ORGANIC LETTERS

XXXX
Vol. XX, No. XX
000–000

N-Formylation of Amines by Methanol Activation

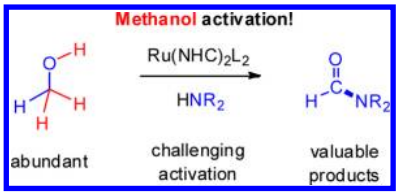
Nuria Ortega, Christian Richter, and Frank Glorius*

Westfälische Wilhelms-Universität Münster, Organisch-Chemisches Institut, Corrensstrasse 40, 48149 Münster, Germany

glorius@uni-muenster.de

Received March 11, 2013

ABSTRACT



The homogeneous catalyzed dehydrogenation of methanol in a synthetically valuable cross-coupling reaction was achieved. By the use of a simple ruthenium-N-heterocyclic carbene complex, MeOH and primary or secondary amines can be converted into formamides.

Methanol, the simplest alcohol, is a raw material used to prepare hundreds of products present in our daily life, and by volume, it is one of the top five chemicals shipped around the world per year. As one of the most basic chemicals, methanol can be converted into key building blocks, such as acetic acid, formaldehyde, and olefins, and can also be used as a fuel source.[1] However, all the industrial transformations of methanol to higher oxidation states require the use of harsh conditions and significant energy consumption. Consequently, an alternative to these processes that could activate methanol to form interesting building blocks in a greener and more sustainable manner would be highly desirable.[2]

In recent years, great advances have been made in the area of alcohol activation. A remarkable example is the acceptorless dehydrogenative coupling of primary alcohols (ADC) to give the corresponding esters, which is an environmentally friendly and atom-efficient alternative to the classic approach based on the esterification of carboxylic acids. Established methods typically require activation of the carboxylic acid or the use of stoichiometric amounts of condensing reagents, generating a considerable amount of waste. In stark contrast, the ADC transformation generates hydrogen gas as the only byproduct. Despite previous reports concerning this transformation, the breakthrough in this field was made by Milstein, utilizing Pincer complexes based on ligand cooperativity of a pyridine aromatization/dearomatization process.[3] This pioneering work opened the door to the application of this concept to very creative and elegant approaches, which led to different types of substrates, such as amides,[4] imines,[5] imides,[6] acetals,[7] and even heterocycles, including pyrroles[8] (Scheme 1).

Despite significant advances in the activation of alcohols, the use of smaller alcohols still constitutes a big challenge. Even though the potential in terms of further applications of the oxidized intermediate is very appealing, limited progress has been made in the dehydrogenation of

(1) For more detailed information about methanol production and use, see: www.methanol.org.

(2) Constable, D. J.; Dunn, P. J.; Hayler, J. D.; Humphrey, G. R.; Leazer, J. L., Jr.; Linderman, R. L.; Lorenz, K.; Manley, J.; Pearlman, B. A.; Wells, A.; Zaks, A.; Zhang, T. Y. *Green Chem.* **2007**, *9*, 411.

(3) (a) Zhang, J.; Leitus, G.; Ben-David, Y.; Milstein, D. *J. Am. Chem. Soc.* **2005**, *127*, 10840. (b) Gunanathan, C.; Milstein, D. *Acc. Chem. Res.* **2011**, *44*, 588. (c) Milstein, D. *Top. Catal.* **2010**, *53*, 915.

(4) (a) Gunanathan, C.; Ben-David, Y.; Milstein, D. *Science* **2007**, *317*, 790. (b) Prechtl, M. H. G.; Wobser, K.; Theyssen, N.; Ben-David, Y.; Milstein, D.; Leitner, W. *Catal. Sci. Technol.* **2012**, *2*, 2039. (c) Prechtl, M. H. G.; Ben-David, Y.; Giunta, D.; Busch, S.; Taniguchi, Y.; Wisniewski, W.; Görls, H.; Mynott, R. J.; Theyssen, N.; Milstein, D.; Leitner, W. *Chem.—Eur. J.* **2007**, *13*, 1539.

(5) Gnanaprakasam, B.; Milstein, D. *Angew. Chem.* **2010**, *122*, 1510. *Angew. Chem., Int. Ed.* **2010**, *49*, 1468.

(6) Zhang, J.; Senthilkumar, M.; Gosh, S. C.; Hong, S. H. *Angew. Chem.* **2010**, *122*, 6535. *Angew. Chem., Int. Ed.* **2010**, *49*, 6391.

(7) Gunanathan, C.; Shimon, L. J. W.; Milstein, D. *J. Am. Chem. Soc.* **2009**, *131*, 3146.

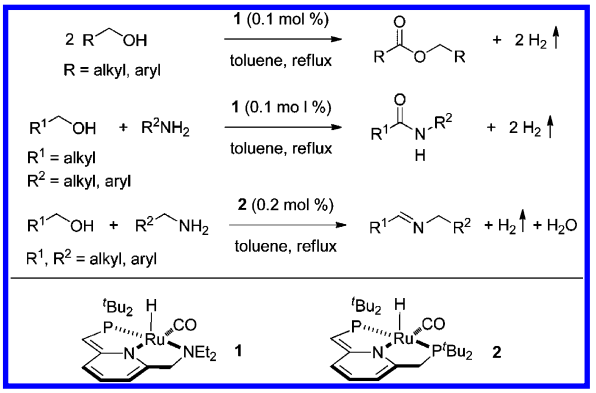
(8) Schley, N. D.; Dobereiner, G. E.; Crabtree, R. H. *Organometallics* **2011**, *30*, 4171.

(9) (a) Morton, D.; Cole-Hamilton, D. J. *J. Chem. Soc., Chem. Commun.* **1988**, 1154. (b) Shinoda, S.; Yamakawa, T. *J. Chem. Soc., Chem. Commun.* **1990**, 1511. (c) Pearson, D. M.; Waymouth, R. M. *Organometallics* **2009**, *28*, 3896.

10.1021/ol400639m

methanol.[9] Apparently, the energy barrier to the activation of smaller alcohols appears to be too uphill for the established catalysts.[10] So far the use of methanol has been only successfully applied by Beller very recently,[11] who reported a Ru catalyzed dehydrogenation of methanol to generate hydrogen gas, as well as the Ir catalyzed hydroxymethylation by direct coupling of methanol with allenes by Krische.[10] Yet, in the field of smaller alcohols activation, in the past year Beller[12] and Gusev[13] reported the first catalytic acceptorless dehydrogenations of ethanol to form ethyl acetate, by the development of new Ru and Os based catalysts. Consequently, we proposed that the activation of

Scheme 1. Selected Examples of Acceptorless Dehydrogenative Coupling

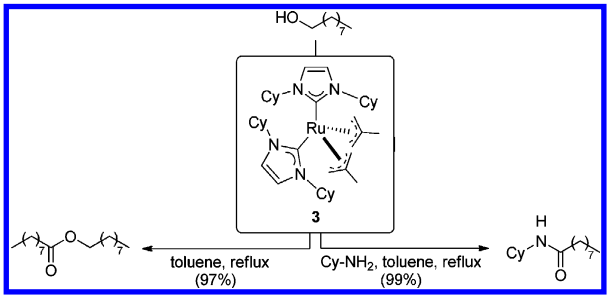


methanol and thereof successful application into interesting transformations may be achieved by the design of new and more reactive catalytic systems.

An interesting feature of Milstein-type complexes is that, under a hydrogen atmosphere, they can catalyze the reverse reaction of the ADC, promoting the hydrogenolysis of esters, amides, ketones, or ureas under mild and neutral conditions, to the corresponding alcohols and amines.[14] Based on our interest in the development of new catalysts for the hydrogenation of (hetero)aromatic compounds, we recently reported a ruthenium-N-heterocyclic carbene (NHC) system which can reduce quinoxalines,[15] benzofurans,[16] thiophenes, and benzothiophenes[17] with high levels of regio- and enantioselectivity. During these studies, the Ru-NHC complex (**3**) used for the racemic reactions proved to be a highly reactive and efficient catalyst in most of the transformations. Therefore, we decided to test this catalyst as a promoter for ADC processes. As test reactions we explored ester and amide formation. To our delight, on heating 1-nonanol in an open system under an argon flow in refluxing toluene, in the presence of 0.1 mol % of the Ru complex **3**, we obtained the corresponding ester in 97% isolated yield. Moreover, we also obtained the corresponding amide in 99% isolated yield under similar conditions starting from 1-nonanol and cyclohexylamine (Scheme 2). Although the acceptorless dehydrogenative coupling processes using Ru-NHC complexes were previously reported,[18] these require basic conditions and additional ligands for activation of the catalyst (such as phosphines, pyridine or acetonitrile). The present system, in contrast, is base- and phosphine-free. The reaction proceeds equally well using the isolated complex **3**, or by preforming the catalyst starting from a commercially available Ru precursor, the corresponding imidazolium salt, and base in the reaction vessel.

With these promising results in hand, we proceeded to test the activity of our Ru catalyst in the challenging methanol activation, in particular, in a synthetically valuable cross-coupling reaction with amines. In this reaction

Scheme 2. Formation of Esters and Amides Catalyzed by Complex **3**[a]



[a] Ester formation: Catalyst **3** (0.015 mmol), nonanol (15 mmol), and toluene (15 mL) were heated at reflux under an Ar flow for 24 h. Amide formation: Catalyst **3** (0.03 mmol), nonanol (2.25 mmol), cyclohexylamine (1.5 mmol), and toluene (1.5 mL) were heated at reflux under an Ar flow for 24 h. Isolated yields are given. Cy = cyclohexyl.

(10) Moran, J.; Preetz, A.; Mesch, R. A.; Krische, M. J. *Nat. Chem.* **2011**, *3*, 287.

(11) Nielsen, M.; Aberico, E.; Baumann, W.; Drexler, H.-J.; Junge, H.; Gladiali, S.; Beller, M. *Nature* **2013**, *495*, 85.

(12) (a) Nielsen, M.; Junge, H.; Kammer, A.; Beller, M. *Angew. Chem.* **2012**, *124*, 5809. *Angew. Chem., Int. Ed.* **2012**, *51*, 5711. (b) Nielsen, M.; Kammer, A.; Cozzula, D.; Junge, H.; Gladiali, S.; Beller, M. *Angew. Chem.* **2011**, *123*, 9767. *Angew. Chem., Int. Ed.* **2011**, *50*, 9593.

(13) (a) Spasyuk, D.; Smith, S.; Gusev, D. A. *Angew. Chem.* **2012**, *124*, 2826. *Angew. Chem., Int. Ed.* **2012**, *51*, 2772. (b) Spasyuk, D.; Gusev, D. A. *Organometallics* **2012**, *31*, 5239.

(14) (a) Zhang, J.; Leitus, G.; Ben-David, Y.; Milstein, D.; Balaraman, E.; Ben-David, Y.; Milstein, D. *Angew. Chem.* **2006**, *118*, 1131. *Angew. Chem., Int. Ed.* **2006**, *45*, 1113. (b) Balaraman, E.; Gnanaprakasam, B.; Shimon, L. J. W.; Milstein, D. *J. Am. Chem. Soc.* **2010**, *132*, 16756. (c) Balaraman, E.; Ben-David, Y.; Milstein, D. *Angew. Chem.* **2011**, *123*, 11906. *Angew. Chem., Int. Ed.* **2011**, *50*, 11702. (d) Langer, R.; Leitus, G.; Ben-David, Y.; Milstein, D. *Angew. Chem.* **2011**, *123*, 2168. *Angew. Chem., Int. Ed.* **2011**, *50*, 2120. (e) Balaraman, E.; Fogler, E.; Milstein, D. *Chem. Commun.* **2012**, *48*, 1111. (f) Tanaka, R.; Yamashita, M.; Nozaki, K. *J. Am. Chem. Soc.* **2009**, *131*, 14168.

(15) Urban, S.; Ortega, N.; Glorius, F. *Angew. Chem.* **2011**, *124*, 3844. *Angew. Chem., Int. Ed.* **2011**, *50*, 3803.

(16) (a) Ortega, N.; Urban, S.; Beiring, B.; Glorius, F. *Angew. Chem.* **2012**, *124*, 1742. *Angew. Chem., Int. Ed.* **2012**, *51*, 1710. (b) Ortega, N.; Beiring, B.; Urban, S.; Glorius, F. *Tetrahedron* **2012**, *68*, 5185.

(17) Urban, S.; Beiring, B.; Ortega, N.; Paul, D.; Glorius, F. *J. Am. Chem. Soc.* **2012**, *134*, 15241.

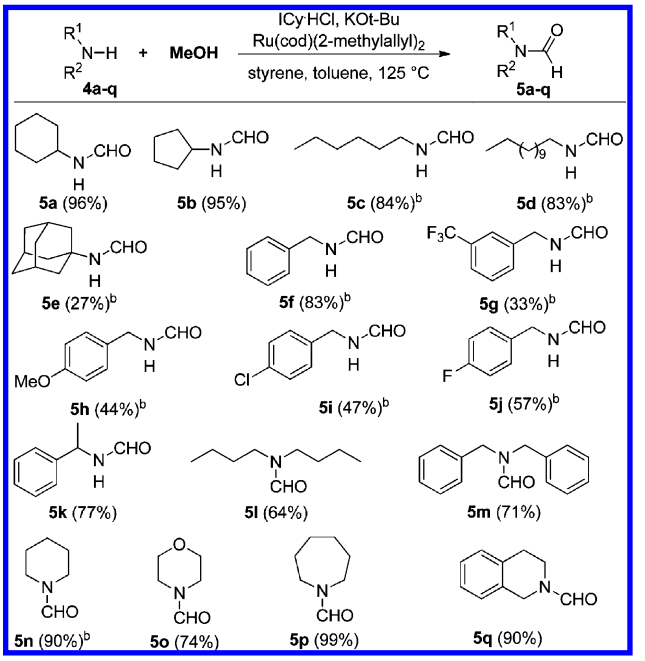
(18) (a) Nordstrøm, L. U.; Vogt, H.; Madsen, R. *J. Am. Chem. Soc.* **2008**, *130*, 17672. (b) Dam, J. H.; Osztrovszky, G.; Nordstrøm, L. U.; Madsen, R. *Chem.—Eur. J.* **2010**, *16*, 6820. (c) Ghosh, S. C.; Muthaiah, S.; Zhang, Y.; Xu, X.; Hong, S. H. *Adv. Synth. Catal.* **2009**, *351*, 2643. (d) Chen, C.; Zhang, Y.; Hong, S. H. *J. Org. Chem.* **2011**, *76*, 10005.

the corresponding formamides would be obtained. Formamides are very important in the synthesis of pharmaceutically active compounds, useful reagents in Vilsmeier formylation reactions,[19] and formamidines.[20] Most reported N-formylations of amines involve moisture sensitive, expensive, or toxic reagents,[21] and therefore the use of methanol as a cheap and readily available formylating agent would be very attractive.[22] The most significant difficulties to overcome in developing this method, besides the activation of methanol itself, is to control the selectivity in the cross-coupling reaction and to avoid further reactions of the products.[23]

The study for the activation of methanol started using our previously optimized conditions for amide synthesis. Unfortunately, under these conditions we observed traces of the desired product, recovering the cyclohexylamine unreacted. However, when the amount of methanol was increased to 3.3 equiv, we obtained *N*-cyclohexylformamide in 63% isolated yield, with no side products observed. Attempts to improve the yield of the reaction by varying the equivalents of reactants, concentration, solvent, or temperature unfortunately were unsuccessful.[24] However, we observed that the reaction also proceeded in a sealed tube, albeit with a lower yield (26%). It was also noted that when we opened the reaction vessel, a release of pressure from the system occurred (presumably from evolution of hydrogen gas). Thus, we considered the possibility of the addition of a sacrificial hydrogen acceptor to trap the hydrogen generated during the catalytic cycle, shifting the equilibrium and driving the reaction to a better yield. After testing a series of different additives,[24] styrene proved to be the best choice, leading to a 96% conversion to the desired formamide under optimized conditions. Even though the use of styrene as a hydrogen acceptor is not ideal for green methods, it is a cheap reagent and generates ethylbenzene, which is nontoxic and is easy to separate from the products. Interestingly, we never observed methylation of the amine, which could be generated by reductive amination of the formaldehyde with the amine, as a consequence of the borrowing hydrogen process.

Subsequently, we explored the scope and limitations of the method, testing a range of different amines (Scheme 3). Sterically nonhindered primary amines reacted smoothly to give the desired products in very clean reactions and high yields (**5a**–**d**). For more hindered amines, such as the adamantylamine (**4e**) the yield decreased dramatically. The reaction worked well for the benzylamine, giving **5f** in good

Scheme 3. Scope for the N-Formylation of Amines[a]



[a] General conditions: [Ru(cod)[2-methylallyl)$_2$] (0.03 mmol), KOt-Bu (0.075 mmol), and ICy·HCl (dicyclohexylimidazolium chloride) (0.06 mmol) were stirred at 70 °C in toluene (1.5 mL) for 12 h, with subsequent addition of the amine **4a**–**q** (1.5 mmol), methanol (5 mmol), and styrene (4.5 mmol), and the reaction mixture was heated at 125 °C for 24 h. [b] Reaction carried out with 4% catalyst loading. Isolated yields are given.

yield, and to test the tolerance to functional groups, we used different benzylamine derivatives (**4g**–**i**). We observed that the reaction is not affected by the presence of halogens or the methoxy group (no loss or transformation of these functional groups), but we obtained lower yields than expected (in comparison to the benzylamine) due to further reaction of the formamide. In the case of phenylethylamine (**5k**), when we used enantiomerically pure starting material, no erosion of the enantiomeric purity was observed. The reaction also works well for secondary amines (which are usually less reactive or not reactive at all in dehydrogenative processes), presenting good yields for linear substrates (**5l**–**m**) and good to excellent for cyclic amines (**5n**–**q**). However, the reaction does not proceed for less nucleophilic amines such as anilines or in the presence of good coordinating groups including pyridines or carboxylic acids.

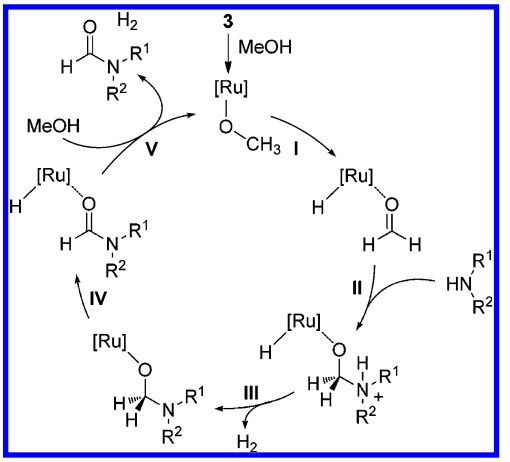
To investigate the mechanism of the reaction, we ran additional experiments for the cross-coupling of methanol with cyclohexylamine. First of all, we confirmed that the reaction works equally well with the isolated catalyst **3** as with the catalyst formed in situ, precluding the possibility that traces of base could catalyze the reaction. In fact, when we ran the reaction with an excess of base, the yield decreased dramatically. To test the importance of the cyclohexyl substituent in the NHC ligand, we replaced ICy with other NHCs, such as IPr or IMes, but we obtained a lower conversion (below 15%). Reaction with the ruthenium precursor in the absence of any NHC

(19) Downie, I. M.; Earle, M. J.; Heaney, H.; Shuhaibar, K. F. *Tetrahedron* **1993**, *49*, 4015.
(20) Han, Y.; Cai, L. *Tetrahedron Lett*. **1997**, *38*, 5423.
(21) Olah, G. A.; Ohannesian, L.; Arvanaghi, M. *Chem. Rev*. **1987**, *87*, 671.
(22) For the synthesis of N-formamides from methanol and amines under aerobic/oxidative conditions, see: (a) Tumma, H.; Nagaraju, N.; Reddy, K. V. *J. Mol. Catal. A: Chem*. **2009**, *320*, 121. (b) Ishida, T.; Haruta, M. *ChemSusChem* **2009**, *2*, 538. (c) Preedasuriyachai, P.; Kitahara, H.; Chavasiri, W.; Sakurai, H. *Chem. Lett*. **2010**, *39*, 1174.
(23) Afagh, N. A.; Yudin, A. K. *Angew. Chem*. **2010**, *122*, 270. *Angew. Chem., Int. Ed*. **2010**, *49*, 262.
(24) For more details on the optimization reactions, see Supporting Information.

resulted in decomposition of starting materials only.[25] Interestingly, when methanol was replaced with paraformaldehyde, only traces of product **5a** were observed. In addition, when the standard reaction was run in the presence of 1 equiv of additional aldehyde (decanal), again only traces of product **5a** were obtained, and only products derived from the aldol condensation of decanal or addition of the amine to the decanal were observed. These experiments suggest that during the course of the standard reaction free aldehyde is either not present or present only at very low concentrations.

Finally, we investigated the order of events during the catalytic cycle by NMR experiments. We found that already the addition of MeOH at 125 °C to a solution of complex **3** causes a significant change in the structure of the complex and the same NMR signals are observed in a reaction under standard conditions, indicating that the same species is formed. Due to the sensitivity of the species formed and the complexity of the NMR spectrum, the newly formed species could not be defined. Still, some conclusions can be drawn: First, it is apparent that the NHC is still coordinated to the metal center, which fits with the observation that without an NHC no reaction occurs. Second, the methallyl groups of complex **3** are no longer coordinated to the metal center. Up to now the fate of these methallyl groups was unknown. Either they are protonated by MeOH, resulting in the formation of a methoxide complex and the release of isobutene, or they could undergo a rearrangement to a different ligand structure such as trimethylenemethane.[26] We suggest that the formation of a methoxide complex is likely, in which free coordination sites could be reversibly occupied by methanol or the amine, maintaining an octahedral coordination geometry of the Ru^{II}. In agreement with our results and in analogy to Madsen's detailed investigation of the amidation of alcohols by NHC-Ru complexes, we think that the catalytic cycle starts from a methoxide complex and proceeds via β-hydride elimination of the methoxide (**I**), addition of the amine to the coordinated formaldehyde (**II**), extrusion of hydrogen (**III**), and a second β-hydride elimination of the hemiaminal complex, which forms the formamide (**IV**).[27] The coordinated formamide could be exchanged by a methanol molecule, and extrusion of hydrogen is regenerating the methoxide species (**V**) (Scheme 4). Currently we do not know the exact structure of the complex formed in the presence of methanol and are unable to provide a more detailed mechanism at this point. Also, the active involvement of the cyclohexyl ring of the NHC ligand (leading to the intermediate formation of chelate/pincer rings) cannot be excluded at present.

Scheme 4. Proposed Mechanism for the N-Formylation[a]



[a] [Ru] = $ICy_2L^1L^2{}_nRu(II)$ complex; L^1 = anionic ligand (e.g., methoxide); L^2 = neutral ligand (e.g., MeOH, HNR_2); R^1,R^2 = alkyl, H.

In conclusion, we have developed a homogeneous catalyzed dehydrogenation of methanol in a synthetically valuable cross-coupling reaction with amines to form N-formamides. This finding, together with experimentation leading to a better mechanistic understanding, should open the door to the conversion of methanol into key building blocks in a green and sustainable manner.

Acknowledgment. We thank Dr. Klaus Bergander and Bernhard Beiring (both WWU Münster) for experimental support and fruitful discussions. Generous financial support by the Deutsche Forschungsgemeinschaft (SFB 858) is gratefully acknowledged. The research of F.G. has also been supported by the Alfried Krupp Prize for Young University Teachers of the Alfried Krupp von Bohlen und Halbach Foundation.

Supporting Information Available. Experimental procedures, spectral data, optimization tables, and preparation of complex **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(25) In our hands, the dehydrogenative activation of methanol to render the corresponding formamide **5a** did not give any product using the NHC-ruthenium catalyst reported by Madsen and co-workers for the amide formation by dehydrogenative coupling of higher alcohols and amines, under the conditions reported by them (ref 18b). Using their catalytic system, under the standard conditions of Scheme 3, provided **5a** in 7% yield.

(26) Wesselbaum, S.; Stein, T.; Klankermayer, J.; Leitner, W. *Angew. Chem.* **2012**, *124*, 7617. *Angew. Chem., Int. Ed.* **2012**, *51*, 7499.

(27) Makarov, I. S.; Fristup, P.; Madsen, R. *Chem.—Eur. J.* **2012**, *18*, 15683.