



**HAL**  
open science

# Vicinal $\alpha,\beta$ -Functionalizations of Amines: Cyclization Versus Dehydrogenative Hydrolysis

Fan Jiang, Mathieu Achard, Christian Bruneau

► **To cite this version:**

Fan Jiang, Mathieu Achard, Christian Bruneau. Vicinal  $\alpha,\beta$ -Functionalizations of Amines: Cyclization Versus Dehydrogenative Hydrolysis. *Chemistry - A European Journal*, 2015, 21 (41), pp.14319–14323. 10.1002/chem.201502431 . hal-01231155

**HAL Id: hal-01231155**

**<https://univ-rennes.hal.science/hal-01231155>**

Submitted on 15 Jun 2022

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

# Vicinal $\alpha,\beta$ -Functionalizations of Amines : Cyclization Vs Dehydrogenative Hydrolysis

Fan Jiang, Mathieu Achard,\* and Christian Bruneau

[a] Dr. F. Jiang, Dr. M. Achard, Dr. C. Bruneau  
UMR6226 CNRS, Institut des Sciences Chimiques de Rennes, Université de Rennes1, OMC : Organometallics : Materials and Catalysis  
Campus de Beaulieu, 35042 Rennes Cedex (France)  
Fax: (+33) 223236939  
E-mail: mathieu.achard@univ-rennes1.fr

**Abstract:** Direct vicinal  $\alpha,\beta$ -difunctionalization of tertiary cyclic amines is achieved in the presence of ruthenium or iridium transition metal complexes featuring phosphine-sulfonate chelates. By varying the reaction conditions,  $\alpha$ -alkylated lactams were obtained *via* a formal dehydrogenative hydrolysis where one molecule of hydrogen is generated from water.

In regard to their wide applications in industry as monomers or as agrochemicals and pharmaceuticals, amines and amides constitute valuable intermediates and the development of straightforward and environmentally benign approaches for the preparation of amines and related alkaloids is highly desired and at the centre of active research activities.<sup>[1]</sup> Hydrogen autotransfers known as hydrogen borrowing or hydrogen shuttling have found interesting applications in synthesis.<sup>[2]</sup> Since the pioneering discoveries of Guerbet who demonstrated that the treatment of alcohols with their corresponding alkoxide base led to the formation of the  $\beta$ -dimeric alcohols,<sup>[3]</sup> the use of homogeneous transition metal catalysts broadened the scope of applicability of this transformation.<sup>[2,4]</sup> These processes are not limited to alcohols or carbonyl derivatives and similar methodology can be judiciously employed with alcohols and amines to perform *N*-alkylation giving the corresponding amines.<sup>[2,5-7]</sup> A short time after the pioneering results of Watanabe<sup>[5b]</sup> and Grigg<sup>[5a]</sup> on *N*-alkylation of amines with alcohols, the use of the well-defined ruthenium complex  $\text{RuH}_2(\text{PPh}_3)_4$  enabled the formation of pyrrolidine and piperidine from aminoalcohols.<sup>[5c]</sup> These breakthroughs highlighted that hydrogen borrowing transformations match biological pathways and afford excellent alternatives to traditional approaches involving the use of halogenated reagents or masked/protected carbonyl derivatives to access similar compounds. Metallo-catalyzed hydrogen transfer processes can also involve iminium and enamine intermediates to successfully perform deuterations and dealkylations of tertiary amines.<sup>[8]</sup> Interestingly, during dealkylation of tertiary amines, Murahashi demonstrated that the use of water and acid led to the corresponding secondary amine and aldehyde arising from a dehydrogenative hydrolysis where water act as a formal oxidant.<sup>[8c]</sup> Several groups judiciously took advantage of these generated iminium/enamine intermediates in the presence of homogeneous catalysts to perform  $\alpha$ -functionalization of tertiary cyclic amines,<sup>[9]</sup>  $\alpha,\beta$ -deuteration of amines<sup>[10]</sup>, including some enantioselective approaches.<sup>[11]</sup> Well-defined ruthenium complexes enabled lactam formation from secondary amines and water.<sup>[12,13]</sup> However to the best of our knowledge, reports dealing on direct  $\alpha,\beta$ -difunctionalization of saturated tertiary cyclic amines via hydrogen transfers are so far unknown.<sup>[14]</sup> These transformations are very appealing and would well-complement recent organic neutral redox transformations which require the presence of functional group on the starting molecule to trigger such functionalization.<sup>[15]</sup> In 2010, we demonstrated that transition metal complexes-catalyzed hydrogen transfers can be applied in the preparation of various  $\beta$ -alkylated amines through the transient formation of enamine and  $\alpha,\beta$ -unsaturated iminium intermediates.<sup>[16]</sup> More recently we also showed that the generation of vinamidinium intermediates<sup>[17]</sup> arising from 1,3-propanediols and amines led to various julolidines through electrocyclization/ $\beta$ -alkylation sequence.<sup>[18]</sup>

Here we disclose the application of our catalytic systems with the use of 2-hydroxybenzaldehyde derivatives and cyclic tertiary amines to afford straightforward access to the corresponding functionalized cyclic hemiaminal ethers<sup>[19]</sup> *via* vicinal  $\alpha,\beta$ -difunctionalization. The unprecedented formation of  $\alpha$ -alkylated lactams from the starting tertiary cyclic amines is also successfully achieved by a formal *endo*-cyclic dehydrogenative hydrolysis involving the iminium intermediates (Figure 1).

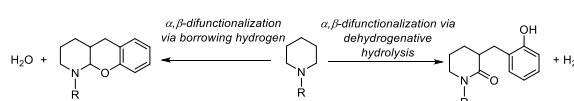


Figure 1. Selective  $\alpha,\beta$ -difunctionalizations.

We first started our investigations on the reaction of salicylaldehyde **1a** to access to the corresponding cyclic hemiaminal ether **3aa**. Due to its lower reactivity and higher stability toward dealkylation, *N*-phenylpiperidine **2a** was initially

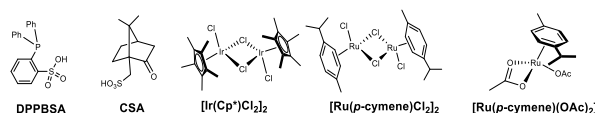
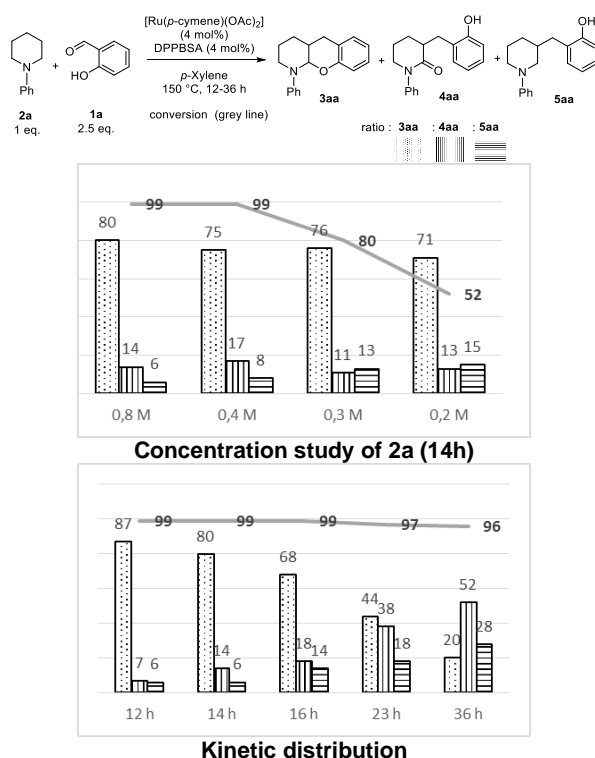


Figure 2. Metal precursors and ligands used in this study.

evaluated (Figure 3). As we previously reported, arene ruthenium complexes embedded with phosphine-sulfonate and bearing chloride sigma ligand  $[\text{Ru}(\text{p-cymene})(\text{DPPBS})\text{Cl}]$ <sup>[16a]</sup> exhibited low activity during the  $\beta$ -alkylation of *N*-phenylpiperidine with aldehydes.<sup>[16b]</sup>

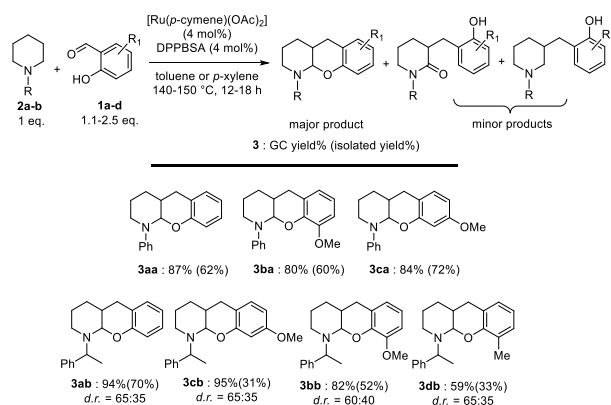
Similar low reactivity was also observed with salicylaldehyde **1a** and *N*-phenylpiperidine **2a**. To our delight, the replacement of  $[\text{Ru}(\textit{p}\text{-cymene})\text{Cl}_2]_2$  by  $[\text{Ru}(\textit{p}\text{-cymene})(\text{OAc})_2]$ <sup>[20]</sup> along with DPPBSA (Figure 2) afforded



**Figure 3.**  $\alpha,\beta$  functionalization of *N*-phenyl piperidine **2a**.

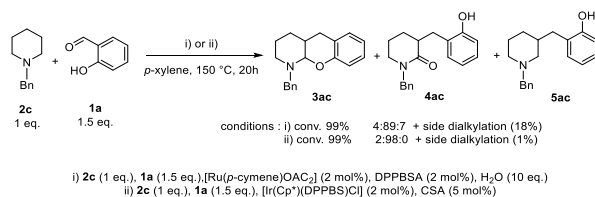
the expected cyclized hemiaminal ether **3aa** and therefore this reaction was selected for further optimization (Figure 3). Analysis of the reaction of *N*-phenylpiperidine **2a** with salicylaldehyde **1a** at 150 °C in the presence of  $[\text{Ru}(\textit{p}\text{-cymene})\text{OAc}]_2$  along with DPPBSA revealed the favored formation of the expected cyclized hemiaminal ether **3aa** together with the  $\beta$ -alkylated lactam **4aa** and the reduced uncyclized  $\beta$ -alkylated amine **5aa** arising from formal C $\beta$ -alkylation.<sup>[16b]</sup> Owing to the presence of a rigid backbone on salicylaldehyde **1a** or to a concerted pathway, hemiaminal ether **3aa** was exclusively obtained as a *cis* isomer. Concentrations above 0.4 M were found to be crucial to observe complete conversion whereas the ratio of **3**:**4**:**5** was comparable at lower concentration. The use of an excess of salicylaldehyde was beneficial to ensure selective cyclization and lower amount of aldehyde resulted in higher ratio of the reduced product **5aa**. Kinetic dependent distribution was also noticed and shorter reaction times favored the product **3aa** arising from borrowing process. Although a mixture 44:38:18 of **3aa**:**4aa**:**5aa** was observed after 23 hours reaction time, these results clearly demonstrated that the lactam **4aa** and reduced compound **5aa** arose from a catalyzed intermolecular hydrogen transfer process from **3aa** and the generated water. Following this optimization, the scope for the hemiaminal ethers **3** formation was next evaluated (Chart 1). Thus, reactions of various 2-hydroxybenzaldehydes **1** with *N*-phenylpiperidine **2a** resulted in the formation of hemiaminal ethers **3aa-ca** in up to 87% GC yield. Subsequent purification by column chromatography led to the isolation of **3aa**, **3ba** and **3ca** in 62, 60 and 72% yields, respectively. The use of the *N*-substituted piperidine **2b** bearing the phenylethyl substituent required modification of the reaction conditions involving the use of toluene as solvent with lower amount of 2-hydroxybenzaldehydes **1a-d** (1.1 eq.) to ensure selective hemiaminal formation. Due to the vicinity of the chiral *N*-substituent, up to 65:35 diastereoisomeric ratio was obtained in these cases. The results obtained in Chart 1 demonstrated that the difference of reactivity between **2a** and **2b** takes origin from the corresponding stability/reactivity of the resulting hemiaminal ethers toward hydrolysis.<sup>[21]</sup>

After demonstrating that cyclizations were successful, we next investigated the possibility to selectively produce the corresponding lactam products **4** and thus to prevent side reduction accounting on compounds **5**. For this task, we first evaluated the reaction of *N*-benzylpiperidine **2c** with salicylaldehyde **1a** to selectively form  $\alpha$ -functionalized lactam **4ac** using *p*-xylene as solvent (Scheme 1). Keeping in mind the influence of acidic additives in the pioneering reported results on dehydrogenative hydrolysis or dehydrogenation,<sup>[8c,22]</sup>



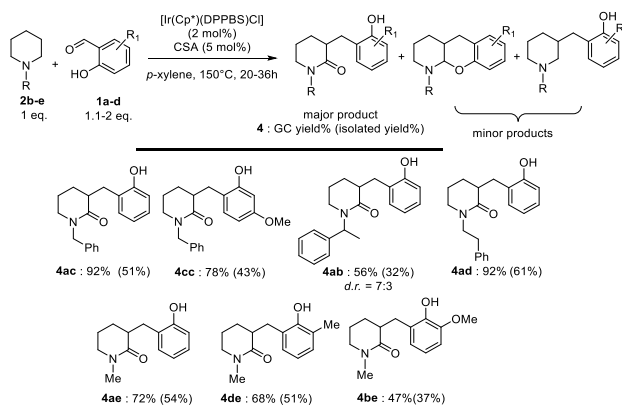
**Chart 1.** Selective hemiaminal ether formation

we postulated that the formation of  $\alpha$ -functionalized lactams would be enhanced by the addition of water or by an external acidic additive.<sup>[12,13]</sup> As results, optimization of the reaction conditions led to the development of two catalytic systems to efficiently produce lactam **4ac**. Using  $[\text{Ru}(p\text{-cymene})(\text{OAc})_2]/\text{DPPBSA}$  catalytic system, addition of extra water in conditions i) had a positive effect toward the formation of lactam **4ac** but side dialkylations occurred. In contrast, the use of the well-defined iridium complex  $[\text{Ir}(\text{Cp}^*)(\text{DPPBS})\text{Cl}]$  along with camphor sulfonic acid was found to be suitable leading to the selective formation of lactam **4ac** and only traces of side dialkylated products were detected demonstrating that an excess of water was not required to ensure selective lactam formation. With our best reaction conditions in hand, the access to various lactams **4** was next investigated (Chart 2). The reaction of various 2-hydroxybenzaldehyde derivatives **1** under dehydrogenative process cleanly afforded lactams **4** in up to 92% GC yield. It is noteworthy that in the case of **2b**, the resulting lactam **4ab** was obtained as two diastereoisomers in a 7:3 ratio and the major diastereoisomer was clearly isolated in



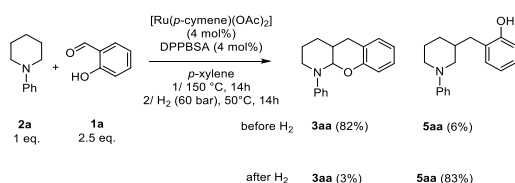
**Scheme 1.** Selective dehydrogenative hydrolysis of **3ac**

32% yield. Lactams arising from *N*-methylpiperidine **2e** were also obtained and successful crystallization of **4ae** confirmed the structure.<sup>[22]</sup> Rationalization of these results was next undertaken. First we postulated that reduced products **5** arose from the in-situ side reduction of hemiaminal **4** with the metal hydride species. Thus we performed tandem cyclization/hydrogenolysis (Scheme 2). Reaction of piperidine **2a** with salicylaldehyde **1a** in the presence of catalytic amount of  $[\text{Ru}(p\text{-cymene})(\text{OAc})_2]/\text{DPPBSA}$  resulted in the formation of a mixture of **3aa/5aa** in 82:6 ratio with complete conversion. Then, the mixture was subjected to hydrogen pressure leading to the selective formation of  $\beta$ -alkylated amine **5aa**, thus demonstrating that the catalytic system was able to reduce hemiaminal ether in the presence of hydrogen source. On the basis of these results, formation of the hemiaminal ethers could arise from the sequential  $\beta$ -alkylation of the generated cyclic enamine **I** with salicylaldehyde **1** to afford the  $\alpha,\beta$ -unsaturated iminium intermediate **II** (Figure 4). Thus, the reduction of this latter by the generated metal hydride species gave the iminium intermediate **III** as zwitterionic and/or cationic species. Under our reaction conditions, **III** might readily undergo a *syn* addition due to the rigidity of the aryl backbone to afford **3** whereas side reduction of **III** in the presence of metal hydride species affords **5**.



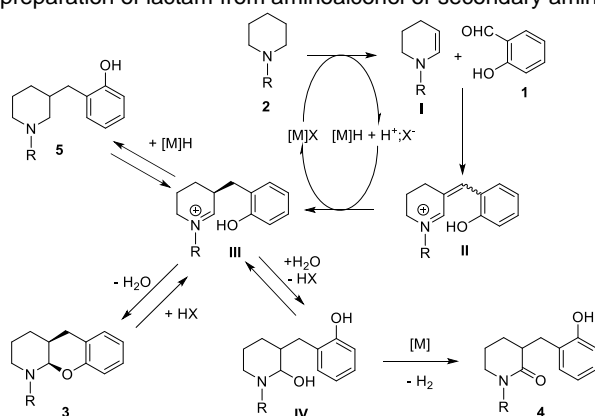
**Chart 2.** Iridium-catalyzed  $\alpha$ -functionalized lactam **4** formation.

Since no unsaturated  $\alpha,\beta$ -unsaturated hemiaminal ethers were detected during these studies, the concerted cycloaddition of **I** and salicylaldehyde is unlikely. Depending on the reaction conditions and the nature of the exocyclic *N*-substituent, protonation of the hemiaminal ether **3** gives back iminium **III** which in the presence of water affords the hemiaminal **IV**. All these



**Scheme 2.** Tandem cyclization/hydrogenolysis.

transformations are assumed to be reversible but longer reaction time and acidic media favor dehydrogenation of **IV** to produce alkylated lactams **4** along with the liberation of one molecule of hydrogen. This last intermediate is in line with the postulated cyclic hemiaminal key intermediate for the preparation of lactam from aminoalcohol or secondary amine.<sup>[12,13]</sup>



**Figure 4.** Rationalized mechanism

In conclusion we have demonstrated that hydrogen transfer catalysts can be judiciously employed to selectively afford not only functionalized amines but functionalized hemiaminal ethers and lactams keeping intact the exocyclic *N*-moiety with generation of water or hydrogen as the only side product. The formation of lactams arose from a formal dehydrogenative hydrolysis of the corresponding hemiaminal ethers. Taken together, these results showed that hydrogen transfer processes enabling the generation of reactive intermediates might open new inspirations for vicinal or attractive distal  $\alpha,\beta$ -functionalization of amines via sequential or multicomponent reactions.

## Acknowledgements

The authors thank the European Union and Synflow consortium (FP-7 integrated project Synflow, NMP-2009-3.2-1 no. 246461; <http://synflow.eu>) for financial support of this project. Thanks are also due to Prof. C. Claver, Prof D. Heller and Dr. A. Igau, for helpful comments.

**Keywords:** Dehydrogenative Hydrolysis • Borrowing Hydrogen • Alkylation • Cyclization • Chelate

- [1] S. A. Lawrence, *Amines: Synthesis, Properties and Applications*, Cambridge University Press 2004.
- [2] a) S. Bähn, S. Imm, L. Neubert, M. Zhang, H. Neumann, M. Beller, *ChemCatChem* **2011**, *3*, 1853; b) J. Moran, M. J. Krische, *Pure Appl Chem* **2012**, *84*, 1729; c) C. Gunanathan, D. Milstein, *Science* **2013**, *341*, 249; d) Q. Yang, Q. Wang, Z. Yu, *Chem. Soc. Rev.* **2015**, *44*, 2305.
- [3] M. Guerbet, *C. R. Acad. Sci.* **1909**, CXLIX, 129.
- [4] a) C. S. Cho, B. T. Kim, T.-J. Kim, S. C. Shim, *J. Org. Chem.* **2001**, *66*, 9020; b) K. Taguchi, H. Nakagawa, T. Hirabayashi, S. Sakaguchi, Y. Ishii, *J. Am. Chem. Soc.* **2004**, *126*, 72; c) G. Cami-Kobeci, J. M. J. Williams, *Chem. Commun.* **2004**, 1072; d) A. P. Da Costa, M. Viciano, M. Sanáu, S. Merino, J. Tejada, E. Peris, B. Broto *Organometallics* **2008**, *27*, 1305; e) R. Yamaguchi, S. Kawagoe, C. Asai, K. -I. Fujita, *Org. Lett.* **2008**, *10*, 181; f) B. Blank, S. Michlik, R. Kempe, *Chem. Eur. J.* **2009**, *15*, 3790; g) D. Gnanamgari, E. L. Sauer, N. D. Schley, C. Butler, C. D. Incarvito, R. H. Crabtree, *Organometallics* **2009**, *28*, 321; h) B. Blank, R. Kempe, *J. Am. Chem. Soc.* **2010**, *132*, 924; i) O. Saidi, A. J. Blacker, M. M. Farah, S. P. Marsden, J. M. J. Williams, *Chem. Commun.* **2010**, 1541; j) Y. Obora, S. Ogawa, N. Yamamoto, *J. Org. Chem.* **2012**, *77*, 9429; k) T. Kuhahara, T. Fukuyama, I. Ryu, *Org. Lett.* **2012**, *14*, 4703; l) J. C. Leung, L. M. Geary, T.-Y. Chen, J. R. Zbieg, M. J. Krische, *J. Am. Chem. Soc.* **2012**, *134*, 15700; m) G. R. M. Dowson, M. F. Haddow, J. Lee, R. L. Wingad, D. F. Wass, *Angew. Chem. Int. Ed.* **2013**, *52*, 9005; n) D. Shen, D. L. Poole, C. C. Shotton, A. F. Kornahrens, M. P. Healy, T. J. Donohe, *Angew. Chem. Int. Ed.* **2015**, *54*, 1642.
- [5] a) R. Grigg, T. R. B. Mitchell, S. Sutthivaiyakit, N. Tongpenyai, *J. Chem.Soc. Chem. Commun.* **1981**, 611; b) Y. Watanabe, Y. Tsujii, Y. Oshugi, *Tetrahedron Lett.* **1981**, *22*, 2667; c) S. -I. Murahashi, K. Kondo, T. Hakata, *Tetrahedron Lett.* **1982**, *23*, 229.
- [6] a) A. Tillack, D. Hollmann, D. Michalik, M. Beller, *Tetrahedron Lett.* **2006**, *47*, 8881; b) C. Gunanathan, D. Milstein *Angew. Chem. Int. Ed.* **2008**, *47*, 8661; c) 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; d) J. He,

- J. W. Kim, K. Yamaguchi, N. Mizuno, *Angew. Chem. Int. Ed.* **2009**, *48*, 9888; e) S. Agrawal, M. Lenormand, B. Martin-Matute, *Org. Lett.* **2012**, *14*, 1456; f) W. M. J. Ma, T. D. James, J. M. J. Williams, *Org. Lett.* **2013**, *15*, 4850; g) D. Pingen, O. Diebolt, D. Vogt, *ChemCatChem* **2013**, *5*, 2905; h) V. R. Jumde, E. Cini, A. Porcheddu, M. Taddei, *Eur. J. Org. Chem.* **2015**, 1068; i) V. R. Jumde, L. Gonsalvi, A. Guerriero, M. Peruzzini, M. Taddei, *Eur. J. Org. Chem.* **2015**, 1829.
- [7] a) K. -I. Fujita, T. Fuji, R. Yamaguchi, *Org. Lett.* **2004**, *6*, 3525; b) G. Cami-Kobeci, J. M. J. Williams, *Chem. Commun.* **2004**, 1072; c) A. P. Da Costa, M. Viciano, M. Sanáu, S. Merino, J. Tejada, E. Peris, B. Broyo *Organometallics* **2008**, *27*, 1305; d) R. Yamaguchi, S. Kawagoe, C. Asai, K. -I. Fujita, *Org. Lett.* **2008**, *10*, 181; e) B. Blank, S. Michlik, R. Kempe, *Chem. Eur. J.* **2009**, *15*, 3790; f) D. Gnanamgari, E. L. Sauer, N. D. Schley, C. Butler, C. D. Incarvito, R. H. Crabtree, *Organometallics* **2009**, *28*, 321; g) O. Saidi, A. J. Blacker, M. M. Farah, S. P. Marsden, J. M. J. Williams, *Chem. Commun.* **2010**, 1541; h) S. Michlik, R. Kempe, *Chem. Eur. J.* **2010**, *16*, 13193; i) R. Kawahara, K. -I. Fujita, R. Yamaguchi, *J. Am. Chem. Soc.* **2010**, *132*, 15108; j) M. A. Berliner, S. P. A. Dubant, T. Makowski, K. Ng, B. Sitter, C. Wager, Y. Zhang, *Org. Process. Res. Dev.* **2011**, *15*, 1052; k) J. Norinder, A. Börner, *ChemCatChem* **2011**, *3*, 1407; l) R. Kawahara, K. -I. Fujita, R. Yamaguchi, *Adv. Synth. Catal.* **2011**, *353*, 1161; m) P. Qu, C. Sun, J. Ma, F. Li, *Adv. Synth. Catal.* **2014**, *356*, 447; n) S. Ruch, T. Irrgang, R. Kempe, *Chem. Eur. J.* **2014**, *20*, 13279.
- [8] a) N. Yoshimura, I. Moritani, T. Shimamura, S. I. Murahashi, *J. Am. Chem. Soc.* **1973**, *95*, 3038; b) S. -I. Murahashi, T. Hirano, T. Yano, *J. Am. Chem. Soc.* **1978**, *100*, 348; c) S. -I. Murahashi, T. Watanabe, *J. Am. Chem. Soc.* **1979**, *101*, 7429.
- [9] a) I. Jovel, S. Prateptongkum, R. Jackstell, N. Vogl, C. Weckbecker, M. Beller, *Chem. Commun.* **2010**, 46, 1956; b) X. -Z. Shu, Y. -F. Yang, X. -F. Xia, K. -G. Ji, X. -Y. Liu, Y. -M. Liang, *Org. Biomol. Chem.* **2010**, *8*, 4077.
- [10] L. Neubert, D. Michalik, S. Bähn, S. Imm, H. Neumann, J. Atzrodt, V. Derdau, W. Holla, M. Beller, *J. Am. Chem. Soc.* **2012**, *134*, 12239.
- [11] a) A. E. Putra, Y. Oe, T. Ohta, *Eur. J. Org. Chem.* **2013**, 6146; b) Z. -Q. Rong, Y. Zhang, R. H. Bing Chua, H. -J. Pan, Y. Zhao, *J. Am. Chem. Soc.* **2015**, *137*, 4944.
- [12] J. R. Kushnudinova, Y. Ben-David, D. Milstein, *J. Am. Chem. Soc.* **2014**, *136*, 2998.
- [13] a) T. Naota, S. I. Murahashi, *Synlett* **1991**, 693; b) K. -I. Fujita, Y. Takahashi, M. Owaki, K. Yamamoto, R. Yamaguchi, *Org. Lett.* **2004**, *6*, 2785; c) L. U. Nordstrøm, H. Vogt, R. Madsen, *J. Am. Chem. Soc.* **2008**, *130*, 17672; d) A. Nova, D. Balcells, N. D. Schley, G. E. Dobreiner, R. H. Crabtree, O. Eisenstein, *Organometallics* **2010**, *29*, 6548; e) S. Muthaiah, S. C. Ghosh, J.-E. Jee, C. Chen, J. Zhang, S. H. Hong, *J. Org. Chem.* **2010**, *75*, 3002; f) D. Pingen, D. Vogt, *Catal. Sci. Technol.* **2014**, *4*, 47.
- [14] For a related oxidative process involving platinum see : X. -F. Xia, X. -Z. Shu, K. -G. Ji, Y. -F. Yang, A. Shaukat, X. -Y. Liu, Y. -M. Liang, *J. Org. Chem.* **2010**, *75*, 2893.
- [15] W. Chen, YK. Kang, R. G. Wilde, D. Seidel, *Angew. Chem. Int. Ed.* **2014**, *53*, 5179.
- [16] a) B. Sundararaju, Z. Tang, M. Achard, G. V. M. Sharma, C. Bruneau, *Adv. Synth. Catal.* **2010**, *352*, 3141; b) B. Sundararaju, M. Achard, G. V. M. Sharma, C. Bruneau, *J. Am. Chem. Soc.* **2011**, *133*, 10340; c) K. Yuan, F. Jiang, M. Achard, C. Bruneau, *Angew. Chem. Int. Ed.* **2012**, *51*, 8876.
- [17] a) C. Jutz, R. M. Wagner, *Angew. Chem. Int. Ed.* **1972**, *11*, 315; b) C. Jutz, R. M. Wagner, H. -G. Löbering, *Angew. Chem. Int. Ed.* **1974**, *13*, 737.
- [18] A. Labed, F. Jiang, I. Labed, A. Lator, M. Peters, M. Achard, A. Kabouche, Z. Kabouche, G. V. M. Sharma, C. Bruneau, *ChemCatChem* **2015**, *7*, 1090.
- [19] For the reactivity of cyclic hemiaminal ethers see: a) I. D. Jurberg, B. Peng, E. Wöstefeld, M. Wasserloos, N. Maulide, *Angew. Chem. Int. Ed.* **2012**, *51*, 1950.
- [20] E. Kossoy, Y. Diskin-Posner, G. Leitun, D. Milstein, *Adv. Synth. Catal.* **2012**, *354*, 497.
- [21] a) J. Sandoval-Lira, L. Fuentes, L. Quintero, H. Höpfl, J. M. Hernandez-Perez, J. L. Teran, F. Sartillo-Piscil, *J. Org. Chem.* **2015**, *80*, 4481; b) J. Miro, M. Sanchez-Rosello, J. Gonzales, C. del Pozo, S. Fustero, *Chem. Eur. J.* **2015**, *21*, 5459.
- [22] a) A. Dobson, S. D. Robinson, *Inorg. Chem.* **1977**, *16*, 137; b) T. C. Johnson, D. J. Morris, M. Wills, *Chem. Soc. Rev.* **2010**, *39*, 81.
- [23] See supporting information. CCDC 1401407 contains the supplementary crystallographic data for **4ae**