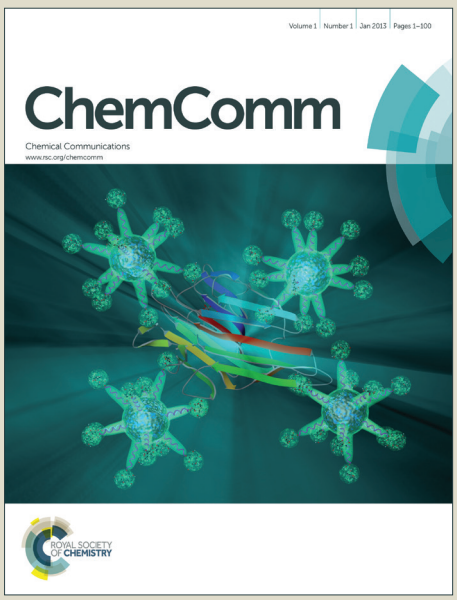
ChemComm

Accepted Manuscript



ROYAL SOCIETY OF CHEMISTRY

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Dr Kathryn Hadfield
Publishing Editor
Chemical Communication
RSC, Thomas Graham House
Science Park, Milton Road, Cambridge
UK, CB4 OWF

Dear Dr. Hadfield:

We have also revised the manuscript according to referee's comments (in file: RSC deprotection revised CC-7). In order to make it clear, all revised parts are list below. We also hope to apply for a 4-page communication for this paper.

1, In page 1, a few typing errors were found and corrected for author's names, "Mingshou Wang, Linjin Dang, Xianfu Sheng" should be "Minshou Wang, Lingjing Dang, Xianfu Shen".

2, In page 1, left column, line 16, "for the the" has been corrected to "for the".

3, In page 1, left column, line 18, "to yield an aldimines" has been changed to "to yield imines".

4, In page 1, left column, line 18, "The second step is the addition of nucleophiles to the sulfinyl imines and give *N*-tert-butanesulfinyl amines" has been changed to "The second step is the additions of nucleophiles towards the sulfinyl imines to give *N*-tert-butanesulfinyl amines" .

5, In page 1, left column, line 29, "Herein we" has been replaced by "Herein, we".

6, In page 1, right column, Scheme 2, the molecular structures for **1a**, **2a** and **3a** have been reformulated.

7, In page 2, left column, line 12, "The reaction underwent more efficiently in the absence of base" has been changed to "The reaction underwent efficiently in the absence of bases". Also in page 2, left column, Table 2, entry 9, "96%"was revised as "97%" .

8, In page 2, left column, line 38, "to our delight" has been changed to "delightfully".

9, In page 3, table 3, the structures for compound **1V** and **2V** were reformulated.

10, In page 3, left column, line 7, "We first elaborated the amine salts" has been changed to "We firstly elaborated the amine salts".

11, In page 3, left column, line 10, "3b" has been changed to "**3b**"; line 15, "analysis" has been changed to "analyses"; line 20 "1y" to "**1y**", line 21 "3c" to "**3c**"; line 24, "1b" to "**1b**".

12, In page 3, right column, title for Scheme 4, "to elaborate the pathway" has been changed to "to elaborate the possible pathway".

13, In page 4, left column, line 32, "National Basic Research Program of China (973 Program 2009CB522300)" has been changed to "Program for Changjiang Scholars and Innovative Research Team in University (IRT13095)".

We also send ChemDraw files, namely all figures and Schemes, to your office. The graphic content for table of contents entry has been provided according to the required size and maximun words (in file: Graphic content for deprotection). For enquires and suggestions made by referees: we did observe small amount of iodide compound (less than 5%) in the case of substrate **1w**, the indole ring was halogenated. In order to give readers more information about this iodine mediated deprotection, we hope to include the mechanistic discussion in page 3. However, this paragraph "For iodine catalyzed process, path A might operate. Further oxidation of tert-butylsulfinic acid (4#) in the presence of iodine might lead to other by-products (5b and 6b) as well as tert-butanol (4b). For reactions in the presence of bases, the pathway might be directed to Path B (Scheme 5) due to the basic condition. Formation of tert-butyl radical might lead to tert-butyl iodide, which afforded tert-butanol upon hydrolysis. In the presence of excess sodium carbonate, small part of the initially formed sodium tert-butylsulfinate (7#) was further oxidized to compound 7b (Scheme 4), an important supporting evidence of path B." was deleted according to the suggestion of referees.

Thanks for attention!

Sincerely yours,

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ARTICLE TYPE

Iodine Mediated Deprotection of *N-tert*-Butanesulfinyl Amines: A Functional Group Compatible Method

Wen Chen, Jian Ren, Minshou Wang, Lingjing Dang, Xianfu Shen, Xiaodong Yang and Hongbin Zhang*

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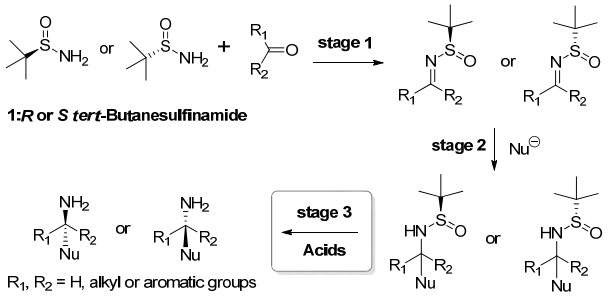
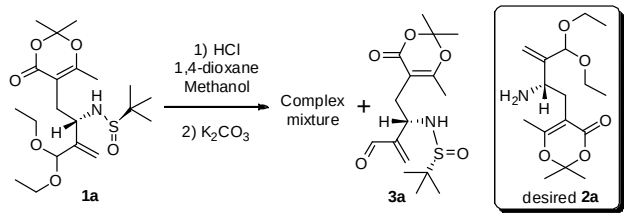
In the presence of iodine, a functional group compatible method for the deprotection of *tert*-butanesulfinyl and *p*-toluenesulfinyl units was developed.

Since the introduction of enantiomerically pure *tert*-butanesulfinamide in asymmetric organic synthesis by Ellman in 1997,[1] this synthetic reagent has gained an ever increasing popularity in chemical society.[2] The chiral *tert*-butanesulfinamide has been widely used in the synthesis of agrochemicals, pharmaceuticals and natural products as a reliable and versatile reagent for the introduction of amine units.[2e] As indicated in Scheme 1, the procedure is common for the synthesis of amines from chiral *tert*-butanesulfinamide. The first step is the condensation of **1** with ketones or aldehydes to yield imines. The second step is the additions of nucleophiles towards the sulfinyl imines to give *N-tert*-butanesulfinyl amines. The final step for the preparation of amines is the deprotection of the *tert*-butanesulfinyl group under acidic conditions.[1,2b] We recently started a research program towards the synthesis of amines bearing acid sensitive functional groups, a method for the deprotection of *tert*-butanesulfinyl group under neutral or basic reaction condition was needed. Although the syntheses of amines based upon *tert*-butanesulfinamide are prevailed in the literatures, we noticed that few nonacidic conditions are reported for deprotection of *N-tert*-butanesulfinyl amines.[3] Herein, we report a highly functional group compatible method for the deprotection of *tert*-butanesulfinyl groups and some mechanism insights towards this iodine mediated process.



Scheme 1. Synthesis of amines based on *tert*-butanesulfinamide

Recently, we conducted a deprotection of substrate **1a** in order to get amine **2a** bearing two acid sensitive ketal groups (Scheme 2). The initial experiment was conducted with 2N HCl in dioxane and methanol. This reaction unfortunately provided a complex mixture, with small amount of compound **3a** (1%) being isolated.



Scheme 2. Deprotection of *tert*-butanesulfinyl group under acidic conditions.

Although in the literature, there are thiophenolysis based methods for the deprotection of *tert*-butanesulfinyl [3a] or *p*-toluenesulfinyl [4] units, unfortunately we failed to get the desired amine (**2a**) under the condition of thiophenolysis. The Dess-Martin periodinane oxidation [5] also failed to give the desired product, with sulfinyl amine **3a** being obtained in 47% yield. These results prompted us to seek alternative ways for the deprotection of *tert*-butanesulfinyl unit in the presence of an acid sensitive group. We began our research with screening of reaction conditions by treatment of sulfinyl amine **1a** with additives in the presence of bases. Some of the reaction conditions are listed in Table 1. To our delight, addition of iodine finally led to the desired amine (**2a**) in 71% isolated yields (Entry 12).

Table 1 Studies on the deprotection of *tert*-butanesulfinyl amine **1a** [a]

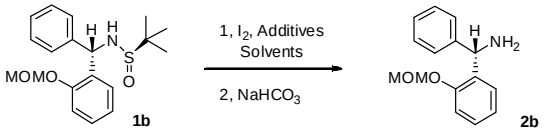
entry	Additives	Bases, Solvents	Yields
1	KI, $CuSO_4$	K_2CO_3, EtOH-H_2O (1:1)	0% [b]
2	IBD,$CuSO_4$	DMAP (0.2 eq.), EtOH	0% [c]
3	*n*-Bu_4NBr	K_2CO_3, PhMe-H_2O (2:1)	0% [d]
4	I_2 (0.5 eq.)	K_2CO_3, DMAP, THF-H_2O	**2**: trace[e,f]
5	I_2 (2.5 eq.)	K_2CO_3 (3.0 eq.),THF-H_2O	**2**: 14%[f]
6	I_2 (2.5 eq.)	DMAP (3.0 eq.),THF-H_2O	**2**: 10%[f]
7	I_2 (2.5 eq.)	Na_2CO_3 (3.0 eq.),THF-H_2O	**2**: 27%[f]
8	I_2 (2.5 eq.)	K_2CO_3 (3.0 eq.),THF-H_2O	**2**: 44%[g]
9	I_2 (2.5 eq.)	Na_2CO_3 (3.0 eq.), Acetone-H_2O	**2**: 21%[g]
10	I_2 (2.5 eq.)	Na_2CO_3 (3.0 eq.), MeCN-H_2O	**2**: 51%[g]
11	I_2 (2.5 eq.)	$KHCO_3$ (6.0 eq.),THF-H_2O	**2**: 53%[g]
12	I_2 (2.5 eq.)	Na_2CO_3 (3.0 eq.),THF-H_2O	**2**: 71%[g]

[a] Yields represent isolated yields. Reactions were conducted at 0.25 mmol scale in designated solvents (5 mL) at 20 °C for 14 hours. [b] K_2CO_3 (2.0 eq.), KI (2.0 eq.) and $CuSO_4$ (0.2 eq.). [c] IBD (2.0 eq.),

$CuSO_4$ (0.2 eq.). [d] *n*-Bu_4NBr (0.2 eq.), K_2CO_3 (2.0 eq.). [e] K_2CO_3 (0.5 eq.), DMAP (0.5 eq.). [f] THF : H_2O = 1:1. [g] DMAP (0.2 eq.) was added, Organic solvents : H_2O = 1:1.

In order to develop a general iodine mediated method for the deprotection of both *tert*-butanesulfinyl and *p*-toluenesulfinyl units, *tert*-butanesulfinyl amine **1b** was then prepared and used as a typical substrate for screening of other possible reaction conditions. It was found that bases such as sodium carbonate or DMAP were not necessary for deprotection of compound **1b** bearing moiety less labile to acid hydrolysis. The reaction underwent efficiently in the absence of bases and required only catalytic amounts of iodine (entry 5, 0.2 eq.). Although the reaction could be conducted at room temperature (entry 5), elevating the reaction temperature (50 °C oil bath, entry 9) could significantly shorten the reaction times. To the best of our knowledge, this is the first example of iodine catalyzed deprotection of a *tert*-butanesulfinyl amine, a complementary process to the acid hydrolysis.

Table 2 Screening of optimal reaction conditions for the deprotection of *tert*-butanesulfinyl amines [a]

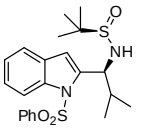
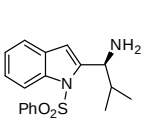
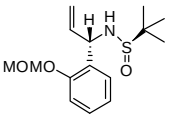
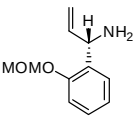
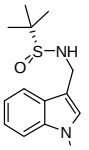
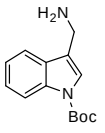
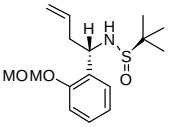
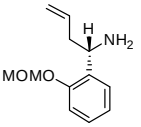
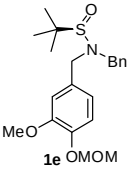
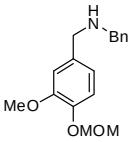
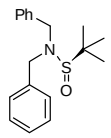
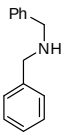
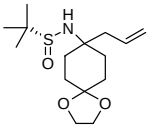
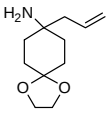
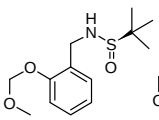
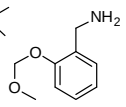
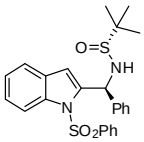
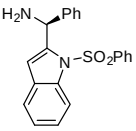
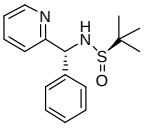
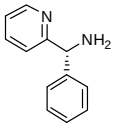
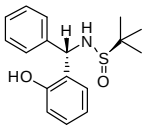
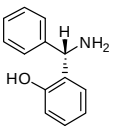
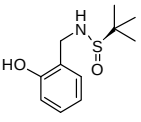
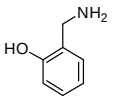
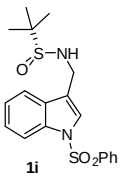
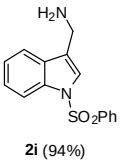
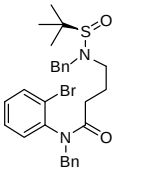
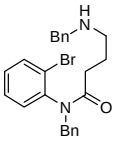
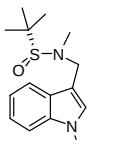
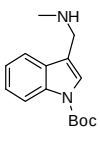
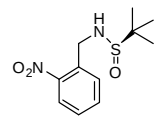
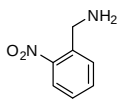
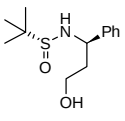
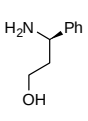
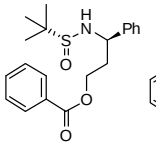
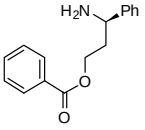


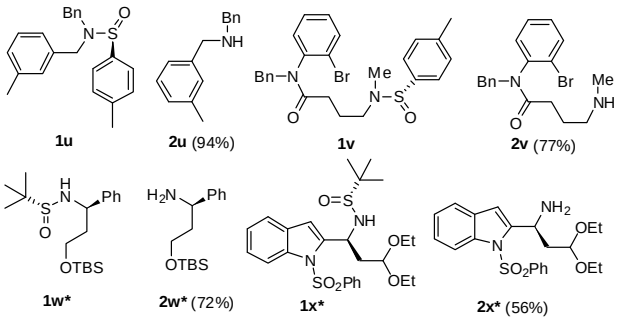
entry	Iodine, Additive	Solvent, Temperature.	Time; Yields
1	I_2 (2.5 eq.), Na_2CO_3 (3.0 eq.), DMAP (0.2 eq.)	THF/H_2O, rt	16 h, 81%[b]
2	I_2 (2 eq.),DMAP (0.2 eq.)	THF/H_2O, rt	12 h, 95%[b]
3	I_2 (2 eq.), None	THF/H_2O, rt	12 h, 95%[b]
4	I_2 (0.2 eq.), DMAP (0.1 eq.), $CuSO_4$ (0.1 eq.)	THF/H_2O, rt	72 h, 87%[b]
5	I_2 (0.2 eq.), None	THF/H_2O, rt	72 h, 70%[c]
6	I_2 (0.2 eq.), None	MeCN/H_2O, 50°C	12 h, 69%[d]
7	I_2 (0.2 eq.), None	EtOH/H_2O, 50 °C	12 h, 63%[d]
8	I_2 (0.2 eq.), None	Acetone/H_2O, 50 °C	12 h, 82%[d]
9	I_2 (0.2 eq.), None	THF/H_2O, 50 °C	12 h, 97%[d]
10	None	THF/H_2O, 50 °C	96 h, 0%[d]

[a] Yields represent isolated yields at 0.25 mmol scale of **1b**, and the reactions could be conducted either under air or nitrogen in solvents (5 mL). [b] THF/H_2O = 1/1. [c] THF/H_2O = 3/1. [d] Organic solvents /H_2O = 5/1.

With the optimal reaction conditions (Table 1, entry 12 for acid sensitive substrates; Table 2, entry 9 for regular substrates) in hand, we next conducted a number of deprotections, the results are summarized in Table 3. The new deprotection procedures afforded the amines in good to excellent isolated yields and a number of functional groups are well tolerated. Delightfully, this method could also be used for the deprotections of *p*-toluenesulfinyl units (Table 3, substrate **1u** and **1v**).

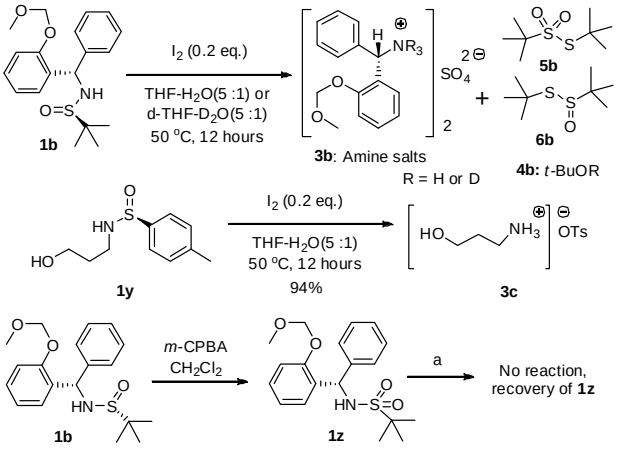
Table 3 Deprotections of *tert*-butanesulfinyl amines and *p*-toluene-sulfinyl amines [a]

Substrates	Products (yields)	Substrates	Products (yields)
 **1c**	 **2c** (74%)	 **1l**	 **2l** (86%)
 **1d**	 **2d** (89%)	 **1m**	 **2m** (83%)
 **1e**	 **2e** (84%)	 **1n**	 **2n** (99%)
 **1f**	 **2f** (85%)	 **1o**	 **2o** (91%)
 **1g**	 **2g** (81%)	 **1p**	 **2p** (80%)
 **1h**	 **2h** (99%)	 **1q**	 **2q** (78%)
 **1i**	 **2i** (94%)	 **1r**	 **2r** (70%)
 **1j**	 **2j** (94%)	 **1s**	 **2s** (87%)
 **1k**	 **2k** (85%)	 **1t**	 **2t** (95%)



[a] Yields represent isolated yields at 0.5 mmol scale. [*]**1w** and **1x** (acid sensitive substrates): Na_2CO_3 (3.0 eq.), I_2 (2.5 eq.), DMAP (0.2 eq.), THF-H_2O (1 : 1, 10 mL) at room temperature, see supporting information.

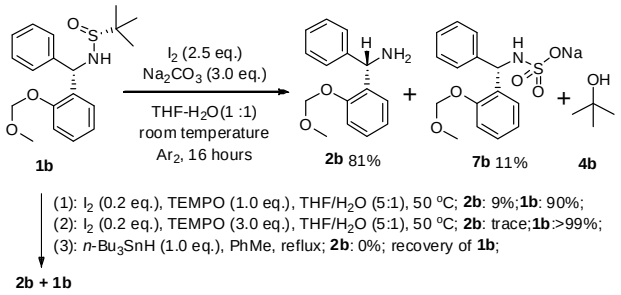
In order to get some insights towards this iodine catalyzed process, a number of experiments with *tert*-butanesulfinyl amine **1b** were carried out. We firstly elaborated the amine salts (Scheme 3, also see supporting information) obtained in the aqueous phase. Based on HRMS analysis (ESI-MS), the salt was identified as compound **3b**, a sulfate of amine **2b**. It was deduced that the sulfate ion might come from the oxidation of sulfinyl unit by iodine. Next we carried out the reaction in deuterated THF and D_2O in a seal tube. *tert*-Butanol (**4b**), di-*tert*-butyl thiosulfonate (**5b**) and di-*tert*-butyl thiosulfinate (**6b**) were identified (based on NMR and ESI-MS analyses of the reaction mixture) in the reaction system. These compounds might be by-products from further oxidation of *tert*-butylsulfinic acid.[6] Di-*tert*-butyl thiosulfonate (**5b**) was isolated and fully characterized by NMR and HRMS. Deprotection of *p*-toluenesulfinyl unit with compound **1y** was also conducted (Scheme 3), formation of *p*-toluenesulfate **3c** was confirmed by NMR and ESI-MS analyses. To make sure *tert*-butanesulfonyl amine **1z** was not involved as an intermediate in this deprotection process, control experiment with **1z**, obtained by oxidation of **1b** with *m*-CPBA, was also carried out. No deprotection of *tert*-butanesulfonyl group occurred under the identical reaction conditions (Scheme 3).



a: I_2 (0.2 eq.), THF/H_2O (5:1), 50 °C; or I_2 (2.5 eq.), Na_2CO_3 (3.0 eq.), THF/H_2O (1:1)

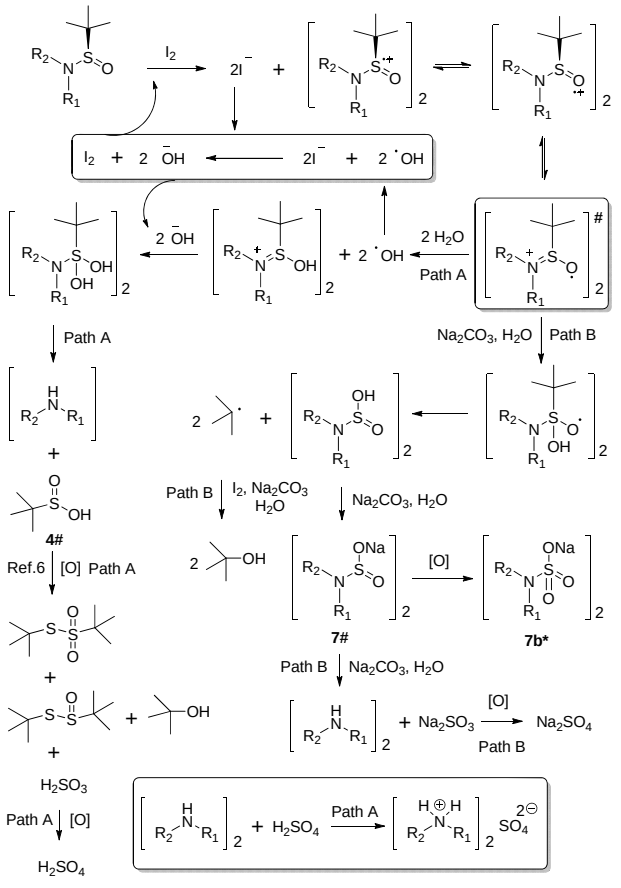
Scheme 3. Some reactions to elaborate the reaction pathway

Deprotection in the presence of excess sodium carbonate (3.0 eq) was conducted to exclude the possible hydrolysis of acids (HI acid, which might be generated in the reaction process). Although more iodine (2.5 eq) was required, amine **2b** was obtained in 81% yields together with compound **7b** (Scheme 4).[7] It could be concluded that iodine, rather than acids generated in situ, plays the key role in this deprotection process.



Scheme 4. Further reactions to elaborate the possible pathway

We next conducted the reaction in the presence of a stable oxyl radical, 2,2,6,6-tetramethyl-1-oxylpiperidine (TEMPO),[8] and found that the deprotections were significantly inhibited (Scheme 4). It was noteworthy that no reaction was observed by treatment of *tert*-butanesulfinyl amine **1b** with *n*-Bu_3SnH, a radical initiator. Based on evidence collected, a single electron transfer initiated pathway was proposed for this iodine mediated deprotection of sulfinyl units (Scheme 5).



Scheme 5. Proposed pathway for iodine mediated deprotection of *tert*-butanesulfinyl units

Conclusions

In summary, we have developed an iodine mediated single electron transfer process for the deprotection of *tert*-butanesulfinyl and *p*-toluenesulfinyl units. For most substrates used in this research, the yields are good to excellent with only catalytic amount of iodine. Our new methods are especially useful for the deprotection of *N*-*tert*-butanesulfinyl amines with acid sensitive structure motifs and should be found more applications in the synthesis of complex natural products.

Notes and references

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† Electronic Supplementary Information (ESI) available: [details of experimental procedure, spectral data and copies of all new compounds]. See DOI: 10.1039/b000000x/

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7 Deprotection of **1b** in deuterated-THF and D_2O in the presence of excess sodium carbonate was also carried out and only **2b**, **7b** and *tert*-butanol (**4b**) were detected by NMR experiments. By-products **5b** and **6b** were not detected in the presence of excess base due to a different pathway (see Scheme 5).

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