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A Mild Ligand-Free Iron-Catalyzed Liberation of Alcohols from Allylcarbonates

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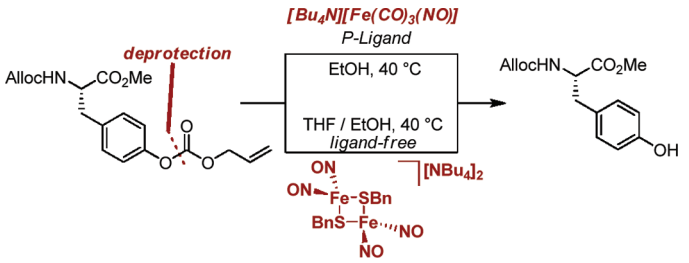
ABSTRACT



Different from most carbonates the allyloxy carbonyl protecting group can be cleaved under neutral conditions using metal catalysis. However, most of the catalysts employed to date are based upon precious metals. Herein we present two protocols for the mild Fe-catalyzed liberation of alcohols from allylcarbonates that are characterized by broad functional group tolerance and exclusive chemoselectivity.

The selective protection and deprotection of heterofunctional groups is often a prerequisite for performing complex molecule synthesis.[1,2] Apart from aspects such as selective introduction of the protecting group and orthogonality toward several reaction conditions, the mild and selective removal of the protecting group is of utmost importance. Carbonates possess several advantages as protecting groups.[3] They are inexpensive, are stable under a variety of reaction conditions, and can be tuned with regard to their reactivity by adjusting the steric and electronic properties of the remaining substituent. Common carbonate protecting groups such as e.g. BOC (*t*-butyloxy carbonyl), Fmoc (fluorenylmethyloxycarbonyl), or Cbz (Z) (carbonylbenzyloxy) are cleaved under acidic, basic, or reductive reaction conditions. The related Alloc-group (allyloxycarbonyl) on the other hand offers the chance to be cleaved in the prescence of low-valent metal complexes via an allylic substitution mechanism under neutral reactzion conditions. Whereas in the latter type of deprotection reaction Pd-complexes are commonly used,[4,5] we present herein a mild method for the cleavage of allyl carbonates for the liberation of the desired alcohol using the readily available and stable ferrate $[Bu_4N][Fe(CO)_3(NO)]$ (TBAFe)[6] as a catalyst and isopropyl thiol as an allyl scavenger at 40 °C in ethanol.

Based upon recent studies by us and others on Fe-catalyzed allylic substitutions,[7] transesterifications,[8] and

(1) (a) Green, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; John Wiley and Sons: New York, 1999. (b) Kocienski, P. J. *Protecting Groups*; Georg Thieme Verlag: Stuttgart-New York, 2004.

(2) Although protection strategies are still often necessary, a protecting group free synthesis of complex molecules is the ultimate synthetic goal; see: Young, I. S.; Baran, P. S. *Nat. Chem.* **2009**, *1*, 193.

(3) A review on the use of alkyl carbonates in organic synthesis is found in: Parrish, J. P.; Salvatore, R. N.; Jung, K. W. *Tetrahedron* **2000**, *56*, 8207.

(4) (a) Review: Guibé, F. *Tetrahedron* **1998**, *54*, 2967. (b) Thieriet, N.; Gomez-Martinez, P.; Guibé, F. *Tetrahedron Lett.* **1999**, *4*, 2505. (c) Zorn, C.; Gnad, F.; Salmen, S.; Herpin, T.; Reiser, O. *Tetrahedron Lett.* **2001**, *42*, 7049. (d) Guibé, F.; Dangles, O.; Balavoine, G. *Tetrahedron Lett.* **1986**, *27*, 2365.

(5) Most recently a Ru-catalyzed intracellular cleavage of an allyl carbamate under physiological conditions was reported: Streu, C.; Meggers, E. *Angew. Chem.* **2006**, *118*, 5773. *Angew. Chem., Int. Ed.* **2006**, *45*, 5645.

(6) TBAFe is prepared in one step starting from pure $Fe(CO)_5$. For the preparation see ref 7d.

(7) (a) Plietker, B. *Angew. Chem.* **2006**, *118*, 1497. *Angew. Chem., Int. Ed.* **2006**, *45*, 1469. (b) Plietker, B. *Angew. Chem.* **2006**, *118*, 6200. *Angew. Chem., Int. Ed.* **2006**, *45*, 6053. (c) Plietker, B.; Dieskau, A.; Möws, K.; Jatsch, A. *Angew. Chem.* **2008**, *120*, 204. *Angew. Chem., Int. Ed.* **2008**, *47*, 198. (d) Holzwarth, M.; Dieskau, A.; Tabassam, M.; Plietker, B. *Angew. Chem.* **2009**, *121*, 7387. *Angew. Chem., Int. Ed.* **2009**, *48*, 7251. (e) Jegelka, M.; Plietker, B. *Org. Lett.* **2009**, *11*, 3462. (f) Jegelka, M.; Plietker, B. *Chem.—Eur. J.* **2011**, *17*, 10417. (g) Mayer, M.; Czaplik, W. M.; Jacobi von Wangelin, A. *Adv. Synth. Catal.* **2010**, *352*, 2147. (h) Trivedi, R.; Tunge, J. A. *Org. Lett.* **2009**, *11*, 5650. (i) Hashmi, A. S. K.; Szeimies, G. *Chem. Ber.* **1994**, *127*, 1075.

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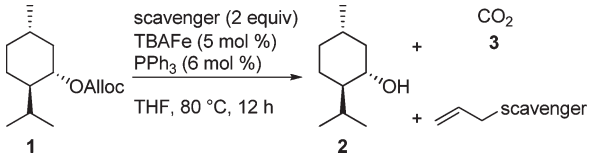
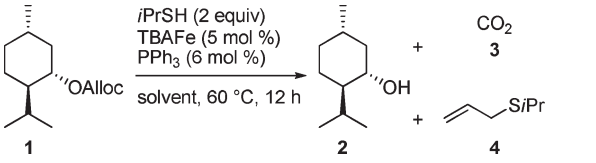
Table 1. Fe-Catalyzed Liberation of Alcohols: Influence of the Allyl Scavenger[a]



entry	scavenger	conv (%)[b]
1	$NaBH_4$	28
2	BH_3*Et_3N	–
3	$PhSiH_3$	–
4	$[NH_4][HCO_3]$	–
5	PhSH	96
6	*i*PrSH	97

[a] All reactions were performed on a 1.0-mmol scale in the presence of allyl alkyl carbonates (1.0 mmol), scavenger (2.0 mmol), TBAFe (0.05 mmol), and PPh_3 (0.06 mmol) in THF (1 mL) under a N_2 atmosphere. [b] Determined by GC-integration using dodecane as external standard.

Table 2. Fe-Catalyzed Liberation of Alcohols: Influence of the Solvent[a]



entry	solvent	conv (%)[b]
1	DMSO	77
2	DMF	17
3	CH_3CN	69
4	EtOH	99
5	1,4-Dioxane	93
6	THF	55
7	MTBE	80
8	Dichloromethane	–
9	Toluene	78

[a] All reactions were performed on a 1.0-mmol scale in the presence of allyl alkyl carbonates (1.0 mmol), *i*PrSH (2.0 mmol), TBAFe (0.05 mmol), PPh_3 (0.06 mmol) in the given solvent (1 mL) under a N_2 atmosphere. [b] Determined by GC-integration using dodecane as external standard.

hydrosilylations,[9] we wondered whether it would be possible to develop this type of nucleophilic catalysis further into a novel deprotection method for allyl alkyl carbonates applying an iron-based alternative[10] to the established palladium-based systems.[4,5] Moreover, a practical, timely deprotection reaction is characterized by traceless removal of the deprotection side products. Hence, a special emphasis was placed upon the identification of a volatile allyl scavenger that delivers a volatile allylation product, which allows for easy removal of all impurities and byproducts by simple evaporation of the crude reaction mixture. Various allyl scavengers have been employed in the corresponding Pd-catalyzed deallylation reaction. Hence, at the outset of our investigations different scavengers were tested in the deprotection of sterically hindered menthol derived carbonate **1** under the reaction conditions that proved successful in the allylic substitutions (Table 1).[7]

From these results it is obvious that thiols are most suitable for the deprotection. For reasons of convenience we selected isopropyl thiol as the scavenger of choice for further optimizations for three main reasons. Apart from the acceptable smell, the volatility of the scavenger and allylated scavenger plus its low price fulfilled all the criteria for an applicable deprotection protocol. Since both reaction temperature and catalyst perfomance needed to be optimized we subsequently turned our attention toward a screening of solvent effects (Table 2).

The reaction proceeds in quantitative conversions in polar solvents. Both ethanol and 1,4-dioxane (entries 4 and 5, Table 2) gave full conversion after 12 h at 60 °C. At this point the influence of ligands was investigated. A variety of different monodentate ligands were tested. Bulky electron-rich phosphines were the most potent ones. Using either PCy_3 or $PMes_3$ (Mes = 2,4,6-trimethylphenyl), full conversion was obtained using 2.5 mol % TBAFe, 2.8 mol % ligand at 40 °C. At this temperature only ethanol allowed for good conversion rates (conditions A, Scheme 1). Recently we disclosed a related study in which we were able to show that TBAFe in the presence of an excess thiol is transferred into electron-rich binuclear Fe-complexes of the type $[Bu_4N]_2[(NO)_2Fe(SR)]_2$.[11] These carbonyl-free complexes allow for a regioselective sulfenylation already at temperatures of 40 °C under ligand-free conditions. Alternativley, the acitve species can be prepared in situ starting from the readily available oxidized complex $[(NO)_2Fe(SR)]_2$, potassium hydride, and TBABr. We envisioned complexes of this type to be formed under the given deprotection conditions. To our delight $[Bu_4N]_2$-$[(NO)_2Fe(SR)]_2$ is equally capable of deprotecting menthol derivative **1** quantitatively even in the absence of any ligand (conditions B, Scheme 1).

With the optimized conditions in hand we subsequently turned our attention toward an exploration of the scope and limitation of this process (Table 3).

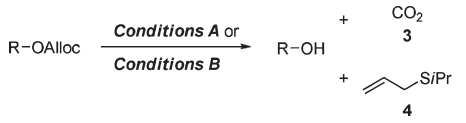
(8) (a) Magens, S.; Ertelt, M.; Jatsch, A.; Plietker, B. *Org. Lett.* **2008**, *10*, 53. (b) Magens, S.; Plietker, B. *J. Org. Chem.* **2010**, *75*, 3715. (c) Magens, S.; Plietker, B. *Chem.—Eur. J.* **2011**, *17*, 8807.

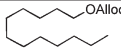
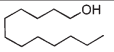
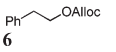
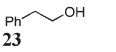
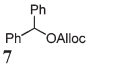
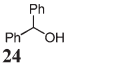
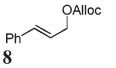
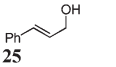
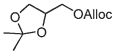
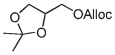
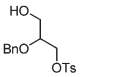
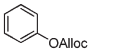
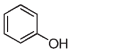
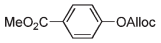
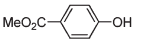
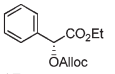
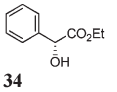
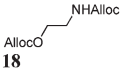
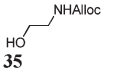
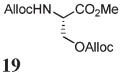
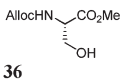
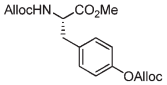
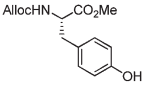
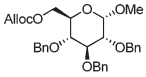
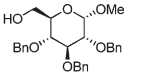
(9) (a) Dieskau, A.; Begouin, J. M.; Plietker, B. *Eur. J. Org. Chem.* **2011**, 5291. (b) Shaikh, N. S.; Enthaler, S.; Junge, K.; Beller, M. *Angew. Chem.* **2008**, *120*, 2531. *Angew. Chem., Int. Ed.* **2008**, *47*, 2497.

(10) For recent reviews on Fe-catalysis, see: (a) *Advances in Sustainable Metal Catalysis: Iron Catalysis (Topics in Organometallic Chemistry)*; Plietker, B., Ed.; Springer-Verlag: Heidelberg, 2011. (b) *Iron Catalysis in Organic Synthesis*; Plietker, B., Ed.; Wiley-VCH, Weinheim, 2008. (c) Correa, A.; Garcḳa Manchano, O.; Bolm, C. *Chem. Soc. Rev.* **2008**, *37*, 1108. (d) Bolm, C.; Legros, J.; Le Paih, J.; Zani, L. *Chem. Rev.* **2004**, *104*, 6217. (e) Dieskau, A.; Plietker, B. *Eur. J. Org. Chem.* **2009**, 775.

(11) Holzwarth, M. S., Frey, W.; Plietker, B. *Chem. Commun.* **2011**, DOI:10.1039/C1CC14599A.

Table 3. Fe-Catalyzed Liberation of Alcohols: Substrate Scope[a]

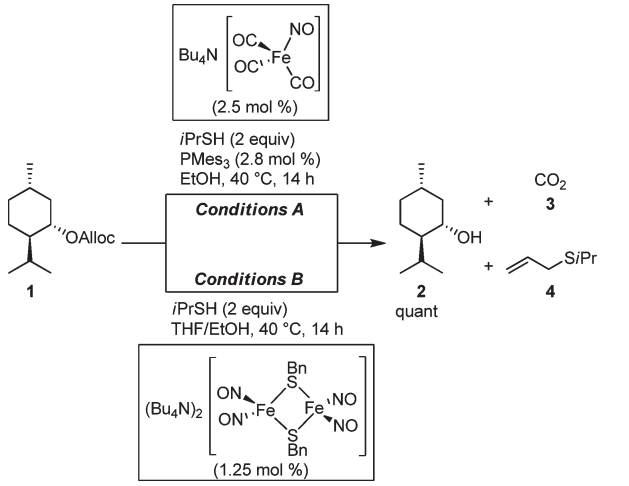


entry	substrate	product	A yield (%)[b]	B yield (%)[b]
1	 **5**	 **22**	98	99
2	 **6**	 **23**	98	95
3	 **7**	 **24**	93	96
4	 **8**	 **25**	82	72
5	 **9**	 **26**	96	96
6	 **10** (R = TBS)	 **27**	85	81
7	**11** (R = THP)	**28**	94	97
8	**12** (R = Bz)	**29**	>99	94
9	**13** (R = Fmoc)	**30**	50	53
10	 **14**	 **31**	79	74
11	 **15**	 **32**	98	99
12	 **16**	 **33**	96	96
13	 **17**	 **34**	87 (> 99)[d]	93 (> 99)[d]
14	 **18**	 **35**	94	88
15	 **19**	 **36**	83[c] (> 98)[e]	79[c] (> 98)[e]
16	 **20**	 **37**	91[c] (> 98)[f,12]	94[c] (> 98)[f,12]
17	 **21**	 **38**	86	90

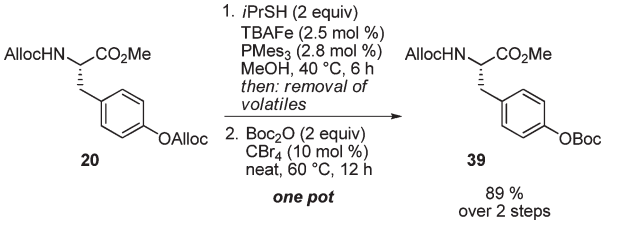
[a] All reactions were performed on a 1.0-mmol scale in the presence of allyl alkyl carbonates (1.0 mmol), *i*PrSH (2.0 mmol) under *conditions A:* TBAFe (0.025 mmol), $PMes_3$ (0.028 mmol) in EtOH (1 mL) under a N_2 atmosphere; or *conditions B:* $[Fe(NO)_2(SBn)]_2$ (0.0125 mmol), KH (0.025 mmol), TBABr (0.025 mmol) in THF/EtOH (0.3/1 mL). [b] Isolated yields. The enantiomeric excess as a percent value is given in parentheses. [c] MeOH was used instead of EtOH. [d] The enantiomeric excess was determined by chiral HPLC. [e] Established by ^{19}F NMR spectroscopy using the Mosher ester methodology. [f] Enantiopurity was established by comparison of optical rotation with literature values.

A variety of functional groups are stable under both deprotection conditions. Acid labile or base sensitive protecting groups are not reactive (entries 5−10, Table 3).

Scheme 1. Fe-Catalyzed Alloc-Deprotection



Scheme 2. Chemoselective One-Pot Fe-Catalyzed Transprotection

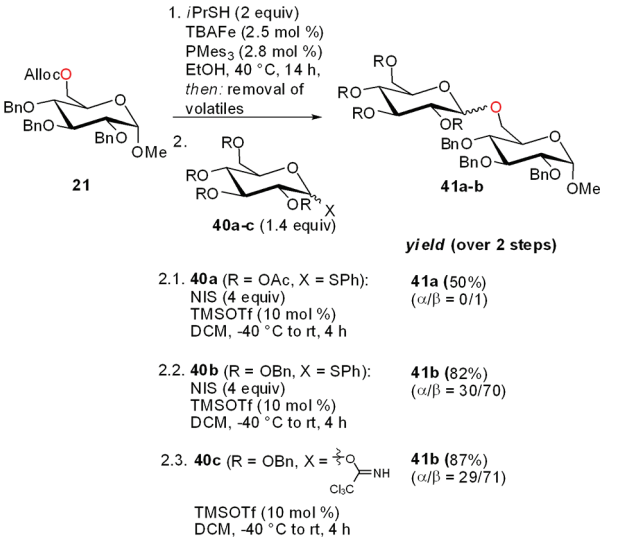


Furthermore carbamates are stable under the given conditions thus allowing for a selective monodeprotection of *N,O-bis*-alloc-protected aminoethanol **18**, serine derivative **19**, and tyrosine derivative **20** (entries 14−16, Table 3). To avoid possible transesterification processes, MeOH was used as the solvent. As already observed in the Fe-catalyzed transesterifcations the mild and neutral reaction conditions allow for a successful deprotection without epimerization of labile stereocenters. In all cases the desired product was obtained with almost full conservation of enantiopurity (entries 13, 15−17, Table 3). Both catalytic systems display a similar reactivity and hence might be regarded as equally suitable.

These results set the stage for a selective Fe-catalyzed transprotection of tyrosine derivative **20**. Hence, when **20** is subjected to the deprotection conditions with subsequent addition of Boc_2O[12] and catalytic amounts of CBr_4, the desired *O*-Boc-*N*-Alloc-protected tyrosine derivative **39** was obtained in 89% yield over two steps in a one-pot operation (Scheme 2). The analogous transformation employing standard protocols[1,4a] using catalytic amounts of $[(Ph_3P)_4Pd]$ and allyl scavengers such as

(12) Chankeshwara, S. V.; Chebolu, R.; Chakraborti, A. K. *J. Org. Chem.* **2008**, *73*, 8615.

Scheme 3. Fe-Catalyzed One-Pot Deprotection–Glycosylation[a]



[a] The α/β-ratio was determined by integration of OMe-groups in the ^{1}H NMR spectra.

dimedone, morpholine, or $NaBH_4$ led to mixtures of mono- and bisdeprotected product as well as to the corresponding allyl ethers and amines through decarboxylative coupling.

With these results in hand we finally set out to explore the utility of our deallylation reaction in carbohydrate chemistry. Indeed Fe-catalyzed O-deprotection of **21** and subsequent addition of the glycosyl donors **40a**–**c** using standard coupling procedures led to the formation of the desired disaccharide **41** in good yields and, depending on the glycosyl donor, good to excellent α–β-selectivities (Scheme 3). Notably not only thiophenyl but also chloroacetimidate activated glycosyl donors can be successfully converted to the corresponding disaccharides.

Iron catalysis has recently faced a tremendous comeback in the field of organometallic catalysis. The use of only catalytic amounts of the well-defined complex TBAFe $[Bu_4N[Fe(CO)_3(NO)]$ allows for neutral reaction conditions thus preventing undesired side reactions even on multifunctional organic scaffolds. The presented study underlines these previous observations. In the presence of only catalytic amounts of the air stable and readily accessible complex TBAFe and $PMes_3$ as a ligand, allyl alkyl carbonates are liberated in the presence of a variety of different functional groups without corruption of labile stereocenters. Further studies revealed a binuclear species derived from TBAFe in the presence of an excess of thiol to be of comparable reactivity, however, under ligand-free conditions. Future work along these lines includes an extension of these methods to the deprotection of allyl carbamates and their application in peptide synthesis as well as in novel glycosylation reactions.

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Supporting Information Available. Characterization data for all new compounds and experimental procedures are included. This material is available free of charge via the Internet at http://pubs.acs.org.