Angewandte
Communications

CO_2 Utilization | Hot Paper

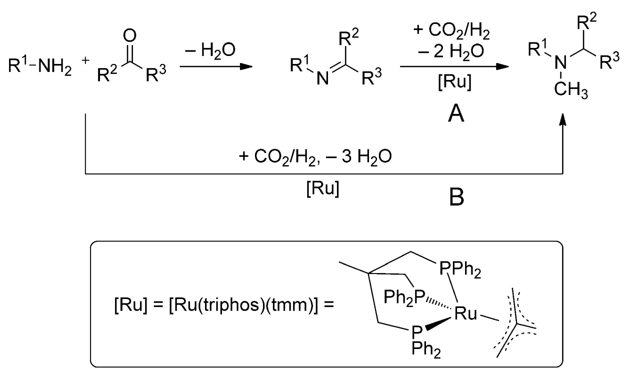
DOI: 10.1002/anie.201403711

Ruthenium-Catalyzed Reductive Methylation of Imines Using Carbon Dioxide and Molecular Hydrogen**

Kassem Beydoun, Ghazi Ghattas, Katharina Thenert, Jürgen Klankermayer, and Walter Leitner*

***Abstract:** The use of the well-defined [Ru(triphos)(tmm)] catalyst, CO_2 as C_1 source, and H_2 as reducing agent enabled the reductive methylation of isolated imines, as well as the direct coupling of amines with aldehydes and the subsequent reductive methylation of the in situ formed imines. The method, which afforded the corresponding N-methyl amines in very good to excellent yields, was also used for the preparation of the antifungal agent butenafine in one step with no apparent waste, thus increasing the atom efficiency of its synthesis.*

The sustainable utilization of carbon dioxide (CO_2) as renewable C_1 building block in order to reduce the predominant dependence on petrochemical feedstocks for the chemical supply chain is attracting continued attention.[1] In particular the hydrogenation of CO_2 to methanol has been studied extensively,[2] and the first organometallic catalytic systems for this transformation were presented recently.[3] The formation of a methyl group through the reduction of CO_2 has a high potential to be developed into a general synthetic principle, but until recently was limited to the stoichiometric use of expensive and waste-producing reductants.[4] Recently, we described the catalytic methylation of amines with carbon dioxide as C_1 source and molecular hydrogen as reductant.[5] The mono- and dimethylation of aromatic amines could be achieved with the highly versatile triphos-based ruthenium catalyst [Ru(triphos)(tmm)] (triphos = 1,1,1-tris(diphenylphosphinomethyl)ethane, tmm = trimethylene methane; Scheme 1).[6] Subsequently, Beller and co-workers extended the transformation to aliphatic amines by using an in situ generated catalyst system comprised of the triphos ligand, a ruthenium precursor, and LiCl.[7] Meanwhile, heterogeneously catalyzed hydrogenative N-methylations of primary and secondary amines were also described.[8]



Scheme 1. Catalytic reductive methylation of imines with CO_2 and H_2 (step A), and one-step synthesis of unsymmetrical tertiary N-methyl amines through a three-component coupling of primary amines, aldehydes ($R^2 = H$), and CO_2 (step B).

Herein, we report the reductive N methylation of structurally diverse and readily accessible imines with CO_2 and H_2, and the effective synthesis of unsymmetrical tertiary N-methyl amines (Scheme 1, step A). Exploiting the chemoselectivity of the [Ru(triphos)(tmm)] catalyst enables an unprecedented three-component coupling reaction of primary amines, aldehydes, and CO_2 to produce tertiary N-methyl amines in one step, generating water as the only by-product (Scheme 1, step B).

Tertiary amines are key structural motifs in various biologically active natural compounds and consequently an integral part of numerous pharmaceutical products.[9] The synthesis of tertiary amines can be achieved through the reduction of amides to imines,[10] followed by their reductive alkylation. At present, the Pd-catalyzed amination of arylhalides is one of the preferred methods for the synthesis of substituted amines.[11] Additionally, imine derivatives can be transformed to tertiary amines through stoichiometric hydrostannation followed by nucleophilic substitution using alkylhalides.[12] The catalytic hydrogenative methylation of imines with CO_2 provides a flexible and convergent alternative strategy for the production of these important chemicals in accordance with the principles of green chemistry.[13]

In an initial set of experiments, we investigated suitable conditions for the reductive methylation of imines using *N*-(1-phenylethylidene)aniline as model substrate (Table 1). The active catalyst was formed from [Ru(triphos)(tmm)] (2.5 mol %) in the presence of trifluoromethanesulfonylimide

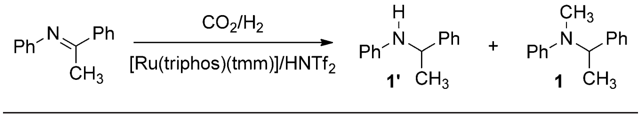
---

[*] Dr. K. Beydoun, G. Ghattas, K. Thenert, Prof. Dr. J. Klankermayer, Prof. Dr. W. Leitner
Institut für Technische und Makromolekulare Chemie
RWTH Aachen University
Worringerweg 1, 52074 Aachen (Germany)
E-mail: jklankermayer@itmc.rwth-aachen.de
Prof. Dr. W. Leitner
Max-Planck-Institut für Kohlenforschung
45470 Mülheim an der Ruhr (Germany)

[**] This work was supported in part by the Cluster of Excellence "Tailor-Made Fuels from Biomass", which is funded by the Excellence Initiative by the German Federal and State Governments to promote science and research at German universities and the project "Sustainable Chemical Synthesis (SusChemSys)". SusChemSys is co-financed by the European Regional Development Fund (ERDF) and the state of North Rhine-Westphalia (Germany), under the operational program "Regional Competitiveness and Employment" 2007–2013.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201403711.

Table 1: Ruthenium-catalyzed reductive methylation of *N*-(1-*p*henylethylidene)aniline with CO_2 and H_2.[a]



Entry	[Ru] [mol %]	*T* [°C]	*t* [h]	Yields **1'**:**1** [%][b]
1[c]	2.5	80	15	99:0
2	2.5	80	15	85:11
3	2.5	100	15	43:53
4	2.5	100	24	6:88
5[d]	5	100	24	0:96 (83)

[a] Reaction conditions: *N*-(1-*p*henylethylidene)aniline (1.0 mmol), [Ru(triphos)(tmm)]/$HNTf_2$ (1:2), THF (2.0 mL), CO_2/H_2 (20/60 bar). [b] Determined by GC using *n*-dodecane as internal standard. Yield of isolated product given in parentheses. Quantitative conversion observed in all cases. [c] Reaction without CO_2. [d] $HNTf_2$ (10 mol %).

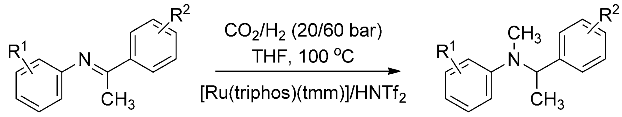
($HNTf_2$) at a Ru/acid ratio of 1:2. Using a catalyst loading of 2.5 mol % in THF at 80 °C and 60 bar hydrogen pressure resulted in the quantitative formation of the hydrogenation product *N*-(1-phenylethyl)aniline (**1'**), confirming the effectiveness of the system to catalyze the hydrogenation of imines (Table 1, entry 1). The application of an additional pressure of 20 bar of CO_2 under otherwise identical conditions resulted in the formation of **1'** in 85 % yield (GC), together with 11 % (GC) of *N*-methyl-*N*-(1-phenylethyl)aniline (**1**), which is the desired product of the reductive methylation (Table 1, entry 2). A slight increase of the temperature to 100 °C gave **1** as the main product in 53 % yield (GC; Table 1, entry 3). Higher reaction temperatures (> 140 °C) resulted in the decomposition of the imine substrate. However, extension of the reaction time to 24 hours at 100 °C resulted in the formation of **1** in 88 % yield (GC, Table 1, entry 4). At a catalyst loading of 5 mol %, the desired product **1** was isolated in 83 % yield (GC: 96 % yield; Table 1, entry 5).

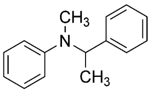
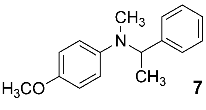
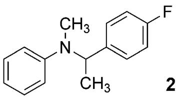
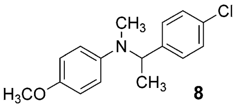
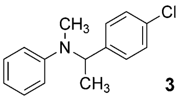
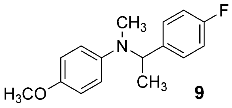
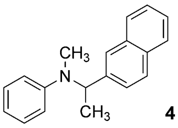
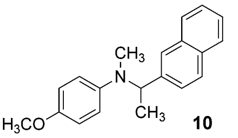
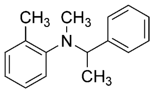
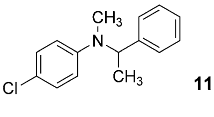
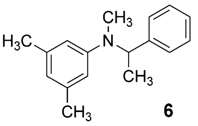
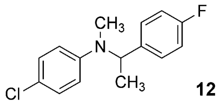
The use of $HNTf_2$ as the co-catalyst provided the desired product **1** with high selectivity, whereas the use of methanesulfonic acid (MSA) or *p*-toluenesulfonic acid (*p*-TsOH) led to the hydrolysis of the C=N bond and subsequent methylation of the aniline. A change of the reaction solvent from THF to toluene or 1,4-dioxane slowed down the methylation reaction and resulted mainly in the formation of the hydrogenation product **1'** at 100 °C (see the Supporting Information for details).

The methylation of a broad range of arylethylidenes was investigated using the optimized reaction conditions (Table 2). Imines derived from unsubstituted aniline were reductively methylated to give amines **1**–**4** with very good yields of up to 83 % (Table 2, entries 1–4). Electron-donating groups at the aniline ring were fully tolerated, even if they result in a considerable steric encumbrance (Table 2, entries 5–10). However, the electron-withdrawing chloro substituent led to noticeably lower yields of products **11** and **12** (Table 2, entries 11 and 12). These latter results are largely due to a pronounced acid-catalyzed cleavage of the C=N bond, as indicated by the formation of the 4-chloro-*N*,*N*-dimethylaniline derivatives as the main side products in 15 % and 30 % yield, respectively. Structural variation at the other aryl group had a less pronounced effect, again indicating a slightly higher reactivity of substrates with electron-donating substituents (see yields of products **1** > **3** > **2**, **7** > **8** > **9**, **11** > **12**).

The Ru-catalyzed methylation was readily extended to *N*-benzylideneanilines to give products **13**–**15** with good to excellent yields (Table 3). This broadens the synthetic potential of the method significantly, as the benzyl group is widely used as protecting group for amine functionalities[14] and allows further structural modification at the CH_2 group.[15] Fluorinated benzylidene imines afforded the *N*-(3-*f*luorobenzyl)-*N*-methylanilines products **13** and **14** in excellent yields of 82 % and 91 %, respectively (Table 3, entries 1 and 2), whereas the nonsubstituted *N*-benzyl product **15** was obtained in moderate yield under the standard reaction conditions (Table 3, entry 3).

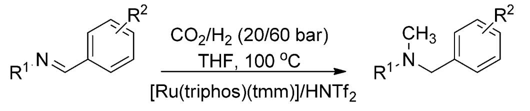
Table 2: Ruthenium-catalyzed methylation of imines with CO_2 and H_2.[a]

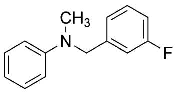
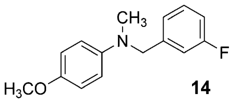
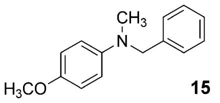


Entry	Product	Yield [%][b]	Entry	Product	Yield [%][b]
1	 **1**	96 (83)	7	 **7**	93 (78)
2	 **2**	74 (37)	8	 **8**	87 (50)
3	 **3**	80 (37)	9	 **9**	82 (60)
4	 **4**	96 (80)	10	 **10**	70 (47)
5	 **5**	80 (58)	11	 **11**	60 (44)
6	 **6**	86 (72)	12	 **12**	40 (20)

[a] Reaction conditions: Imine (0.5 mmol), [Ru(triphos)(tmm)] (5 mol %), $HNTf_2$ (10 mol %), THF (2.0 mL), CO_2/H_2 (20/60 bar), 100 °C. [b] Determined by GC using *n*-dodecane as internal standard. Yields of isolated products given in parentheses.

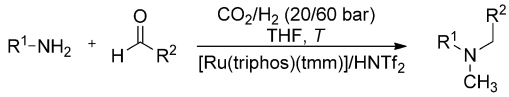
Table 3: Ruthenium-catalyzed reductive methylation of *N*-benzylideneaniline with CO_2 and H_2.[a]

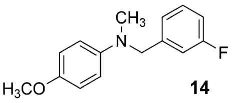
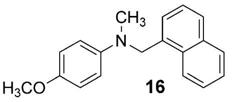
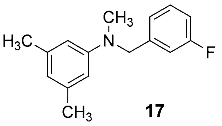
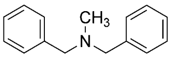
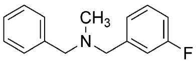


Entry	Product	Yield [%][b]
1	 **13**	97 (82)
2	 **14**	97 (91)
3	 **15**	57 (41)

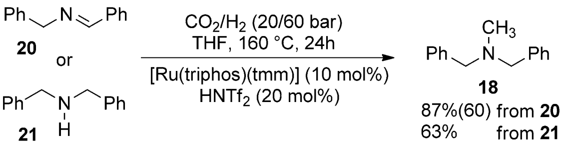
[a] Reaction conditions: benzylidene amine derivative (0.5 mmol), [Ru(triphos)(tmm)] (5 mol%), $HNTf_2$ (10 mol%), THF (2.0 mL), CO_2/H_2 (20/60 bar), 100 °C, 24 h. [b] Determined by GC using *n*-dodecane as internal standard. Yields of isolated products given in parentheses.

Table 4: Ruthenium-catalyzed one-step formation of tertiary N-methyl amines through three-component coupling of primary amines, aldehydes, and CO_2 with H_2 as reductant.[a]



Entry	Product	T [°C]	Yield [%][b]
1	 **14**	100	92
2	 **16**	100	63 (40)
3	 **17**	100	90 (74)
4	 **18**	160	61
5	 **19**	160	51 78[c]

[a] Reaction conditions: amine derivative (0.5 mmol), [Ru(triphos)(tmm)] (5 mol%), $HNTf_2$ (10 mol%), THF (2.0 mL), CO_2/H_2 (20/60 bar), 100 °C, 20 h. [b] Determined by GC using *n*-dodecane as internal standard. Yields of isolated products given in parentheses. [c] [Ru(triphos)(tmm)]/$HNTf_2$ = 10/20 mol%.

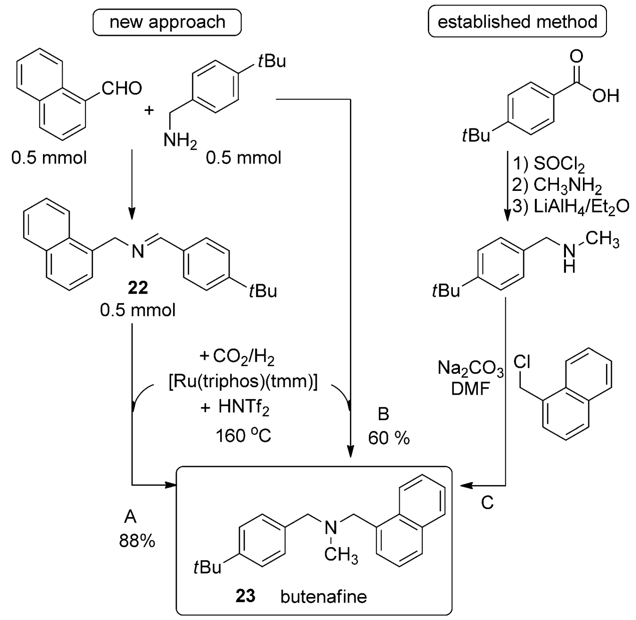


Scheme 2. Ruthenium-catalyzed synthesis of dibenzylmethyl amine (**18**), starting from *N*-benzylbenzylidene amine (**20**) and dibenzyl amine (**21**) using CO_2 and H_2.

With a standard set of reaction conditions for the N methylation of isolated imines in hand, we attempted to couple the in situ formation of imines with this method. Provided that the hydrogenative methylation of the imines is the preferred reaction within the complex network of possible pathways, a direct three-component coupling of the primary amines, carbonyl substrates, and CO_2 can be envisaged. We were very pleased to obtain the unsymmetrical tertiary amines in fair to excellent yields from aniline derivatives and aromatic aldehydes under standard reaction conditions (Table 4, entries 1–3). The use of benzyl amine required higher reaction temperatures, but also gave the desired products in moderate yields, which could be further optimized to synthetically useful values at higher catalyst loadings (Table 4, entries 4 and 5).

The high reactivity of the imines is corroborated by the preparation of dibenzylmethyl amine **18** starting either from *N*-benzylbenzylidene amine **20** or dibenzylamine substrate **21**. The full conversion of **20**, affording **18** in 87% yield (GC), was achieved under optimized conditions using 10 mol% catalyst loading at 160 °C (Scheme 2). Starting from dibenzylamine **21** as substrate, compound **18** was obtained in only 63% yield (GC) under identical conditions. The difference in reactivity is attributed to the lower basicity of imine **20** in comparison to amine **21**; the lower basicity of the imine enables its N methylation at a lower acid/Ru loading.[5] The use of aliphatic imines did not result in the formation of the reductively methylated product.

In order to probe the practical utility of this protocol, we decided to evaluate the Ru-catalyzed reductive methylation for the synthesis of butenafine **23** (*N*-(4-tert-butylbenzyl)-*N*-methyl-1-naphthalene amine), an antimycotic agent that exhibits fungicidal activity particularly against dermatophytes, aspergilli, dimorphic, and dematiaceous fungi.[16] The established method to prepare butenafine comprises a four-step synthesis that starts from *para*-tert-butylbenzoic acid[17] and produces large amounts of inorganic salts as by-products. In addition, the required solvent changes between the various reaction steps are associated with a low space–time yield and a high E factor (E factor = total waste [kg]/product [kg]). Our route starts from 1-naphthalene aldehyde and 4-tert-butylbenzyl amine as commercially available substrates. Using the standard reaction conditions for the methylation of imines, butenafine **23** was obtained in 88% yield (GC) from the corresponding imine **22** (Scheme 3, pathway A). The direct three-component coupling gave **23** in a remarkable yield of 60% in a single step, even under these non-optimized conditions (Scheme 3, pathway B). The methylation method uses CO_2 and H_2 as extremely cheap components for the formation of the methyl group, results in an atom economy of 85%, and forms H_2O as the only by-product. This example clearly emphasizes the promising potential of the new



Scheme 3. Novel synthesis of antifungal agent butenafine **23** (pathways A and B) in comparison to the established method (pathway C).

methodology for the sustainable synthesis of biologically active molecules.

In conclusion, the catalytic reductive *N*-methylation of imines using CO_2 as C_1 source and H_2 as reducing agent is a promising synthetic method to obtain tertiary amines that bear one CH_3 group. The catalytic system comprises the readily available complex [Ru(triphos)(tmm)] and an acid of a non-coordinating anion as co-catalysts. The reaction can be carried out with the isolated imines or as direct three-component coupling reaction starting from primary amines, aldehydes, and CO_2. Both methods were successfully used to prepare a range of unsymmetrical tertiary amines. The practical utility of this novel methodology was further demonstrated with the synthesis of butenafine as a model pharmaceutical product, indicating a significant potential to improve the atom and step economy of the synthesis of this substrate class by using carbon dioxide as building block.

Experimental Section

General procedure for the one-step synthesis of tertiary N-methyl amines through three-component coupling: Under an argon atmosphere, a solution of the catalyst [Ru(triphos)(tmm)] (0.019 g, 0.025 mmol) and the co-catalyst $HNTf_2$ (0.014 g, 0.05 mmol) in THF (1 mL) was transferred by cannula to a carefully degassed and dried stainless-steel autoclave (10 mL). A mixture of the primary amine (0.5 mmol) and the aldehyde (0.5 mmol), dissolved in THF (1 mL), was then added by cannula to the autoclave. The autoclave was pressurized at room temperature with CO_2 to 20 bar and then with H_2 to a total pressure of 80 bar. The reaction mixture was mechanically agitated with a magnetic stir bar and heated to 100 °C in an oil bath. After 20 hours, the autoclave was cooled in an ice bath and then carefully vented. The crude mixture was analyzed by ^{1}H NMR spectroscopy using mesitylene as internal standard and the results confirmed by gas chromatography using dodecane as internal standard.

Received: March 25, 2014

Keywords: amines · carbon dioxide · homogeneous catalysis · hydrogenation · methylation

---

[1] a) A. Behr, *Carbon Dioxide Activation by Metal Complexes*, Wiley-VCH, Weinheim, **1988**; b) W. Leitner, *Coord. Chem. Rev.* **1996**, *153*, 257; c) H. Arakawa, M. Aresta, J. N. Armor, M. A. Barteau, E. J. Beckman, A. T. Bell, J. E. Bercaw, C. Creutz, E. Dinjus, D. A. Dixon, K. Domen, D. L. DuBois, J. Eckert, E. Fujita, D. H. Gibson, W. A. Goddard, D. W. Goodman, J. Keller, G. J. Kubas, H. H. Kung, J. E. Lyons, L. E. Manzer, T. J. Marks, K. Morokuma, K. M. Nicholas, R. Periana, L. Que, J. Rostrup-Nielson, W. M. H. Sachtler, L. D. Schmidt, A. Sen, G. A. Somorjai, P. C. Stair, B. R. Stults, W. Tumas, *Chem. Rev.* **2001**, *101*, 953; d) *Carbon Dioxide as Chemical Feedstock* (Ed.: M. Aresta), Wiley-VCH, Weinheim, **2010**; e) M. Peters, B. Köhler, W. Kuckshinrichs, W. Leitner, P. Markewitz, T. E. Müller, *ChemSusChem* **2011**, *4*, 1216.

[2] a) L. C. Grabow, M. Mavrikakis, *ACS Catal.* **2011**, *1*, 365; b) W. Wang, S. Wang, X. Ma, J. Gong, *Chem. Soc. Rev.* **2011**, *40*, 3703; c) F. Liao, Y. Huang, J. Ge, W. Zheng, K. Tedsree, P. Collier, X. Hong, S. C. Tsang, *Angew. Chem.* **2011**, *123*, 2210; *Angew. Chem. Int. Ed.* **2011**, *50*, 2162.

[3] a) E. Balaraman, C. Gunanathan, J. Zhang, L. J. W. Shimon, D. Milstein, *Nat. Chem.* **2011**, *3*, 609; b) C. Huff, M. Sanford, *J. Am. Chem. Soc.* **2011**, *133*, 18122; c) S. Wesselbaum, T. vom Stein, J. Klankermayer, W. Leitner, *Angew. Chem.* **2012**, *124*, 7617; *Angew. Chem. Int. Ed.* **2012**, *51*, 7499; d) Z. Han, L. Rong, J. Wu, L. Zhang, Z. Wang, K. Ding, *Angew. Chem.* **2012**, *124*, 13218; *Angew. Chem. Int. Ed.* **2012**, *51*, 13041.

[4] a) O. Jacquet, X. Frogneux, C. Das Neves Gomes, T. Cantat, *Chem. Sci.* **2013**, *4*, 2127; b) Y. Li, X. Fang, K. Junge, M. Beller, *Angew. Chem.* **2013**, *125*, 9747; *Angew. Chem. Int. Ed.* **2013**, *52*, 9568.

[5] K. Beydoun, T. vom Stein, J. Klankermayer, W. Leitner, *Angew. Chem.* **2013**, *125*, 9733; *Angew. Chem. Int. Ed.* **2013**, *52*, 9554.

[6] a) For pioneering work on the use of the triphos ligand in catalysis, see: C. Bianchini, A. Meli, M. Peruzzini, F. Vizza, F. Zanobini, *Coord. Chem. Rev.* **1992**, *120*, 193; for example: b) M. C. Van Engelen, H. T. Teunissen, J. G. de Vries, C. J. Elsevier, *J. Mol. Catal. A* **2003**, *206*, 185; c) B. Boardman, M. J. Hanton, H. Van Rensburg, R. P. Tooze, *Chem. Commun.* **2006**, 2289; d) F. M. A. Geilen, B. Engendahl, A. Harwardt, W. Marquardt, J. Klankermayer, W. Leitner, *Angew. Chem.* **2010**, *122*, 5642; *Angew. Chem. Int. Ed.* **2010**, *49*, 5510; for the synthesis of [Ru(triphos)(tmm)], see: e) T. vom Stein, T. Weigand, C. Merkens, J. Klankermayer, W. Leitner, *ChemCatChem* **2013**, *5*, 439.

[7] Y. Li, I. Sorribes, T. Yan, K. Junge, M. Beller, *Angew. Chem.* **2013**, *125*, 12378; *Angew. Chem. Int. Ed.* **2013**, *52*, 12156.

[8] X. Cui, X. Dai, Y. Zhang, Y. Deng, F. Shi, *Chem. Sci.* **2014**, *5*, 649.

[9] a) Y. Kawabe, H. Ikeda, T. Sakai, K. Kawasaki, *J. Mater. Chem.* **1992**, *2*, 1025; b) T. E. Müller, M. Beller, *Chem. Rev.* **1998**, *98*, 675; c) J. Seayad, A. Tillack, C. G. Hartung, M. Beller, *Adv. Synth. Catal.* **2002**, *344*, 795; d) F. Pohlki, S. Doye, *Chem. Soc. Rev.* **2003**, *32*, 104; e) D. Horton, G. Bourne, M. Smythe, *Chem. Rev.* **2003**, *103*, 893; f) R. Severin, S. Doye, *Chem. Soc. Rev.* **2007**, *36*, 1407; g) T. E. Müller, K. C. Hultzsch, M. Yus, F. Foubelo, M. Tada, *Chem. Soc. Rev.* **2008**, *37*, 3795; h) R. Eelkema, H. L. Anderson, *Macromolecules* **2008**, *41*, 9930; i) R. Lygaitis, V.

Getautis, J. V. Grazulevicius, *Chem. Soc. Rev.* **2008**, *37*, 770; j) Z. J. Ning, H. Tian, *Chem. Commun.* **2009**, 5483.

[10] a) A. A. Núñez Magro, G. R. Eastham, D. J. Cole-Hamilton, *Chem. Commun.* **2007**, 3154; b) D. L. Dodds, J. Coetzee, J. Klankermayer, S. Brosinski, W. Leitner, D. J. Cole-Hamilton, *Chem. Commun.* **2007**, 3154; published addition (Nov 2011); c) J. Coetzee, D. L. Dodds, J. Klankermayer, S. Brosinski, W. Leitner, A. M. Z. Slawin, D. J. Cole-Hamilton, *Chem. Eur. J.* **2013**, *19*, 11039.

[11] a) S. L. Buchwald, C. Mauger, G. Mignani, U. Scholz, *Adv. Synth. Catal.* **2006**, *348*, 23; b) E. A. B. Kantchev, C. J. O'Brien, M. G. Organ, *Angew. Chem.* **2007**, *119*, 2824; *Angew. Chem. Int. Ed.* **2007**, *46*, 2768; c) S. Tasler, J. Mies, M. Langa, *Adv. Synth. Catal.* **2007**, *349*, 2286; d) D. S. Surry, S. L. Buchwald, *Angew. Chem.* **2008**, *120*, 6438; *Angew. Chem. Int. Ed.* **2008**, *47*, 6338; e) N. Marion, S. P. Nolan, *Acc. Chem. Res.* **2008**, *41*, 1440; f) J. F. Hartwig, *Acc. Chem. Res.* **2008**, *41*, 1534; g) C. Torborg, M. Beller, *Adv. Synth. Catal.* **2009**, *351*, 3027.

[12] T. Kawakami, T. Sugimoto, I. Shibata, A. Baba, H. Matsuda, N. Sonoda, *J. Org. Chem.* **1995**, *60*, 2677.

[13] P. T. Anastas, J. C. Warner, *Green Chemistry*: *Theory and Practice*, Oxford University Press, New York, **1998**, p. 30.

[14] a) T. W. Greene, P. G. M. Wuts, *Protecting Groups in Organic Synthesis*, *3rd ed.*, Wiley, New York, **1999**; b) S. Bull, S. Davies, G. Fenton, A. Mulvaney, R. S. Prasad, A. Smith, *Chem. Commun.* **2000**, 337; c) M. Banwell, M. Coster, M. Harvey, J. Moraes, *J. Org. Chem.* **2003**, *68*, 613; d) E. J. Grayson, B. G. Davis, *Org. Lett.* **2005**, *7*, 2361.

[15] a) Y. S. Park, M. L. Boys, P. Beak, *J. Am. Chem. Soc.* **1996**, *118*, 3757; b) J. Clayden, J. Dufour, D. M. Grainger, M. Helliwell, *J. Am. Chem. Soc.* **2007**, *129*, 7488; c) G. Zhang, Y. Ma, S. Wang, Y. Zhang, R. Wang, *J. Am. Chem. Soc.* **2012**, *134*, 12334.

[16] a) W. McNeely, C. M. Spencer, *Drugs* **1998**, *55*, 405; b) A. Singal, *Expert Opin. Drug Metab. Toxicol.* **2008**, *4*, 999.

[17] T. Maeda, T. Yamamoto, M. Takase, K. Sasaki, T. Arika, M. Yokoo, R. Hashimoto, K. Amemiya, S. Koshikawa, US patent 5,021,458, June 4, **1991**.