Catalysis Science & Technology

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: J. Cabrero-Antonino, R. Adam, K. Junge, R. Jackstell and M. Beller, *Catal. Sci. Technol.*, 2017, DOI: 10.1039/C7CY00437K.

ROYAL SOCIETY OF CHEMISTRY

rsc.li/catalysis

View Article Online
DOI: 10.1039/C7CY00437K

Journal Name

COMMUNICATION

Cobalt-catalysed Transfer Hydrogenation of Quinolines and Related Heterocycles Using Formic Acid under mild Conditions†

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

Jose R. Cabrero-Antonino,[a]† Rosa Adam,[a]† Kathrin Junge,[a] Ralf Jackstell[a] and Matthias Beller[a*]

Herein we report the first example of homogeneous non-noble metal catalyzed transfer hydrogenation of *N*-heteroarenes. The combination of $Co(BF_4)_2{\cdot}6H_2O$ with tris(2-(diphenylphosphino)phenyl)phosphine L1 is able to selectively reduce quinolines in the presence of other sensitive functional groups, at mild conditions, using formic acid as hydrogen source.

N-heterocycles are interesting molecules with important applications, mainly as bioactive compounds.[1] In particular 1,2,3,4-tetrahydroquinolines constitute a widespread scaffold present in many natural products (i. e. galipinine) and drugs.[2] Indeed, oxamniquine[3] or flumequine,[4] containing tetrahydroquinoline moiety, are currently in use as antihelmintic or antibacterial agents (Figure 1).

The most straightforward approach for the synthesis of tetrahydroquinolines and related compounds, is the reduction of the parent arene. In terms of sustainability, catalytic hydrogenation[5] and transfer hydrogenation[6] are preferred methodologies for these reductions. Although hydrogenation is the most atom-efficient approach, transfer hydrogenation has also advantages, as it avoids the use of high pressures and allows an easy operational set up. Among the possible hydrogen donors available for transfer hydrogenations, alcohols and formic acid are the most desirable. Specifically formic acid has been intensively investigated as a hydrogen carrier due to its safety, accessibility and high stability.[7]

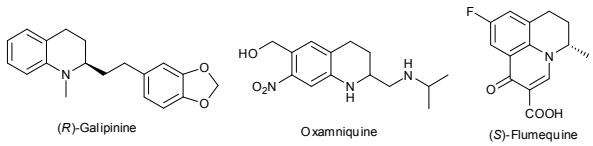


Fig. 1 Examples of natural products and drugs with 1,2,3,4-tetrahydroquinoline structure.

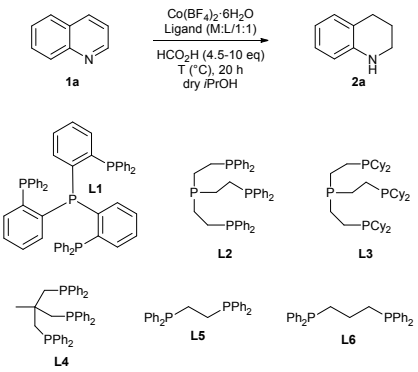
In the last years, many efforts have been done for developing heterogeneous[8] as well as homogeneous catalytic systems for transfer hydrogenations of *N*-heteroarenes. Generally, homogeneous systems have the advantage of acting at milder conditions. However, apart from organocatalytic systems,[9] they are mainly based on precious metals such as Ru,[10] Pd,[11] Ir[12] or Rh.[13] Nowadays, there is a strong tendency of replacing noble metals by earth abundant base metals,[14] due to their lower toxicity and abundance. In this direction, recently several catalysts based on Fe,[15] Co[16] and Mn[17] have been described for the transfer hydrogenation of C-O, C-N and C-C multiple bonds. Interestingly, cobalt and manganese metal nanoparticles in the presence of Li and traces of H_2O have been reported to efficiently reduce quinoline and other arenes.[18] Despite these important achievements, there is still no general methodology available for transfer hydrogenation of *N*-heterocycles in the presence of non-noble metal catalysts. In this regard, here we report the first molecularly-defined base metal catalysed transfer hydrogenation of *N*-heterocycles. Key for the success is the use of a specific tetradentate phosphine. Notably, the reaction proceeds in the absence of any additives.

Previous experience of our group involved formic acid dehydrogenation as well as transfer hydrogenations using iron salts in combination with tetradentante phosphines.[19] Very recently, we have described the combination of $Co(BF_4)_2{\cdot}6H_2O$ with tris(2-(diphenylphosphino)phenyl)phosphine **L1** as an active catalyst for the hydrogenation of *N*-heteroarenes.[20, 21] Inspired by these results, we started to explore the transfer hydrogenation of quinoline **1a** using formic acid as hydrogen source and $Co(BF_4)_2{\cdot}6H_2O$/**L1** as catalyst (Table 1). In a first approach, we performed the reaction at 60 °C, with *i*PrOH as solvent and during 20 h in the presence of different combinations of $Co(BF_4)_2{\cdot}6H_2O$, ligand **L1** and formic acid (4.5 eq) (Table 1, entries 1-4). Interestingly, only when $Co(BF_4)_2{\cdot}6H_2O$, **L1** and formic acid were present, moderate yields of 1,2,3,4-tetrahydroquinoline **2a** were detected. This

[a] *Leibniz-Institut für Katalyse e.V. an der Universität Rostock, Albert-Einstein-Straße 29a, 18059 Rostock, Germany. E-mail: matthias.beller@catalysis.de.*
†These authors contributed equally to this work. *Electronic Supplementary Information (ESI) available:* General experimental procedures, characterisation data and NMR spectra of the isolated products are available. *See DOI: 10.1039/x0xx00000x*

View Article Online
DOI: 10.1039/C7CY00437K

Table 1. Transfer hydrogenation of quinoline (**1a**) using formic acid: Initial optimization of the reaction conditions.



Entry[a]	T (°C)	[Co] (mol%)	Ligand	HCO_2H (eq)	Conv. (%)[b]	**2a** (%)[b]
1	60	5	-	-	-	-
2	60	5	-	4.5	-	-
3	60	5	**L1**	-	-	-
4	60	5	**L1**	4.5	52	48
5	80	5	**L1**	4.5	>99	>99
6	80	4	**L1**	4.5	>99	95
7	80	3	**L1**	4.5	95	84
8	80	2	**L1**	4.5	73	68
9	80	2	**L1**	8	85	84
10	**80**	**2**	**L1**	**10**	**>99**	**97**
11[c]	80	2	**L1**	10	10	9
12	80	2	**L1**	-	-	-
13	80	2	**L2**	10	-	-
14	80	2	**L3**	10	-	-
15	80	2	**L4**	10	2	-
16	80	2	**L5**	10	-	-
17	80	2	**L6**	10	3	-
18[d]	80	-	**-**	10	>99	96

[a]Standard reaction conditions: quinoline (**1a**) (29.6 μL, 0.25 mmol), $Co(BF_4)_2·6H_2O$ (2-5 mol%), ligand (M:L/1:1), HCO_2H (2.5-10 eq) and dry *i*PrOH (2 mL) at 80 °C during 20 h. [b]Conversion of **1a** and yield of product **2a** were calculated by GC using hexadecane as internal standard. [c]Run at 2 h. (Cy = cyclohexyl). [d]Reaction performed with [CoF(**L1**)][BF_4] (2 mol%).

indicates that $Co(BF_4)_2·6H_2O$ and **L1** form an active complex able to catalyse the transfer hydrogenation from formic acid to quinoline **1a** without the need of a base present. Moreover, the lack of activity in the absence of formic acid discards that isopropanol acts as hydrogen source (Table 1, entry 3). To further improve this reaction, we increased the temperature to 80 °C (Table 1, entry 5). To our delight, under these conditions the corresponding hydrogenated product **2a** was obtained in excellent yield. Even at lower catalyst loadings (3 mol%) excellent conversions and selectivities were achieved (Table 1, entries 5-8). By adding a larger excess of formic acid (10 eq.), it was possible to successfully carry out the reaction using 2 mol% of catalyst (Table 1, entry 10).

To investigate in more detail the effect of the phosphine ligand, several bi-, tri- and tetradentate phosphines were tested under the optimized reaction conditions (Table 1, entries 13-17). No activity was detected for any of the ligands, apart from **L1**, indicating that this tetradentate phosphine is unique for forming an active cobalt catalyst. In addition, we also explored the effect of different metal salts (Table S1). Among the cobalt salts tested in the benchmark reaction (Table S1, entries 1-9), $Co(BF_4)_2·6H_2O$ was the most active and only $CoSO_4·7H_2O$ afforded tetrahydroquinoline **2a** in moderate yields (Table S1, entries 1 and 7, respectively). Tetrafluoroborate salts of iron, copper and zinc did not show any activity under the tested conditions (Table S1, entries 10-12). The reaction was also performed using the well-defined [CoF(**L1**)][BF_4] complex[20] (Table 1, entry 18) with excellent results, comparable to the ones with the situ system. To confirm the homogeneous nature of our catalyst, poisoning experiments[22] were performed in the presence of varying amounts of Hg (Table S2). In all the performed tests no significant effects on the transfer hydrogenation of quinoline were observed, indicating that a molecularly defined complex is the catalyst of this reaction.

With regard to the solvent effect, several polar and apolar solvents were explored (Table S3). In general, alcohol type solvents afforded the best conversions and selectivities with a few exceptions (Table S3, entries 1-9), being *i*PrOH the best one (Table S3, entry 1). The addition of water to the reaction media had a detrimental effect in the activity, giving **2a** in low yields (Table S3, entry 2). Polar aprotic solvents, such as ether type, DMF or DMSO, neither gave good results (Table S3, entries 10-13). In contrast, toluene afforded tetrahydroquinoline **2a** in good yields, whereas in *m*-xylene the catalyst was not active (Table S3, entries 14 and 15,).

At this point the reducing agent was also the subject of further investigations (Figure 2). This study showed that the reaction only proceeded with formic acid. Formates or other acids such as acetic acid were completely inactive. Surprisingly, the addition of base inhibited totally the reaction

Once determined the optimized conditions, the general applicability of the protocol was studied through the reaction of several substituted quinolines (Table 2). The Co/**L1** complex demonstrated to be tolerant to several electron-donating and electron-withdrawing substituents. Most of the substrates were hydrogenated at 80 °C, using 10 equivalents of formic acid and catalyst loadings of 2.5-5 mol%. 6-Substituted quinolines **1b-i**, containing electronically different groups, were successfully converted (Table 2, entries 2-9). Gratifyingly, the studied cobalt catalyst demonstrated to be selective to the hydrogenation of the *N*-heteroarene in the presence of carboxylic acid, ester and alkene groups (Table 2, entries 7-9). The demonstrated selectivity can be a key issue in the

View Article Online
DOI: 10.1039/C7CY00437K

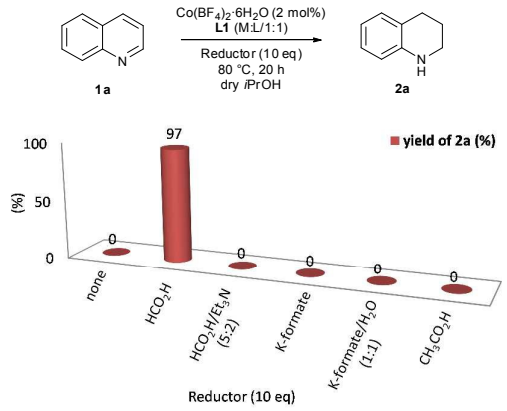
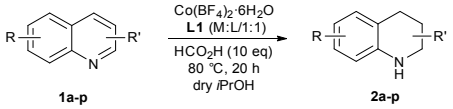


Fig. 2 Yield of product **2a** in the transfer hydrogenation of quinoline (**1a**) using different reducing agents. Standard reaction conditions: quinoline (**1a**) (29.6 μL, 0.25 mmol), $Co(BF_4)_2{\cdot}6H_2O$ (1.70 mg, 0.005 mmol, 2 mol%), ligand **L1** (4.0 mg, 0.005 mmol, 2 mol%), reductor (2.5 mmol, 10 eq) and dry *i*PrOH (2 mL) at 80 °C during 20 h. [b] Conversion of **1a** and yield of product **2a** were calculated by GC using hexadecane as internal standard.

potential application of this methodology to the synthesis of further functionalized tetrahydroquinolines. In addition, 8-substituted quinolines **1j-n** were smoothly hydrogenated affording 1,2,3,4-tetrahydroquinolines in good yields (Table 2, entries 10-14). Finally, more challenging quinaldines **1o** and **1p** could also be converted, although higher temperature (100 °C) and catalyst loadings were required (Table 2, entries 12 and 13).

Table 2. [Co/**L1**]-catalyzed transfer hydrogenation of different substituted quinolines using formic acid.



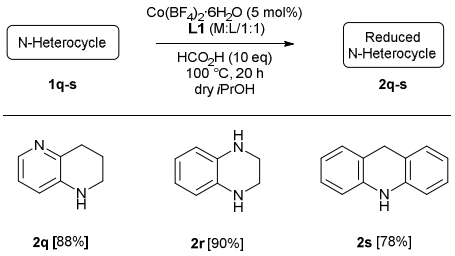
Entry[a]	Substrate **1**	[Co] (mol%)	Conv. (%)[b]	**2** (%)[b]
1		2.5	>99	**2a** [90]
2		2.5	>99	**2b** [90]
3		2.5	>99	**2c** [88]
4		5	85	**2d** [78]
5		5	>99	**2e** [76]
6		5	89	**2f** [80]
7		2.5	>99	**2g** [82]
8		8	>99	**2h** [98]
9[c]		4	>99	**2i** [89]
10		4	97	**2j** [93]
11		2.5	>99	**2k** [93]
12		5	88	**2l** [82]
13		2.5	99	**2m** [90]
14		2.5	>99	**2n** [97]
15[d]		8	84	**2o** [78]
16[d]		5	94	**2p** [84]

[a]Standard reaction conditions: quinoline (0.25 mmol), $Co(BF_4)_2{\cdot}6H_2O$ (2.5-8 mol%), ligand **L1** (M:L/1:1), HCO_2H (95.0 μL, 2.5 mmol, 10 eq) and dry *i*PrOH (2 mL) at 80 °C during 20 h. [b]Conversion of the starting material was calculated by GC using hexadecane as internal standard. Isolated yields of the products are given between brackets. [c]Small amounts (< 5%) of product containing the double bond hydrogenated were detected. [d]Run at 100 °C.

With the aim of broadening the scope of the Co/**L1** catalysed method, the transfer hydrogenation of other *N*-heterocycles was tested at 100 °C, using 5 mol% of catalyst and 10 equivalents of the reducing agent (Scheme 1). Under these conditions naphthyridine **1q**, quinoxaline **1r** or acridine **1s** were converted to the corresponding reduced *N*-heterocycles.

In conclusion, we have described the first methodology based on a homogeneous non-noble metal catalyst for performing the transfer hydrogenation of quinolines and other *N*-heteroarenes. The developed defined cobalt catalyst system uses formic acid as an inexpensive and convenient source of hydrogen. Compared to most other transfer hydrogenations this novel protocol works in the absence of basic additives. Interestingly, the catalyst shows a high selectivity for the reduction of quinoline in the presence of other sensitive groups. The easy operational set up, mild conditions and selectivity of the methodology are significant advantages for its future application in synthetic strategies for obtaining valuable *N*-heterocycles.

View Article Online
DOI: 10.1039/C7CY00437K



Scheme 1. [Co/**L1**]-catalyzed transfer hydrogenation of *N*-heterocycles using formic acid. Standard reaction conditions: substrate (0.25 mmol), $Co(BF_4)_2{\cdot}6H_2O$ (4.25 mg, 0.0125 mmol, 5 mol%), ligand **L1** (M:L/1:1), HCO_2H (95.0 μL, 2.5 mmol, 10 eq), dry *i*PrOH (2 mL) at 100 °C, 20 h. Isolated yields of the products are given.

Financial support from the state of Mecklenburg-Vorpommern and the BMBF is gratefully acknowledged. J.R. C.-A. and R.A. thank the Ramon Areces Foundation for a postdoctoral fellowship. The analytic department of LIKAT is gratefully acknowledged for their support.

Notes and references

1. a) T. L. Gilchrist, *Heterocyclic Chemistry*, Addison Wesley, Essex, England, 3rd edn., 1997; b) J. A. Joule and K. Mills, *Heterocyclic Chemistry*, Wiley-Blackwell, 5th edn., 2013.
2. a) A. R. Katritzky, S. Rachwal and B. Rachwal, *Tetrahedron*, 1996, **52**, 15031-15070; b) J. D. Scott and R. M. Williams, *Chem. Rev.*, 2002, **102**, 1669-1730; c) V. Sridharan, P. A. Suryavanshi and J. C. Menendez, *Chem. Rev.*, 2011, **111**, 7157-7259.
3. R. P. Filho, C. M. de Souza Menezes, P. L. S. Pinto, G. A. Paula, C. A. Brandt and M. A. B. da Silveira, *Biorg. Med. Chem.*, 2007, **15**, 1229-1236.
4. J. Bálint, G. Egri, E. Fogassy, Z. Böcskei, K. Simon, A. Gajáry and A. Friesz, *Tetrahedron: Asymmetry*, 1999, **10**, 1079-1087.
5. a) F. Glorius, *Org. Biomol. Chem.*, 2005, **3**, 4171-4175; b) Y.-G. Zhou, *Acc. Chem. Res.*, 2007, **40**, 1357-1366; c) D.-S. Wang, Q.-A. Chen, S.-M. Lu and Y.-G. Zhou, *Chem. Rev.*, 2012, **112**, 2557-2590; d) Z. X. Giustra, J. S. A. Ishibashi and S.-Y. Liu, *Coord. Chem. Rev.*, 2016, **314**, 134-181.
6. a) G. Brieger and T. J. Nestrick, *Chem. Rev.*, 1974, **74**, 567-580; b) J.-E. Bäckvall, *J. Organomet. Chem.*, 2002, **652**, 105-111; c) S. Gladiali and E. Alberico, *Chem. Soc. Rev.*, 2006, **35**, 226-236; d) J. S. M. Samec, J.-E. Backvall, P. G. Andersson and P. Brandt, *Chem. Soc. Rev.*, 2006, **35**, 237-248; e) D. Wang and D. Astruc, *Chem. Rev.*, 2015, **115**, 6621-6686.
7. a) S. Enthaler, *ChemSusChem*, 2008, **1**, 801-804; b) F. Joó, *ChemSusChem*, 2008, **1**, 805-808; c) T. C. Johnson, D. J. Morris and M. Wills, *Chem. Soc. Rev.*, 2010, **39**, 81-88; d) A. Boddien, F. Gärtner, C. Federsel, P. Sponholz, D. Mellmann, R. Jackstell, H. Junge and M. Beller, *Angew. Chem. Int. Ed.*, 2011, **50**, 6411-6414; e) Q.-Y. Bi, J.-D. Lin, Y.-M. Liu, H.-Y. He, F.-Q. Huang and Y. Cao, *Angew. Chem. Int. Ed.*, 2016, **55**, 11849-11853.
8. a) G. Szoellosi, P. Forgo and M. Bartok, *Chirality*, 2003, **15**, S82-S89; b) A. Kulkarni, R. Gianatassio and B. Torok, *Synthesis*, 2011, 1227-1232; c) B. Abarca, R. Adam and R. Ballesteros, *Org. Biomol. Chem.*, 2012, **10**, 1826-1833; d) R. Liu, T. Cheng, L. Kong, C. Chen, G. Liu and H. Li, *J. Catal.*, 2013, **307**, 55-61; e) L. Tao, Q. Zhang, S.-S. Li, X. Liu, Y.-M. Liu and Y. Cao, *Adv. Synth. Catal.*, 2015, **357**, 753-760.
9. a) M. Rueping, A. P. Antonchick and T. Theissmann, *Angew. Chem. Int. Ed.*, 2006, **45**, 3683-3686; b) Q.-S. Guo, D.-M. Du and J. Xu, *Angew. Chem. Int. Ed.*, 2008, **47**, 759-762; c) I. Chatterjee and M. Oestreich, *Angew. Chem. Int. Ed.*, 2015, **54**, 1965-1968; d) C. R. Shugrue and S. J. Miller, *Angew. Chem. Int. Ed.*, 2015, **54**, 11173-11176; e) Y.-T. Xia, X.-T. Sun, L. Zhang, K. Luo and L. Wu, *Chem. Eur. J.*, 2016, **22**, 17151-17155.
10. V. H. Mai and G. I. Nikonov, *Organometallics*, 2016, **35**, 943-949.
11. Q. Xuan and Q. Song, *Org. Lett.*, 2016, **18**, 4250-4253.
12. a) K.-i. Fujita, C. Kitatsuji, S. Furukawa and R. Yamaguchi, *Tetrahedron Lett.*, 2004, **45**, 3215-3217; b) A. M. Voutchkova, D. Gnanamgari, C. E. Jakobsche, C. Butler, S. J. Miller, J. Parr and R. H. Crabtree, *J. Organomet. Chem.*, 2008, **693**, 1815-1821; c) D. Talwar, H. Y. Li, E. Durham and J. Xiao, *Chem. Eur. J.*, 2015, **21**, 5370-5379.
13. a) P. Frediani, L. Rosi, L. Cetarini and M. Frediani, *Inorg. Chim. Acta*, 2006, **359**, 2650-2657; b) C. Wang, C. Li, X. Wu, A. Pettman and J. Xiao, *Angew. Chem. Int. Ed.*, 2009, **48**, 6524-6528; c) J. Wu, C. Wang, W. Tang, A. Pettman and J. Xiao, *Chem. Eur. J.*, 2012, **18**, 9525-9529; d) L. Zhang, R. Qiu, X. Xue, Y. Pan, C. Xu, H. Li and L. Xu, *Adv. Synth. Catal.*, 2015, **357**, 3529-3537.
14. R. M. Bullock, *Science*, 2013, **342**, 1054.
15. a) C. Sui-Seng, F. Freutel, A. J. Lough and R. H. Morris, *Angew. Chem. Int. Ed.*, 2008, **47**, 940-943; b) A. Naik, T. Maji and O. Reiser, *Chem. Commun.*, 2010, **46**, 4475-4477; c) W. Zuo, A. J. Lough, Y. F. Li and R. H. Morris, *Science* 2013, **342**, 1080-1083; d) R. Bigler, R. Huber and A. Mezzetti, *Angew. Chem. Int. Ed.*, 2015, **54**, 5171-5174; e) L. S. Sharninghausen, B. Q. Mercado, R. H. Crabtree and N. Hazari, *Chem. Commun.*, 2015, **51**, 16201-16204.
16. a) T.-P. Lin and J. C. Peters, *J. Am. Chem. Soc.*, 2013, **135**, 15310-15313; b) G. Zhang and S. K. Hanson, *Chem. Commun.*, 2013, **49**, 10151-10153; c) S. Fu, N.-Y. Chen, X. Liu, Z. Shao, S.-P. Luo and Q. Liu, *J. Am. Chem. Soc.*, 2016, **138**, 8588-8594; d) Z. Shao, S. Fu, M. Wei, S. Zhou and Q. Liu, *Angew. Chem. Int. Ed.*, 2016, **55**, 14653-14657.
17. M. Perez, S. Elangovan, A. Spannenberg, K. Junge and M. Beller, *ChemSusChem*, 2017, **10**, 83-86.
18. F. Nador, Y. Moglie, C. Vitale, M. Yus, F. Alonso and G. Radivoy, *Tetrahedron*, 2010, **66**, 4318-4325.
19. a) A. Boddien, D. Mellmann, F. Gärtner, R. Jackstell, H. Junge, P. J. Dyson, G. Laurenczy, R. Ludwig and M. Beller, *Science*, 2011, **333**, 1733; b) G. Wienhöfer, I. Sorribes, A. Boddien, F. Westerhaus, K. Junge, H. Junge, R. Llusar and M. Beller, *J. Am. Chem. Soc.*, 2011, **133**, 12875-12879; c) G. Wienhofer, F. A. Westerhaus, R. V. Jagadeesh, K. Junge, H. Junge and M. Beller, *Chem. Commun.*, 2012, **48**, 4827-4829; d) G. Wienhöfer, F. A. Westerhaus, K. Junge and M. Beller, *J. Organometallic Chem.*, 2013, **744**, 156-159.

View Article Online
DOI: 10.1039/C7CY00437K

20. R. Adam, J. R. Cabrero-Antonino, A. Spannenberg, K. Junge, R. Jackstell and M. Beller, *Angew. Chem. Int. Ed.*, 2017, DOI: 10.1002/anie.201612290.
21. Previous examples of cobalt catalysed hydrogenation of quinolines with an homogeneous catalyst: a) R. Xu, S. Chakraborty, H. Yuan and W. D. Jones, *ACS Catal.*, 2015, **5**, 6350-6354; with an heterogeneous catalyst: b) F. Chen, A.-E. Surkus, L. He, M.-M. Pohl, J. Radnik, C. Topf, K. Junge and M. Beller, *J. Am. Chem. Soc.*, 2015, **137**, 11718-11724; c) Z. Wei, Y. Chen, J. Wang, D. Su, M. Tang, S. Mao and Y. Wang, *ACS Catal.*, 2016, **6**, 5816-5822.
22. a) Y. Li, S. Yu, X. Wu, J. Xiao, W. Shen, Z. Dong and J. Gao, *J. Am. Chem. Soc.*, 2014, **136**, 4031-4039; b) S. Elangovan, C. Topf, S. Fischer, H. Jiao, A. Spannenberg, W. Baumann, R. Ludwig, K. Junge and M. Beller, *J. Am. Chem. Soc.*, 2016, **138**, 8809-8814.