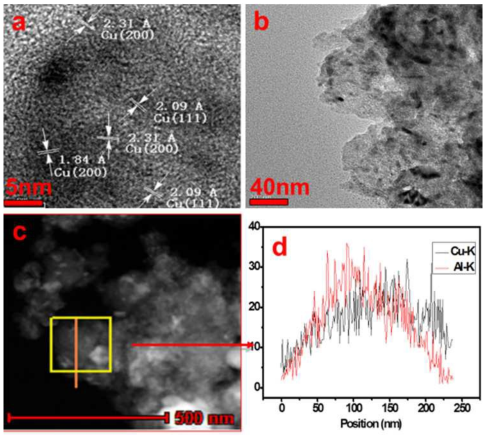
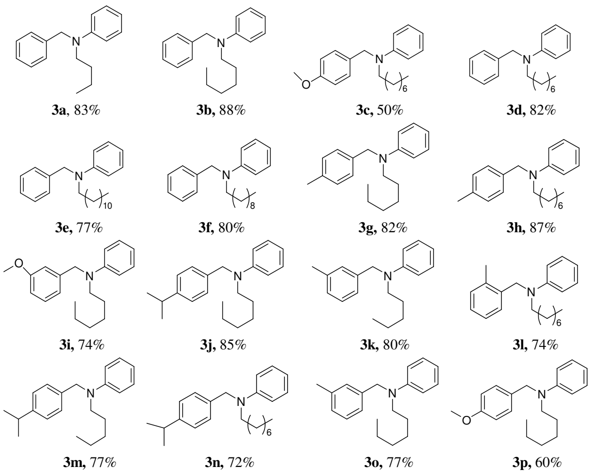


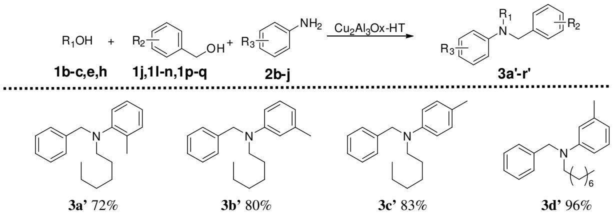
**Figure 2.** TEM (a), HR-TEM (b), HAADF (d) andline-scan EDS analysis (d) images of catalyst $Cu_2Al_3Ox$-HT.

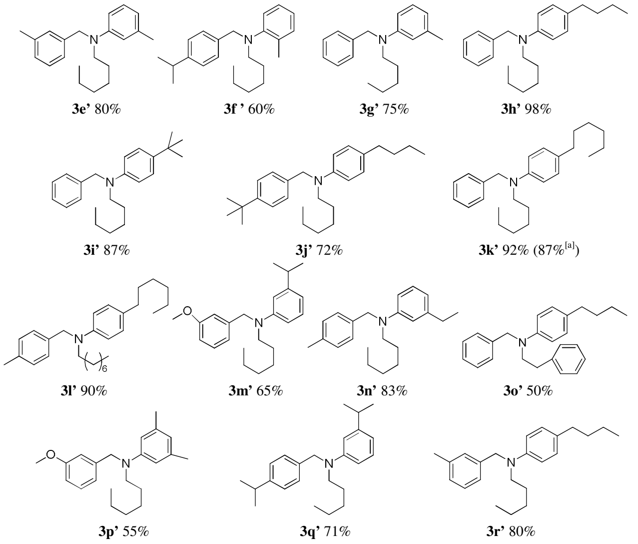
Then, the amination reaction of aniline in the presence of benzyl alcohol and 1-hexanol was chosen as the model reaction to explore the reactivity of the CuAlOx-HT catalysts. Clearly, no reaction was observed if AlOx was used as catalyst directly without the addition of copper species (Table 1, entry 1). With the increasing of Cu : Al ratios in the catalysts, the catalytic performance and also the selectivity to N-benzyl-N-hexyl aniline were improved and 99% conversion of aniline was achieved when $Cu_2Al_3Ox$-HT was used as the catalyst, which resulted in 88% isolated yield of N-benzyl-N-hexyl aniline (Table 1, Entries 2-5). However, both the conversion of aniline and the selectivity of N-benzyl-N-hexyl aniline were decreased if the Cu :Al ratio were further increased. The conversion was only 27% and no N-benzyl-N-hexyl aniline was generated if $Cu_5Al_1Ox$-HT or CuOx-HT was employed (Table 1, Entries 6-8). In addition, $Cu_2Al_3Ox$-CP was used as the catalyst under the same reaction conditions and 99% aniline conversion was observed while the selectivity to N-benzyl-N-hexyl aniline was only 20% (Entry 9). In consideration of the characterization results, it can be imagined that the co-presence of copper and aluminium is important to gain high activity. The suitable Cu : Al ratio to gain high activity may be close to 2 : 3. In addition, the structure of the catalyst, i.e., the Cu : Al ratio of the catalyst and the catalyst activity, decides the product distribution. Higher selectivity to the unsymmetric tertiary amines can be achieved if the AlOx were enriched on the surface of the active CuAlOx-HT catalysts. As a control reaction, a NiCuAlOx catalyst was prepared with the same procedure as the former report[11] and its activity in the one-pot synthesis of unsymmetric amine synthesis was tested. However, the yield to N-benzyl-N-hexyl aniline was only 34% although 89% aniline conversion was obtained (Entry 10). The major products were secondary amines and symmetric tertiary amines. Thus, Thus, the specific structure of the CuAlOx-HT catalyst is essential to gain the good catalytic performance, if taking the results using CuAlOx-CP as catalyst together, it can be concluded that the catalytic performance of the CuAlOx-HT catalyst is unique in the one-pot synthesis of unsymmetric amines.

Following, the catalytic performance of the CuAlOx-HT catalyst in the alcohol amination reactions with respect to amine and alcohol derivatives was explored. First, the amination reactions of aniline with different aromatic and aliphatic alcohols were tested (Scheme2). Various structurally diverse benzyl alcohol derivatives, and aliphatic alcohols were reacted with aniline to yield the corresponding tertiary amines in excellent yields (**3a-3p**). Commonly the yields to the desired products were ~80%. The substituents at different positions on the benzyl alcohol did not significantly affect the reaction rate. Also, aliphatic alcohols with different carbon numbers produced high yields of the tertiary amines, demonstrating the high versatility of the current methodology.



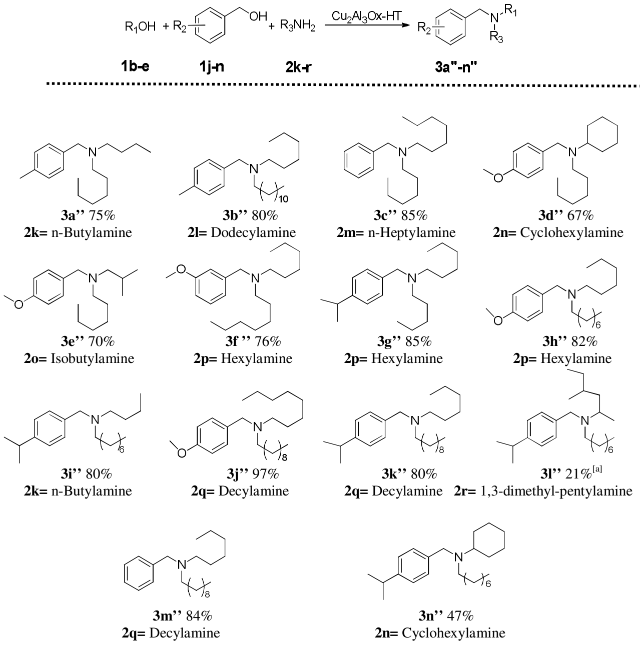
**Scheme 2.** Results of aniline N,N-dialkylation with aryl/aliphatic alcohols. All the numbers are isolated yields. For the reaction conditions, see Table 1, entry 5.





**Scheme 3.** Results of N,N-dialkylation of aniline derivatives with aryl/aliphatic alcohols. All the numbers are isolated yields. [a] The catalyst was reused at the $2^{nd}$run. For the reaction conditions, see Table 1, entry 5.

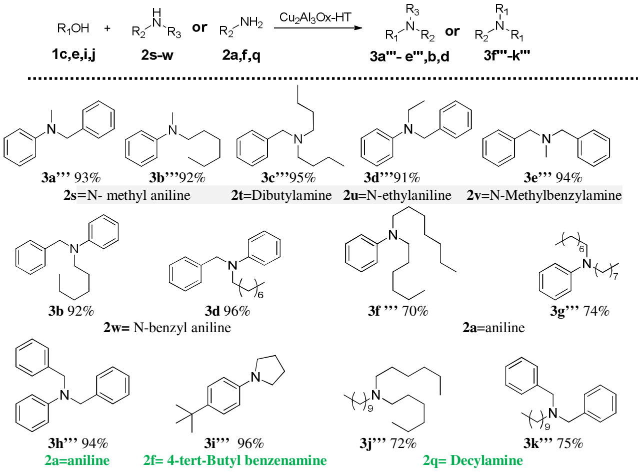
The reaction also proceeded successfully with other structurally and electronically diverse aniline derivatives (Scheme 3, **3a'-3r'**). Clearly, excellent results were obtained and the yields to the unsymmetric tertiary amines reached 96%. It should be mentioned that the substituent at the ortho-position had a substantial effect on the reaction.



**Scheme 4.** Results of N,N-dialkylation of aniline derivatives with aliphatic/aliphatic alcohols. All the numbers are isolated yields. For the reaction conditions, see Table 1, entry 5. [a] Determined by GC-MS.

The applying of aliphatic amines as starting material should be more challenging due to the potential reaction of self-coupling. Nevertheless, the results suggest that CuAlOx-HT is also an excellent catalyst for the N-alkylation of aliphatic amines with two different kinds of alcohols (Scheme 4). Up to 97% yields of the unsymmetric tertiary amines can be obtained (**3a''-3n''**). The reaction is influenced remarkably by the substituent, too. The yield of **3l''** was only 21% when 1,3-dimethylpentylamine, 1-octanol and cumylalcohol were used as the starting materials. It needs to be mentioned that the reaction can not progress well if two aromatic or two aliphatic alcohols were used as the alkylation reagents. Also, if aromatic amines contain electron–poor groups, i.e., F or Cl, were used as the starting materials, almost no desired unsymmetric amines were detectable. Even though, this work offers a synthetically powerful method for the construction of unsymmetrical tertiaryamine.

Meanwhile, in order to show the generality of the current methodology, typical reactions for symmetric or unsymmetric amine synthesis were performed (Scheme 5). Clearly, excellent results can be obtained if secondary amines with different structures were used as the staring materials and up to 96% isolated yields to unsymmetric amines were obtained. Also, symmetric tertiary amines with 70-96% isolated yields can be achieved if primary amine and alcohol were used. These results suggested that the current catalyst is active for the alcohol amination reactions to synthesize versatile tertiary amines with different structures using different amines and alcohols.



**Scheme 5.** Results of symmetric or unsymmetric tertiary amine synthesis with primary and secondary amines as starting materials. All the numbers are isolated yields. For the reaction conditions, see Table 1, entry 5.

In order to clarify the reaction pathway for the unsymmetric tertiary amine synthesis, the reaction of aniline with benzyl alcohol and 1-hexanol was traced by GC-MS with Cu$_2$Al$_3$Ox-HT as catalyst (Fig. 3). As imagined, N-benzylideneaniline was formed at the initial stage. 71% N-benzyl aniline and 13% N-hexyl aniline was produced in 3 h. At this moment, there is no tertiary amine was generated. Following, the desired product, i.e., N-benzyl-N-hexyl aniline was observable and its selectivity was 18% at 5 h. With the increasing of the reaction time, more N-benzyl-N-hexyl aniline was formed and the amount of N-benzyl aniline decreased simutaneously. Finally nearly 90% N-benzyl-N-hexyl aniline was produced in 24 h.

Based on the above discussions, this catalytic should be sensitive to the structure of the starting materials. In another word, the steric effect should be remarkable. So a series of control reactions were performed to prove it. First, in the reaction of aniline with 1-amyl alcohol and benzyl alcohol derivatives, it can be seen that the size and position of the substituents influenced the yields of the desired products significantly. The yield of **a1** was 81% while only 14% **a4** was obtained. Similar rule was observed if the position of methyl group on aniline was changed. For example, the yields of **b1**, **c1** and **d1** were 82-83% but only 32-50% yields of **b2**, **c2** and **d2** were obtained.

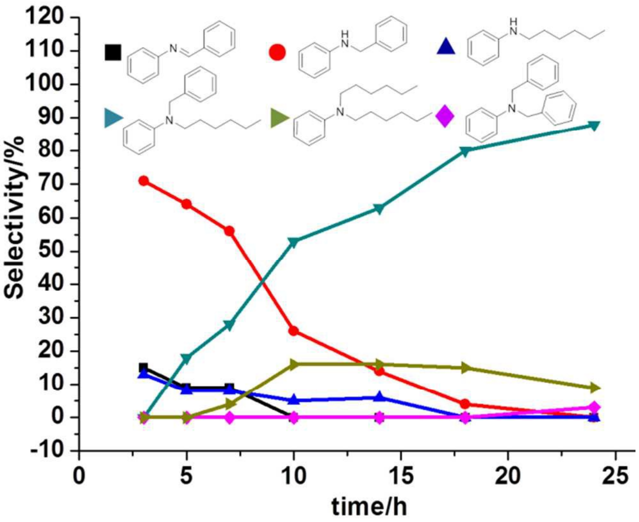
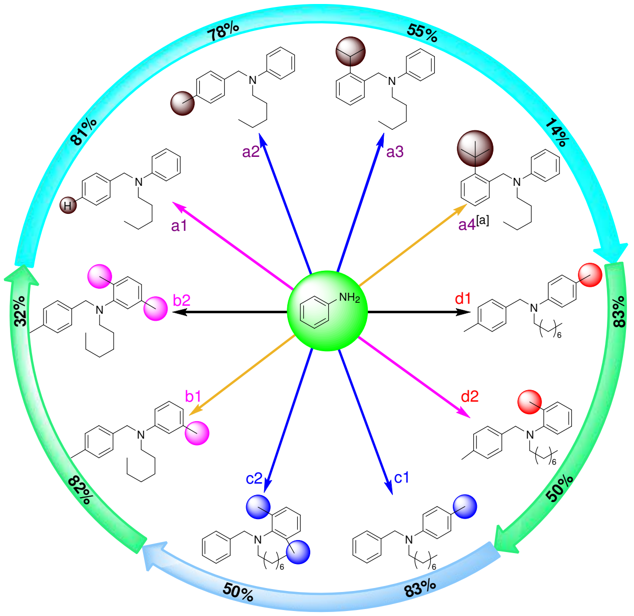


**Figure 3.** Reaction of aniline with benzylalcohol and 1-hexanol vs time



**Scheme 5.** Results of steric effect exploration. [a] Values are yields of the desired products determined by GC-MS.

In conclusion, a simple CuAlOx-HT catalyst was successfully developed for the selective synthesis of unsymmetric tertiary amines by finely controlling its activity and structure with hydrothermal method. This novel catalyst enables the synthesis of unsymmetric amines in a wide variety of primary amines and alcohols. To the best of our knowledge, this is the first example for the efficient one-pot synthesis of unsymmetric tertiary amines. It offers a clean and economic route for unsymmetric tertiary amine synthesis and it may promote the development of amine chemistry.

The authors acknowledge financial support from the National Natural Science Foundation of China (21303228).

## Notes and references

[a]*State Key Laboratory for Oxo Synthesis and Selective Oxidation, Centre for Green Chemistry and Catalysis, Lanzhou Institute of ChemicalPhysics, Chinese Academy of Sciences. E-mail: fshi@licp.cas.cn*
[b]*University of Chinese Academy of Sciences, Beijing, 100049 , China*

† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

1 (a) O. Saidi, A. J. Blacker, M. M. Farah, S. P. Marsden, J. M. J. Williams, *Chem. Commun*. 2010, **46**, 1541-1543; (b) M. H. S. A. Hamid, J. M. J. Williams, *Chem. Commun*. 2007, **7**,725-727; (c) M. H. S. A. Hamid, J. M. J. Williams, *TetrahedronLett*. 2007, **48**, 8263-8265; (d) M. H. S. A. Hamid, C. L. Allen, G. W. Lamb, A. C. Maxwell, H. C. Maytum, A. J. A. Watson, J. M. J. Williams, *J. Am. Chem. Soc*. 2009, **131**, 1766-1774.

2 (a) D. Hollmann, A. Tillack, D. Michalik, R. Jackstell, M. Beller, *Chem. Asian J*. 2007, **2**, 403-410; (b) A. Tillack, D. Hollmann, K. Mevius, D. Michalik, S. Bähn, M. Beller, *Eur. J. Org. Chem*. 2008, **28**, 4745-4750; (c) F. Shi, M. K. Tse, X. Cui, D. Gordes, D. Michalik, K. Thurow, Y. Deng, M. Beller, *Angew. Chem. Int. Ed*. 2009, **48**, 5912-5915; (d) M. Zhang, S. Imm, S. Bähn, H. Neumann, M. Beller, *Angew. Chem. Int. Ed*. 2011, **50**, 11197-11201.

3 (a) K. Fujita, K. Yamamoto, R. Yamaguchi, *Org. Lett*. 2002, **4**, 2691-2694; (b) K. Fujita, Z. Li, N. Ozeki, R. Yamaguchi, *Tetrahedron Lett*. 2003, **44**, 2687-2690; (c) K. Fujita, T. Fujii, R. Yamaguchi, *Org. Lett*. 2004, **6**, 3525-3528; (d) K. Fujita, Y. Enoki, R. Yamaguchi, *Tetrahedron*2008, **64**, 1943-1954; (e) R. Kawahara, K. Fujita, R. Yamaguchi, *J. Am. Chem. Soc*. 2010, **132**, 15108-15111; (f) R. Kawahara, K. Fujita, R. Yamaguchi, *Adv. Synth. Catal*. 2011, **353**, 1161-1168.

4 (a) B. Blank, M. Madalska, R. Kempe, *Adv. Synth. Catal*. 2008, **350**, 749-758; (b) B. Blank, S. Michlik, R. Kempe, *Adv. Synth. Catal*. 2009, **351**, 2903-2911; (c) B. Blank, S. Michlik, R. Kempe, *Chem. Eur. J*. 2009, **15**, 3790-3799; (d) S. Michlik, R. Kempe, *Chem. Eur. J*. 2010, **16**, 13193-13198; (e) S. Michlik, T. Hille, R. Kempe, *Adv. Synth. Cata*. 2012, **354**, 847-862.

5 D. Gnanamgari, E. L. O. Sauer, N. D. Schley, C. Butler, C. D. Incarvito, R. H. Crabtree, *Organometallics*2009, **28**, 321-325.

6 A. Prades, R. Corberán, M. Poyatos, E. Peris, *Chem. Eur. J*. 2008, **14**, 11474-11479.

7 (a) I. Cumpstey, S. Agrawal, E. K. Borbas, B. Martín-Matute, *Chem. Commun*. 2011, **47**, 7827-7829; (b) S. Agrawal, M. Lenormand, B. Martín-Matute, *Org. Lett*. 2012, **14**, 1456-1459; (c) A. Bartoszewicz, R. Marcos, S. Sahoo, A. K. Inge, X. Zou, B. Martín-Matute, *Chem. Eur. J*. 2012, **18**, 14510-14519.

8 (a) C. Gunanathan, D. Milstein, *Angew. Chem. Int. Ed*. 2008, **47**, 8661-8664; (b) K. Yamaguchi, J. He, T.Oishi, N. Mizuno, *Chem. Eur. J*. 2010, **16**, 7199-7207; (c) R. N. Monrada, R. Madsen, *Org. Biomol. Chem*. 2011, **9**, 610-615.

9 (a) M. H. S. A. Hamid, P. A. Slatford, J. M. J. Williams, *Adv. Synth. Catal*. 2007, **349**, 1555-1575; (b) T. D. Dixon, M. K. Whittlesey, J. M. J. Williams, *Dalton Trans*. 2009, **5**, 753-762; (c) G. E. Dobereiner, R. H. Crabtree, *Chem. Rev*. 2010, **110**, 681-703; (d) G. Guillena, D. J. Ramón, M. Yus, *Chem. Rev*. 2010, **110**, 1611-1641; (e) A. J. A. Watson, J. M. J. Williams, *Science*2010, **329**, 635-636; (f) S. Bähn, S. Imm, L. Neubert, M. Zhang, H. Neumann, M. Beller, *ChemCatChem*2011, **3**, 1853-1864; (g) S. Pan, T. Shibata, *ACSCatal*. 2013, **3**, 704-712.

10 (a) Y. Zhang, C. Lim, D. Sim, H. Pan, Y. Zhao, *Angew. Chem. Int. Ed*. 2014, **53**, 399-403; (b) A. Tlili, F. Monnier, M. Taillefer, *Chem. Commun*. 2012, **48**, 6408-6410; (c) D. Zhao, J. Zhang, Z. Xie, *Angew. Chem. Int. Ed*. 2014, **53**, 12902-12906.

11 X. Cui, X. Dai, Y. Deng, F. Shi, *Chem. Eur. J*. 2013, **19**, 3665-3675.

12 (a) H. Yang, X. Cui, Y. Deng, F. Shi, *Nat. Commun*., 2015,**6**, ncomms7478; (b) X. Cui, X. Dai, Y. Zhang, Y. Deng, F. Shi, *Chem. Sci*. 2014, **5**, 649-655; (c) M. Pera-Titus, F. Shi, *ChmSusChem*, 2014, **7**, 720-722; (d) X. Cui, Y. Deng, F.Shi, *ACS Catal*. 2013, **3**, 808-811; (e) Y. Zhang, X. Cui, F. Shi, Y.Deng, *Chem. Rev*. 2012, **112**, 2467-2505; (f) X. Cui, F. Shi, Y. Deng, *Chem. Commun*. 2012, **48**, 7586-7588.