Green Chemistry

COMMUNICATION

View Article Online
View Journal

Cite this: DOI: 10.1039/c8gc00037a

Received 4th January 2018,
Accepted 22nd January 2018

DOI: 10.1039/c8gc00037a

rsc.li/greenchem

Protection of COOH and OH groups in acid, base and salt free reactions†

Xiaotao Zhu,[a,b] Bo Qian,[b] Rongbiao Wei,[a,b] Jian-Dong Huang [a] and Hongli Bao *[b]

We report an iron-catalyzed general functional group protection method with inexpensive reagents. This environmentally benign process does not use acids or bases, and does not produce waste products. Further purification beyond filtration and evaporation is, in most cases, unnecessary. Free COOH and OH groups can be protected in a one-pot reaction.

Protection of functional groups, one of the most essential methodologies in organic chemistry, has been broadly applied in the synthesis of small organic molecules and complex natural products. A large number of classical functional group protection methods have been developed.[1] Consistent with atom economy, the methyl group is frequently used to protect carboxylic acids and the acetylating group is used to protect hydroxyl groups. Methanol,[2] dimethyl sulfate,[3] iodomethane,[4] diazomethane,[5] trimethylsilyl diazomethane,[6] dimethyl carbonate,[7] or organic peroxides[8] have been employed as *O*-methylation agents in the protection of carboxylic acids and *O*-acylation of phenols or alcohols with acid anhydrides,[9] acyl chlorides[10] acetic acid[11] or esters[12] as acylating agents has been reported (Fig. 1a). However, a comprehensive consideration of environmental cost, atom economy and practical operations, which constitute limitations of these traditional methods should not be ignored. For instance, hazardous or harmful methylating and acetylating reagents are often used, resulting in high environmental costs; the use of stoichiometric quantities of an acid or a base as a promoter leads to a large amount of waste salt products which can complicate work-up procedures.

Methyl *t*-butyl ether (MTBE) is a minimally toxic, inexpensive and low-boiling point compound, which has usually been used as a solvent[13] or a *t*-butylating reagent.[14] A typical

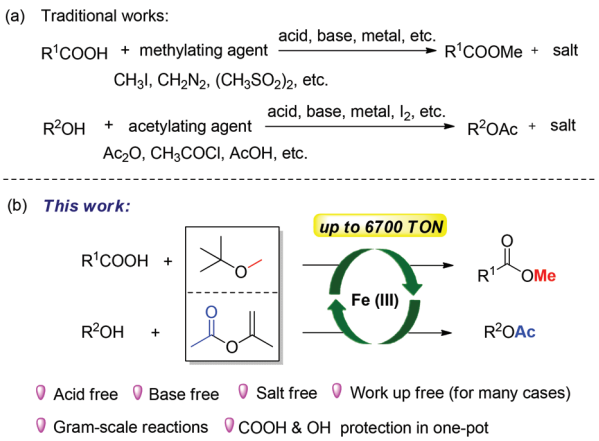


Fig. 1 Acid, base and salt free protection of functional groups.

example of its use describes the *O*-methylation of carboxylic acids using MTBE as the methylating reagent with sulfuric acid. A basic solution is necessary to quench this reaction.[15] Isopropenyl acetate (IPA) is utilized as an acetylation reagent in the catalytic protection of alcohols or phenols using molecular iodine as the catalyst.[16] However, an aqueous solution of sodium thiosulfate must be added to destroy the iodine after the acetylation reaction is complete.[17]

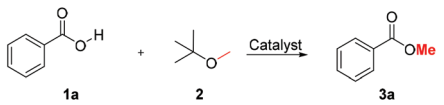
In this work, we established a method which is acid-free and base-free for the protection of carboxylic acids and the hydroxyl group using $Fe(OTf)_3$ as a Lewis acid catalyst under mild reaction conditions. No waste salt is generated in this reaction and the work-up step of the transformation is very simple. The reaction products can be obtained by removal of the catalyst *via* filtration and removal of the solvent or low boiling by-products *via* evaporation.

Initially, the esterification of benzoic acid (**1a**) was investigated using MTBE as both the methylating reagent and the solvent in the presence of a metal catalyst (Table 1). Metal catalysts such as $CoCl_2$, $Ni(OTf)_2$, $Cu(OAc)_2$ and $Fe(OTf)_2$ produce no desired product (**3a**) when treated at 90 °C for 8 h (entries 1–4). Only trace amounts of methyl ester (**3a**) and *t*-butyl ester

[a]College of Chemistry, Fuzhou University, Fuzhou, Fujian 350108, P. R. China
[b]State Key Laboratory of Structural Chemistry, Key Laboratory of Coal to Ethylene Glycol and Its Related Technology, Fujian Institute of Research on the Structure of Matter, University of Chinese Academy of Sciences, 155 Yangqiao Road West, Fuzhou, Fujian 350002, P. R. China. E-mail: hlbao@fjirsm.ac.cn

†Electronic supplementary information (ESI) available. See DOI: 10.1039/c8gc00037a

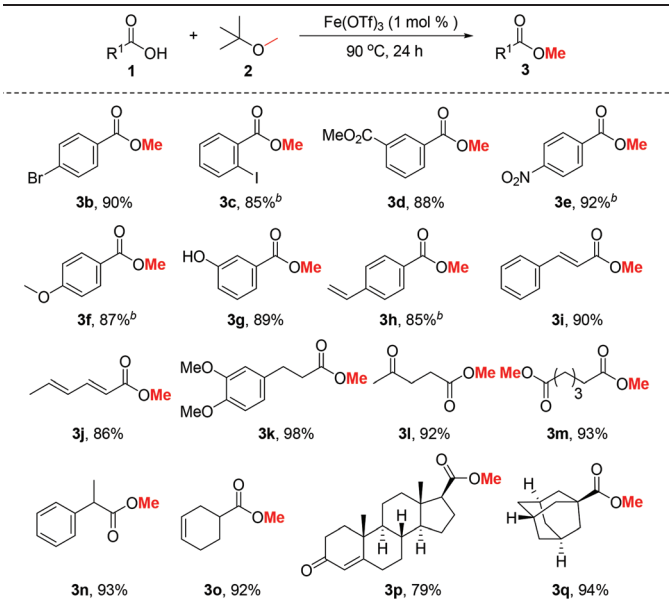
Table 1 Optimization of the reaction conditions[a]



Entry	Catalyst (mol %)	Temp. (°C)	Yield[b] (%)
1	$CoCl_2$ (10)	90	—[c]
2	$Ni(OTf)_2$ (10)	90	—[c]
3	$Cu(OAc)_2$ (10)	90	—[c]
4	$Fe(OTf)_2$ (10)	90	—[c]
5	$FeCl_3$ (10)	90	Trace
6	$Fe(OTf)_3$ (10)	90	99
7	$Fe(OTf)_3$ (10)	80	98
8	$Fe(OTf)_3$ (10)	75	92
9	$Fe(OTf)_3$ (10)	70	69
10	$Fe(OTf)_3$ (10)	60	56
11	$Fe(OTf)_3$ (10)	50	21
12	$Fe(OTf)_3$ (10)	25	—[c]
13	$Fe(OTf)_3$ (5)	90	89
14	$Fe(OTf)_3$ (2.5)	90	48
15	$Fe(OTf)_3$ (1)	90	29
16	$Fe(OTf)_3$ (1)	90	90[d]
17	$Fe(OTf)_3$ (0.5)	90	87[d]
18	$Fe(OTf)_3$ (0.5)	90	85[e]

[a] Reaction conditions: Benzoic acid (**1a**) (0.4 mmol, 1 equiv.), MTBE (**2**) (1 mL), 8 h. [b] Yields of product (**3a**) were determined by GC analysis with 1,4-dimethoxybenzene as an internal standard. [c] Methyl ester (**3a**) was not detected. [d] **1a** (20 mmol, 1 equiv.), MTBE (**2**) (10 mL), 24 h, ^{1}H NMR yield. [e] **1a** (50 mmol, 1 equiv.), MTBE (**2**) (25 mL), 24 h, ^{1}H NMR yield.

Table 2 *O*-Methylation of various carboxylic acids with MTBE[a]



[a] Reaction conditions: Carboxylic acids (**1**) (5 mmol, 1 equiv.), $Fe(OTf)_3$ (1 mol%), MTBE (2.5 mL), 90 °C, 24 h, isolated yield. [b] **1** (2 mmol, 1 equiv.), $Fe(OTf)_3$ (5 mol%), MTBE (2 mL), 24 h.

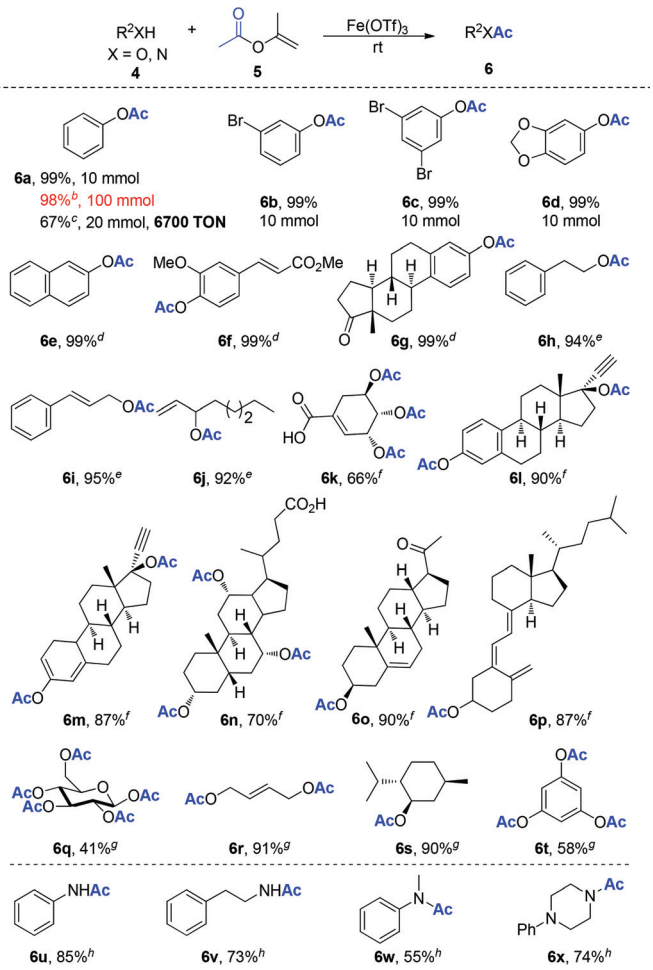
are observed in the presence of $FeCl_3$ (entry 5), which prompt the investigation of other iron catalysts. When 10 mol% of $Fe(OTf)_3$ is used as the catalyst, *O*-methylation proceeds smoothly and the product, methyl benzoate (**3a**) is obtained in 99% yield (entry 6). Further temperature screening shows that 90 °C is the optimal temperature for the reaction (entries 7–12), because *t*-butyl ester could be detected at low temperatures. The yields of **3a** decrease to 89%, 48% and 29%, respectively, when the catalyst loading is decreased to 5, 2.5 and 1 mol% (entries 13–15). Interestingly, the reaction proceeded better on a large reaction scale with low catalyst loading at high concentration. For example, 20 mmol of **1a** (2.44 g) could be protected to afford product **3a** in 90 and 87% yields with 1 and 0.5 mol% of $Fe(OTf)_3$, respectively (entries 16 and 17). Furthermore, 50 mmol of **1a** also afforded the desired product in 85% yield (entry 18).

With the optimal reaction conditions identified, the scope of carboxylic acid was studied on a 2 or 5 mmol reaction scale (Table 2). The large scale reactions are carried out at high concentration with 1 or 5 mol% of $Fe(OTf)_3$. Both electron-withdrawing and electron-donating benzoic acid substituents are well tolerated in the *O*-methylation reaction, affording the corresponding methyl esters (**3b–3h**) in good to excellent yields (85–92%). Cinnamic acid and (2*E*,4*E*)-hexa-2,4-dienoic acid are highly reactive, and can be converted into products **3i** and **3j** in 90% and 86% yields, respectively. Aliphatic acids are compatible under standard reaction conditions, producing the desired products. Acids containing primary, secondary or tertiary alkyl groups afford methyl esters (**3k–3q**) with good to excellent yields (79–98%). The double methylation product (**3m**) is generated from the primary aliphatic acid (**1m**) containing two acid groups and the derivatives of natural products or drugs, such as **1p** and **1q**, can also be protected to deliver the desired esters (**3p** and **3q**). It should be noted that when the reaction reaches completion, protective products in most cases can be directly isolated with excellent purity by removal of the catalyst *via* filtration and removal of the solvent under vacuum.

Using the conditions of the *O*-methylation reaction, we found that 10 and 100 mmol of phenol (**4a**) reach full conversion at room temperature in the presence of 0.1 mol% of $Fe(OTf)_3$, affording the product (**6a**) in 99 and 98% yields, separately (Table 3). In particular, when only 0.01 mol% of $Fe(OTf)_3$ is used, 6700 TON could be obtained in the protection of **4a**, showing a high efficiency of the reaction. Substituted phenols can be transformed into the corresponding products (**6b–6g**) with excellent yields. Various primary, secondary and tertiary aliphatic alcohols react readily with IPA affording the esters (**6h–6m**) in moderate to excellent yields (66–95%). Additionally, the acetylating reagent IPA is selective, reacting with hydroxyl groups rather than carboxyl groups (**6n**) or ketones (**6o**) under $Fe(OTf)_3$ catalytic conditions.[18] Products (**6q–6t**) are generated through increasing the catalyst loading and solvent amount. Notably, primary and secondary amines are successfully transferred to the corresponding secondary and tertiary amides (**6u–6x**) in 55–85% yields.

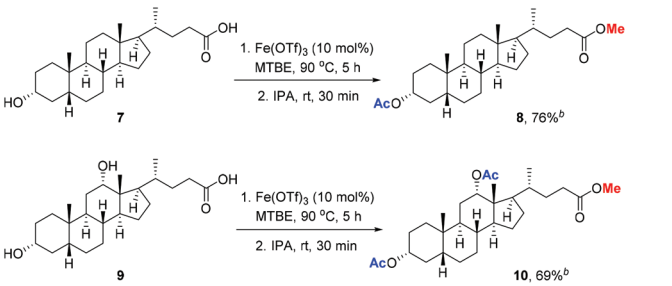
Sequential protection of the COOH and OH groups of complex natural products, such as lithocholic acid (**7**) and deoxycholic acid (**9**), was studied under standard reaction con-

Table 3 *O*-Acetylation of various phenols and alcohols with IPA[a]

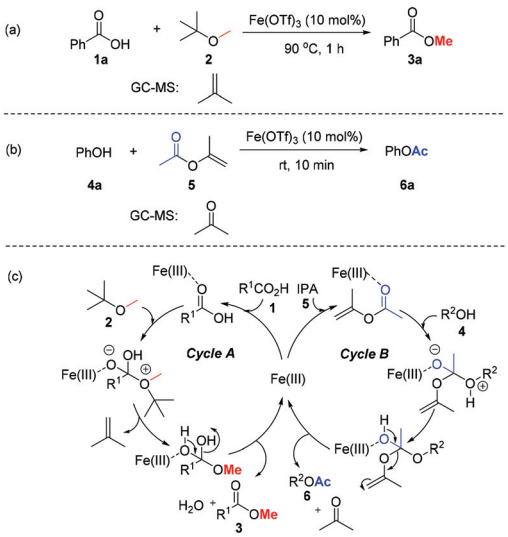


[a] Reaction conditions: **4** (10 mmol, 1 equiv.), $Fe(OTf)_3$ (0.1 mol%), IPA (2.5 mL), 5 h, room temperature, isolated yields. [b] **4** (100 mmol, 1 equiv.), $Fe(OTf)_3$ (0.1 mol%), IPA (25 mL). [c] **4** (20 mmol, 1 equiv.), $Fe(OTf)_3$ (0.01 mol%), IPA (5 mL), 24 h. [d] **4** (5 mmol, 1 equiv.), $Fe(OTf)_3$ (0.2 mol%), IPA (2.5 mL). [e] **4** (5 mmol, 1 equiv.), $Fe(OTf)_3$ (0.5 mol%), IPA (2.5 mL). [f] **4** (2.5 mmol, 1 equiv.), $Fe(OTf)_3$ (1 mol%), IPA (2.5 mL). [g] **4** (1 mmol, 1 equiv.), $Fe(OTf)_3$ (10 mol%), IPA (2.5 mL), 0.5 h. [h] **4** (1 mmol, 1 equiv.), $Fe(OTf)_3$ (10 mol%), IPA (2.5 mL), 24 h.

Table 4 Sequential protection of COOH and OH in a one-pot reaction[a]



[a] Reaction conditions: (1) **7** or **9** (0.5 mmol, 1 equiv.), $Fe(OTf)_3$ (10 mol%), MTBE (1 mL), 90 °C, 5 h. (2) IPA (1 mL), 30 min, room temperature. [b] Isolated yields.



Scheme 1 Preliminary mechanistic study.

ditions and, in a one-pot reaction delivers the compounds (**8** and **10**) in 76% and 69% yields, respectively (Table 4).

In order to probe the reaction mechanism, protections of benzoic acid (**1a**) and phenol (**4a**) were carried out and followed by GC-MS. Isobutylene was detected in the *O*-methylation reaction (Scheme 1a), and acetone was found using GC-MS in the *O*-acetylation reactions (Scheme 1b). Based on these results, a possible mechanism of $Fe(OTf)_3$ catalyzed protection of functional groups is proposed.

A proposed mechanism is presented in Scheme 1c. As shown in cycle A, Fe(III) activates the carboxylic acid, which plays the role of a Lewis acid to facilitate attack by MTBE. Liberation of isobutylene and water promotes the formation of the protected product (**3**) and regeneration of the Fe(III) catalyst. In cycle B, isopropenyl acetate is activated under Fe(III) catalysis, and can be attacked by phenols or alcohols. After release of acetone, the acetylated product (**6**) is formed and Fe(III) is regenerated.

Conclusions

In summary, protection of carboxylic acids and phenols/alcohols has been achieved under mild reaction conditions in the absence of any acid, base or salt. $Fe(OTf)_3$, a Lewis acid catalyst is first used in the transformation in which MTBE is employed as a methylating agent and IPA as an acylating reagent. Various carboxylic acids and phenols or alcohols are tolerated in the catalytic system and afford the desired products in moderate to high yields. For the complex analogues of natural compounds containing carboxylic acid and hydroxyl groups, all of these functional groups can be protected in a one-pot reaction. A gram-scale reaction could be run with high efficiency under solvent-free conditions. This protocol thus provides a simple,

green and effective approach to the protection of carboxylic acids and hydroxyl groups.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We acknowledge the Strategic Priority Research Program of the Chinese Academy of Sciences (Grant no. XDB20000000), The 100 Talents Program, "The 1000 Youth Talents Program" and Haixi Institute of CAS (CXZX-2017-P01) for financial support.

Notes and references

1 P. G. M. Wuts and T. W. Greene, *Protective Groups in Organic Synthesis*, Wiley Interscience, Hoboken, NJ, 5th edn, 2014.
2 (*a*) C. Lescop, C. Müller, B. Mathys, M. Birker, R. de Kanter, C. Kohl, P. Hess, O. Nayler, M. Rey, P. Sieber, B. Steiner, T. Weller and M. H. Bolli, *Eur. J. Med. Chem.*, 2016, **116**, 222; (*b*) H. Sharghi and M. H. Sarvari, *Tetrahedron*, 2003, **59**, 3627; (*c*) G.-S. Zhang, *Synth. Commun.*, 1998, **28**, 1159; (*d*) B. Neises and W. Steglich, *Angew. Chem., Int. Ed. Engl.*, 1978, **17**, 522.
3 (*a*) Ambika, P. P. Singh and S. M. S. Chauhan, *Synth. Commun.*, 2008, **38**, 928; (*b*) A. K. Chakraborti, A. Basak and V. Grover, *J. Org. Chem.*, 1999, **64**, 8014; (*c*) H. Ogawa, Y. Ichimura, T. Chihara, S. Teratani and K. Taya, *Bull. Chem. Soc. Jpn.*, 1986, **59**, 2481.
4 (*a*) J. P. Parrish, E. E. Dueno, S.-I. Kim and K. W. Jung, *Synth. Commun.*, 2000, **30**, 2687; (*b*) D. Mal, *Synth. Commun.*, 1986, **16**, 331.
5 (*a*) R. A. Maurya, C. P. Park, J. H. Lee and D.-P. Kim, *Angew. Chem., Int. Ed.*, 2011, **50**, 5952; (*b*) Y. Sekine, C. Creveling, M. Bell and A. Brossi, *Helv. Chim. Acta*, 1990, **73**, 426; (*c*) T. H. Black, *Aldrichimica Acta*, 1983, **16**, 3.
6 (*a*) S. S. Zimmerman, A. Khatri, E. C. Garnier-Amblard, P. Mullasseril, N. L. Kurtkaya, S. Gyoneva, K. B. Hansen, S. F. Traynelis and D. C. Liotta, *J. Med. Chem.*, 2014, **57**, 2334; (*b*) N. S. Hodnett, *Synlett*, 2003, 2095.
7 (*a*) R. I. Khusnutdinov, N. A. Shchadneva, Yu. Yu. Mayakova, Yu. S. Konovalova, A. N. Khazipova and B. I. Kutepov, *Russ. J. Org. Chem.*, 2017, **53**, 163; (*b*) F. Rajabi and M. R. Saidi, *Synth. Commun.*, 2004, **34**, 4179; (*c*) W.-C. Shieh, S. Dell and O. Repič, *J. Org. Chem.*, 2002, **67**, 2188; (*d*) Y. Lee and I. Shimizu, *Synlett*, 1998, 1063.
8 Q. Xia, X. Liu, Y. Zhang, C. Chen and W. Chen, *Org. Lett.*, 2013, **15**, 3326.
9 (*a*) F. Panahi, R. Fareghi-Alamdari, S. K. Dangolani, A. Khalafi-Nezhad and M. Golestanzadeh, *ChemistrySelect*, 2017, **2**, 474; (*b*) S. Xu, I. Held, B. Kempf, H. Mayr, W. Steglich and H. Zipse, *Chem. – Eur. J.*, 2005, **11**, 4751; (*c*) A. K. Chakraborti and R. Gulhane, *Chem. Commun.*, 2003, 1896; (*d*) K. K. Chauhan, C. G. Frost, I. Love and D. Waite, *Synlett*, 1999, 1743; (*e*) Z.-F. Tao, X. Qian and M. Fan, *Tetrahedron*, 1997, **53**, 13329; (*f*) J. Iqbal and R. R. Srivastava, *J. Org. Chem.*, 1992, **57**, 2001.
10 (*a*) S. Farhadi and S. Panahandehjoo, *Appl. Catal., A*, 2010, **382**, 293; (*b*) G. P. Wild, C. Wiles, P. Watts and S. J. Haswell, *Tetrahedron*, 2009, **65**, 1618; (*c*) S. Bartsch, R. Kourist and U. T. Bornscheuer, *Angew. Chem., Int. Ed.*, 2008, **47**, 1508; (*d*) T. Sano, K. Ohashi and O. Takeshi, *Synthesis*, 1999, 1141; (*e*) K. Ishihara, H. Kurihara and H. Yamamoto, *J. Org. Chem.*, 1993, **58**, 3791.
11 A. G. M. Barrett and D. C. Braddock, *Chem. Commun.*, 1997, 351.
12 (*a*) I. N. Francesco, J.-J. Filippi and S. Antoniotti, *ChemPlusChem*, 2017, **82**, 1; (*b*) N. Iranpoor, H. Firouzabadi and A. Jamalian, *Tetrahedron Lett.*, 2005, **46**, 7963; (*c*) S. S. Rana, J. J. Barlow and K. L. Matta, *Tetrahedron Lett.*, 1981, **22**, 5007.
13 (*a*) T. Ants and S. J. Meeri, *Organomet. Chem.*, 1999, **586**, 145; (*b*) S. Meeri and T. Ants, *Helv. Chim. Acta*, 2003, **86**, 82; (*c*) M. Stroezel, U. Rheude, T. R. Ralf and G. Kalbel, *U.S. Patent*, 6054628, 2000.
14 (*a*) S. Pia, V. Gupta and S. Chilukuri, *J. Mol. Catal. A: Chem.*, 2007, **265**, 109; (*b*) M. Schulz, K. Seiffarth, M. Nuechter and H. Khairi, *EP*, DD288591(A1), 1991.
15 P. Dawar, M. B. Raju and R. A. Ramakrishna, *Tetrahedron Lett.*, 2011, **52**, 4262.
16 (*a*) H. Cao, X.-H. Zhu, D. Wang, Z. Sun, Y. Deng, X.-F. Hou and D. Zhao, *ACS Catal.*, 2015, **5**, 27; (*b*) A. Peeters, R. Ameloot and D. E. De Vos, *Green. Chem.*, 2013, **15**, 1150; (*c*) T. Zeng, G. Song and C.-J. Li, *Chem. Commun.*, 2009, 6249; (*d*) M.-H. Lin and T. V. RajanBabu, *Org. Lett.*, 2000, **2**, 997.
17 N. Ahmed and J. E. van Lier, *Tetrahedron Lett.*, 2006, **47**, 5345.
18 H. J. Hagemeyer and D. C. Hull, *Ind. Eng. Chem.*, 1949, **41**, 2920.

