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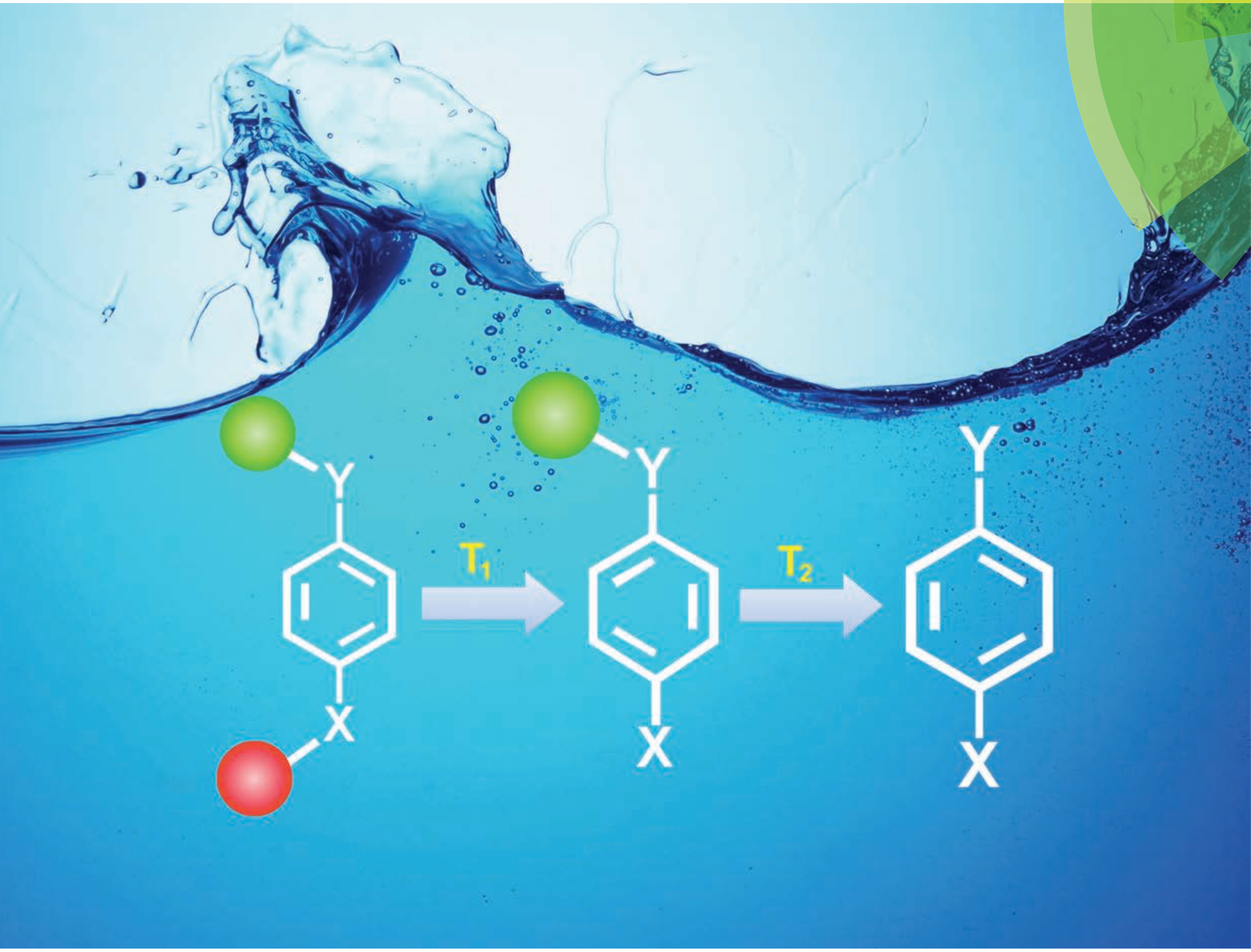

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Water at elevated temperatures (WET): reactant, catalyst, and solvent in the selective hydrolysis of protecting groups†

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Water at elevated temperatures (WET) can act simultaneously as reactant, solvent, and catalyst in reaction processes. WET has been successfully employed in the removal of protecting groups alleviating the need for added strong acids/bases, subsequent neutralization and waste salt elimination. The protocols for the water-mediated removal of several common protecting groups such as *tert*-butyl carbamates (*N*-Boc) from 125 to 150 °C, acetamide (*N*-Ac) at 275 °C and acetate esters (*O*-Ac) at 250 °C are reported for different model aryl compounds. In addition, high yields and selective deprotection of one protecting group in the presence of another by simply tuning the temperature is demonstrated. In order to gain further insights into reaction processes, the aqueous solubilities of several of the reactants, the kinetics and mechanisms associated with some of these reactions are also discussed.

Introduction

Water is considered by many to be a green solvent for conducting reaction processes. Unfortunately, water at ambient temperatures is a poor solvent for most organic reactants. In contrast, however, water at elevated temperatures (WET) has substantially different physiochemical properties and can be employed for conducting a wide range of synthetic transformations and subsequent separations.[1] In particular, as water is heated from ambient temperature to 275 °C the dielectric constant (ε), the auto-ionization constant (K_w), and the density (ρ) of water change continuously. Specifically, the dielectric constant[2] decreases from 78 to approximately 20, the auto-ionization constant[3] increases from 10^{-14} to 10^{-11}, and the density[4] decreases from 1 g cm^{-3} to 0.75 g cm^{-3}. Thus, WET takes on the character of an organic solvent; the solubility of organic molecules increases. In addition, since the auto-ionization constant increases at elevated temperatures, both acid and base catalyzed processes are also enhanced. While these physiochemical properties of WET can provide an effective vehicle for conducting organic transformations, product separation and isolation are also more facile. In principle, simply cooling of the reaction mixture will result in phase separation of the organic products from water. WET, therefore, can provide an attractive and environmentally benign solvent for reactions and processes. Indeed, WET has been used in hydrolysis reactions,[5] Claisen–Schmidt condensation reactions,[6] and Friedel–Crafts alkylation and acylation reactions[7] without the addition of "external" acids or bases. In addition, unique transformations can also be easily achieved. In particular, acetyl and nitro substituents attached to electron-rich aromatic rings can be efficiently removed and replaced by hydrogen.[8] In general, each of these reactions takes place at different rates and therefore at substantially different temperatures. As a result, the properties of water can be tuned by adjusting the temperature to meet specific solvent property and reactivity needs. This unique capability is an opportunity to design greener protocols for acid-catalyzed transformations such as the removal of protecting groups.[9]

The use of protecting groups in multistep organic synthesis is ubiquitous.[10] Commonly however their removal requires strong acidic conditions followed by post-reaction neutralization steps leading to large waste stream. From a green chemistry[9] point of view it would be preferable to develop selective reactions which do not require protecting groups, but the reality is that this is not always possible. As a consequence the development of green protocols for the protection and subsequent removal of these groups have become important considerations. Herein, we address the use of WET to effectively

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and selectively remove some typical protecting groups from amine and alcohol functionalities. We demonstrate that by just tuning the temperature of the water, selective removal of one protecting group in the presence of a second can be realized. The temperatures employed range from 125 °C to 275 °C. In addition, the kinetics and the associated mechanisms for the WET hydrolyses are presented. Typical protecting groups investigated for amines are *tert*-butyl carbamate (*N*-Boc) and acetamide (*N*-Ac) derivative and for alcohols the acetate (*O*-Ac) derivatives. We report the protocols for the deprotection of the individual protecting groups as well as the competitive and selective deprotection of molecules containing two different protecting groups.

Experimental

Materials

Unless otherwise noted, all compounds were purchased from commercial sources. The following reactants and reagents were used without further purification: acetonitrile (Aldrich, HLPC Grade 99+%), water (Aldrich, HPLC grade), *tert*-butyl phenylcarbonate (Aldrich, 97%), aniline (Aldrich, ACS reagent grade ≥99.5%), *p*-methoxyaniline (Aldrich, ACS reagent grade), *p*-chloroaniline (Aldrich, ACS reagent grade), acetanilide (Aldrich, 97%), *p*-acetanisidide (TCI, 98%), 4′-acetoxyacetanilide (TCI, >98%), di-*tert*-butyl dicarbonate (Aldrich, 97%), ethanol (Aldrich), diethyl ether (Aldrich), magnesium sulfate (Aldrich, 98%). The deionized water was obtained in-house using a Barnstead B-Pure dual filter water filtration system, with a resistivity >18 MΩ.

Experimental apparatus and procedure

The reactions were performed in closed 3 mL titanium batch reactors (Fig. 1). These reactors were designed and produced in-house and were sealed with titanium NPT plugs. Titanium was used as the material of construction due to the very low level of transition metals and corrosion resistance of the metal (316 Stainless Steel reactors were found to catalyze unwanted side reactions). The reactors were loaded to have an approximate concentration of 0.033 M in a volume of water of 1.5 mL. The titanium reactors were then placed in a thermostated aluminum heating block. The temperature of the heating block varied by ±1 °C and was maintained using four cartridges heaters (Omega Technologies Co.) and a temperature controller (Omega Model CN76000). An over-temperature probe (I^{2}R Model OTP-1500) was also employed as safety precaution to prevent the block from overheating in the case of a temperature controller failure. The heating block was preheated to desire temperatures ranging from 125 to 275 °C and the pressures in the individual reactors was generated solely by the vapor pressure of the liquid medium (approximately 0.5 to 4 MPa). The reactors reached the reaction temperatures in less than 5 minutes and were withdrawn at various reaction times and quenched in a room temperature water bath. Upon completion, the reactor contents were diluted in acetonitrile in a single phase and separated and quantified using HPLC (HP 1100 with a UV detector using a Phenomenex Luna 5 μm C18(2) reverse phase column) and LCMS (Waters Alliance 2965 Separations Module with a Waters 2998 PDA and a Waters 3100 SQD MS (ESI positive) using a Phenomenex Luna C18(2) column (3 μm, 4.6 × 75 mm).

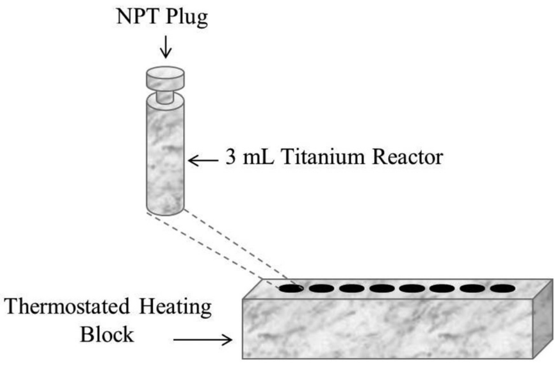


Fig. 1 Titanium batch reactor and thermostated aluminum heating block.

***tert*-Butyl(4-acetamidophenyl)carbamate.** To 2 g (0.00960 mol) of *tert*-butyl(4-aminophenyl)carbamate was added 200 mL anhydrous DCM under nitrogen with stirring in an ice-water bath. 1.0 mL (0.0124 mol) of anhydrous pyridine was added dropwise to the cold solution. The reaction mixture was stirred for 10 minutes and 1 mL (0.0106 mol) of acetic anhydride was added dropwise. After 10 minutes of stirring, the ice-water bath was removed and the reaction proceeded at room temperature for 4 hours. The reaction mixture was neutralized with saturated sodium carbonate under vigorous stirring. Additional water and DCM were added and the organic layer separated, dried, and evaporated under reduced pressure. The product was recrystallized in toluene. The white solid was filtered, washed with toluene, and dried in a vacuum oven overnight yielding 0.903 g of product (82%), mp. 180–186 °C. ^{1}H NMR (DMSO) δ 1.46 (s, 9H), δ 2.00 (s, 3H), δ 7.34 (d, 2H), δ 7.43 (d, 2H), δ 9.20 (s, 1H), δ 9.78 (s, 1H). ^{13}C NMR (DMSO-d6) δ 23.84, δ 28.14, δ 78.81, δ 118.50, δ 119.52, δ 133.89, δ 134.79, δ 152.85, δ 167.86. Elemental analysis: Theoretical: C: 62.38%, H: 7.25%, N: 11.79%. Found: C: 62.35%, H: 7.36%, N: 11.07%. Mass (ESI+): 151.1 *m*/*z*.

***tert*-Butyl(4-pivalamidophenyl)carbamate.** To 0.8 g (0.00384 mol) of *tert*-butyl(4-aminophenyl)carbamate was added 65 mL anhydrous DCM under nitrogen with stirring in an ice-bath. 0.350 mL (0.0043 mol) of anhydrous pyridine was added dropwise to the cold solution. The reaction mixture was stirred for 10 minutes and 0.512 mL (0.00416 mol) of pivaloyl chloride was added dropwise. After 10 minutes of stirring, the ice-water bath was removed and the reaction proceeded at room temperature for 4 hours. The reaction mixture was neutralized with saturated sodium carbonate under vigorous stirring. Additional water and DCM were added and the organic layer separated, dried, and evaporated under reduced pressure. The product was recrystallized from toluene. The white solid was filtered, washed with toluene, and dried in a vacuum oven overnight yielding 0.903 g of product (80%), mp. 214–220 °C. ^{1}H NMR (DMSO-d6) δ 1.21 (s, 9H), δ 1.47 (s, 9H), δ 7.36 (d, 2H), δ 7.49 (d, 2H), δ 9.07 (s, 1H), δ 9.22 (s, 1H). ^{13}C NMR (DMSO) δ 27.29, δ 28.17, δ 38.96, δ 78.79, δ 118.10, δ 120.90, δ 133.78, δ 134.96, δ 152.82, δ 176.09. Elemental analysis: Theoretical: C: 65.73%, H: 8.27%, N: 9.58%. Found: C: 66.00%, H: 8.12%, N: 9.48%. Mass (ESI+): 193.3 *m*/*z*.

4-((*tert*-Butoxycarbonyl)amino)phenyl acetate. A 25 mL round bottom flask was charged with 0.75 g (0.00496 mol) of 4-aminophenyl acetate and 1.37 g (0.00595 mol) of melted (about 40 °C) of di-*tert*-butyl dicarbonate. 0.12 g (5% mol) of ground $Bi(NO_3)_3 \cdot 5H_2O$ was added to the neat mixture. The mixture was stirred at 40 °C for 10 minutes. Water was added to the mixture and the organics were extracted with ethyl acetate. The organic layer was dried with $MgSO_4$, filtered and the solvent removed by rotary evaporation. The crude was purified with on a silica column with hexane–ethyl acetate (80 : 20, 50 : 50). 0.76 g (61%) of product (white solid) isolated. ^{1}H NMR ($CDCl_3$) δ 1.49 (s, 9H), δ 2.25 (s, 3H), δ 6.76 (broad, 1H), δ 6.99–6.95 (dt, 2H), δ 7.34–7.32 (d, 2H). ^{13}C NMR ($CDCl_3$) δ 20.98, δ 28.24, δ 80.48, δ 119.34, δ 121.81, δ 136.03, δ 145.84, δ 152.72, δ 169.66. Elemental analysis: Theoretical: C: 62.14%, H: 6.82%, N: 5.57%. Found: C: 61.61%, H: 7.14%, N: 4.95%. Mass (ES+): 252 *m*/*z*.

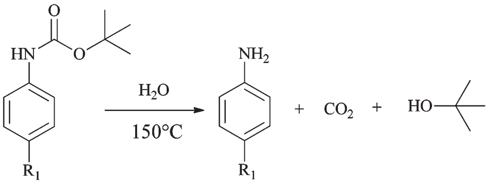
Results and discussion

WET hydrolysis of *tert*-butyl carbamates

Amine protecting groups are frequently employed in multistep synthetic sequences. Among the various amine protecting groups, the *tert*-butyl carbamate (*N*-Boc) group is perhaps the most widely used due to its stability towards a variety of reagents and reaction conditions. In addition, it can be easily cleaved with a strong acid. Typical deprotections protocols involve the use of hydrochloric acid, trifluoroacetic acid or methanesulfonic acid.[11] Recently it has been reported that the hydrolysis of the *N*-Boc group can be achieved in hot water. Specifically, G. Wang *et al.* reported the hydrolysis of *N*-Boc derivatives of a wide variety of aryl amines at 150 °C and concluded that electron-donating groups facilitated the reaction while electron-withdrawing groups retarded the reaction.[5d] Almost simultaneously, J. Wang *et al.* reported the hydrolysis of *N*-Boc derivatives of nitrogen-containing heterocycles (imidazole, pyrazole, benzimidazole, and benzotriazole), aryl amines, and a variety of aliphatic and alicyclic amines in boiling water (100 °C) open to the atmosphere.[5a] In comparing a series of *N*-Boc derivatives of 3- and 4-substituted anilines, they reported that "no obvious electronic substitution effect on the phenyl ring was observed". They further suggested that the dominant influence on the rate of hydrolysis is the relative solubilities of the *N*-Boc derivatives at the reaction temperatures. Could a difference of 50 degrees increase the substrate solubilities and account for these qualitative observations? In principle, this could be the case since the dielectric constant of water at 150 °C is approximately 40, a value similar to acetonitrile which is a relatively good solvent for organic substrates.

In order to gain a deeper mechanistic understanding of this important deprotection protocol, the *tert*-butyl carbamate (*N*-Boc) derivatives of aniline, *p*-methoxyaniline, and *p*-chloroaniline were subject to WET at 150 °C. These three substrates were chosen to explore the effect of electron-donating (*p*-OMe) and electron-withdrawing (*p*-Cl) substituents on the rates of hydrolysis. Each of the hydrolysis rates was followed as a function of time using HPLC and the results are summarized in Table 1 and graphically in Fig. 2. All the reactions proceeded successfully with short reaction times. The rates of hydrolysis

Table 1 WET hydrolysis of *tert*-butyl carbamates[a]



Entry	R_1	Time (min)	Yield[b] (%)
1	H	20	100 ± 0
2	OCH_3 [12]	40	95 ± 5
3	Cl[13]	90	100 ± 0

[a] Reactions were conducted with 0.05 mmol of substrate in 1.5 mL deionized water at 150 °C in a closed vessel (see Experimental section). [b] Yield was calculated using the HPLC data and calibration curves.

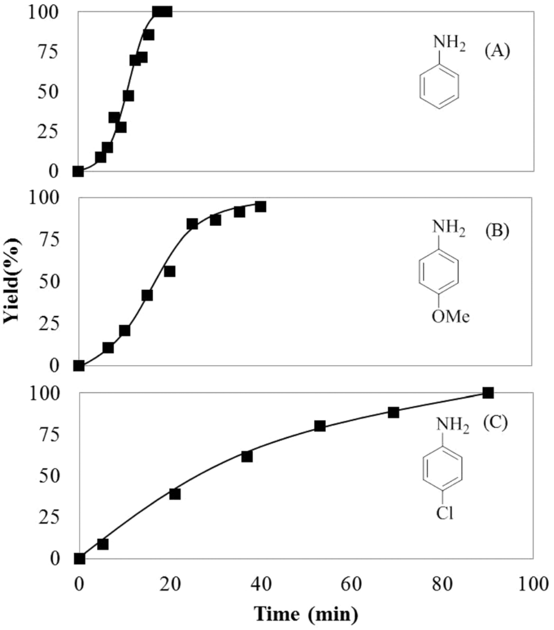


Fig. 2 WET hydrolysis of *tert*-butyl carbamate group from different protected anilines as a function of time at 150 °C: (A) yield of aniline (entry 1), (B) yield of *p*-methoxyaniline (entry 2), (C) yield of *p*-chloroaniline (entry 3).

of the *N*-Boc protecting groups follow the order: aniline > *p*-methoxyaniline > *p*-chloroaniline. In addition, the hydrolysis rates for aniline and *p*-methoxyaniline were characterized by S-shaped curves, whereas the *p*-chloroaniline was not. Also, the hydrolysis of the *N*-Boc derivative of *p*-chloroaniline requires longer reaction times compared to the parent and methoxy substituted aniline.

In all cases, it was observed in the HPLC chromatograms that, in addition to the two peaks associated with the reactant and product, an additional peak appeared shortly after the reaction began, remained through the reaction, and subsequently disappeared at the end of the reaction (see Fig. 3). Employing LC-MS analysis these species were identified as diarylureas as shown in Fig. 4. It is postulated that these species arise from the reaction of the initially formed aniline with the *N*-Boc protected aniline. Under the conditions of the reaction, these diarylureas are ultimately hydrolyzed to yield the corresponding aniline (Fig. 5). Although the removal of the *N*-Boc group from different protected anilines in water has been reported,[5a,d] there has been no mention of urea formation and disappearance.

As seen in Fig. 2, the hydrolysis rate profiles are quite different for the *N*-Boc derivatives of aniline and *p*-methoxyaniline as compared to *p*-chloroaniline. The former are characterized by S-shaped curves while the latter is not. In addition, the electron-donating methoxy and electron-withdrawing chloro substituted substrates reacted more slowly than the parent derivative. These results are conflicting with the conclusions reported by G. Wang *et al.* and appear to be in agreement with those of J. Wang *et al.* Thus, in order to gain a better understanding of the reaction process the following questions are pertinent: Why are the kinetic profiles of the *N*-Boc derivative different? Is mass transfer affecting the rate profiles? Could the different observations arise from different solubilities at 100 °C and 150 °C?

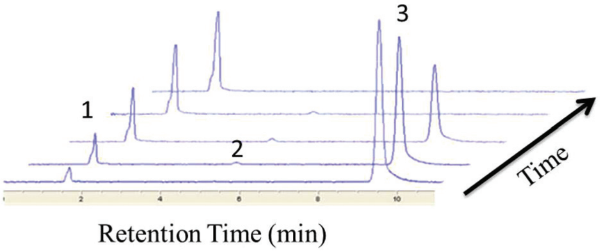


Fig. 3 HPLC chromatograms for the removal of the *N*-Boc group from *tert*-butyl phenylcarbamate showing the appearance of aniline (1), the appearance and disappearance of 1,3-diphenylurea (2) and the disappearance of *tert*-butyl phenylcarbamate (3) as a function of reaction time.

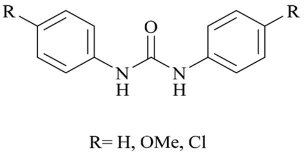


Fig. 4 Diarylureas formed during WET hydrolysis.

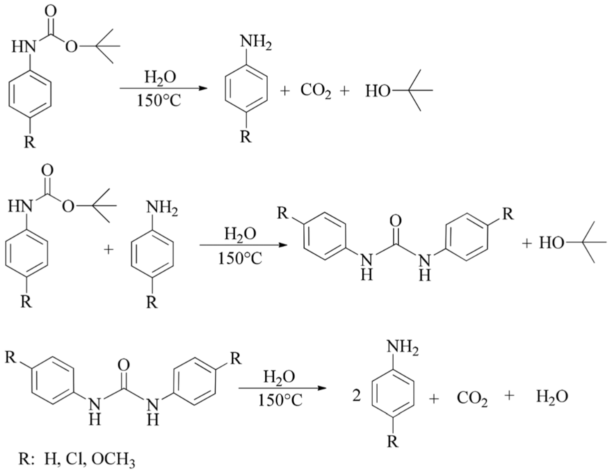


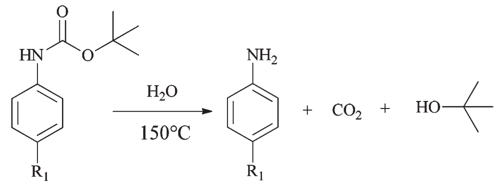
Fig. 5 Equations describing the WET hydrolysis of the *N*-Boc group from protected anilines.

Kinetics of *N*-Boc-derivative hydrolyses. As indicated above the rate profiles for the formation of aniline and *p*-methoxyaniline are described by S-shaped curves. These observations could arise from the operation of autocatalytic processes or possibly from two consecutive first order processes. While each of these reaction does show the presence of a diarylurea, which could be interpreted as an intermediate, these particular species are formed in very small quantities and remain constant throughout most of the reaction – an observation which is not consistent with two consecutive first order reactions. Indeed, the corresponding diarylurea is also observed in the hydrolysis of the *N*-Boc derivative of *p*-chloroaniline even though the corresponding kinetic profile does not exhibit the S-shaped character.

The kinetic data for each of the *N*-Boc derivatives were analyzed using the integrated rate expressions for both pseudo-first order and auto-catalytic processes[14] (see ESI†). The results are displayed in Table 2. It appears that auto-catalysis kinetics fits best for the Boc derivatives of aniline while first order kinetics best describes the *p*-chloroaniline. Based on the correlation coefficients, it is not clear which of these kinetic descriptions fits the Boc derivative of *p*-methoxyaniline.

Since the reactions reported herein were conducted in closed systems, the carbon dioxide produced during the course of reaction is confined to the reaction vessel. As a consequence, it is conjectured that the released carbon dioxide would react with water to form carbonic acid, with *tert*-butanol to form *tert*-butylcarbonic acid, and/or with the amine product to form arylammonium carbamates (see Fig. 6). In principle, each of these species could function as an acid catalyst in the hydrolysis pathway and could account for auto-catalysis kinetics. At this juncture the explanation for the different kinetic descriptions between the Boc derivatives of aniline and *p*-methoxyaniline compared to *p*-chloroaniline is not yet fully understood. However, the significant lower reactivity of the

Table 2 The first-order an autocatalytic rate constants with correlation coefficients[a]



	First order reaction		Auto-catalytic reaction	
R_1	k (min^{-1})	R^2	k (L mol^{-1} min^{-1})	R^2
H	0.19	0.7967	86.76	0.9255
OCH_3	0.08	0.9317	35.63	0.9503
Cl	0.02	0.9779	13.32	0.7960

[a] Initial concentration was calculated at 5 minutes, since this is the time needed to reach reaction temperature (150 °C).

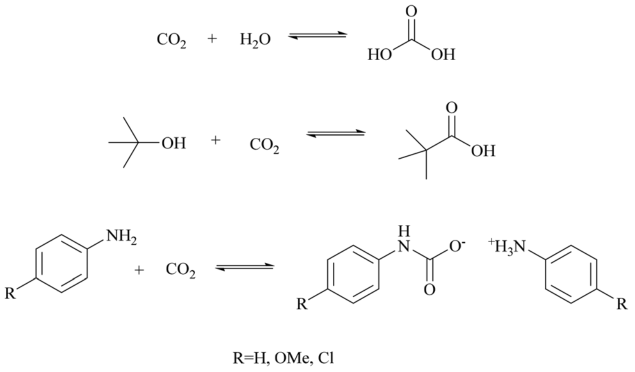


Fig. 6 Formation of carbonic acid, *tert*-butylcarbonic acid, and arylammonium arylcarbamates from CO_2 generated during the WET hydrolysis of the *N*-Boc protecting group.

chloro derivatives suggest that mass transfer may be affecting the rate profile of the reactions. As a consequence, we chose to estimate the solubility of the *N*-Boc substrates in water at 150 °C.

Solubility estimates of *N*-Boc protected aniline derivatives. Experimentally, it would be difficult to accurately determine the solubilities of the *N*-Boc derivatives at elevated temperatures since hydrolysis would compete with the measurements. In addition, accurate sampling of the water solutions at temperatures above 100 °C would be experimentally problematic. As a consequence the solubilities were estimated by experiments coupled with theoretical calculations. The solubilities of analogous model aryl amides which were "hydrolytically stable" were determined experimentally by gravimetric analysis at a series of temperatures below 100 °C. Using a non-ideal solubility equation,[15] the activity coefficients were determined using the experimental data and the solubility at 150 °C for the different model amide substrates were then calculated (see ESI†). The experimental and estimated solubilities of the Boc substrates as well as for the model amide substrates are summarized in Table 3. It should be pointed out that the only difference between the model amides and the actual Boc derivative is an oxygen atom. In order to validate the use of these models, the room temperature (25 °C) solubilities of the actual Boc derivatives employed in this study were experimentally determined and also estimated using COSMOtherm[16] and ACD software packages.[17] The agreement is excellent. It is concluded that (1) the experimental room temperature (25 °C) solubilities of the model amides are comparable to the experimental and calculated solubilities of the corresponding Boc derivatives and (2) the calculated solubilities of the model amides at 150 °C indicate that under the hydrolysis conditions presented here the *N*-phenylpivalamide and *N*-(4-methoxyphenyl)pivalamide would be completely soluble while the *N*-(4-chlorophenyl)pivalamide would only be partially soluble (approximately 22%). It is assumed that the Boc derivatives exhibit similar relative and "absolute" solubilities as the model amides.

While the results reported here clearly show that the Boc derivative of 4-chloroaniline reacts more slowly than the 4-methoxy counterpart, in agreement with J. Wang, the explanation could be a consequence of partial solubility and the accompanying contribution of mass transfer to the overall kinetics. Overall, the facile deprotection protocol proceeds smoothly and quantitatively. The work reported here coupled with recent literature reports[5a,d] demonstrate that WET can be an effective vehicle for the removal of the Boc protecting group.

Competitive and selective WET hydrolyses. The competitive and selective removal of the *tert*-butyl carbamate (*N*-Boc) protecting group in the presence of other amine or alcohol protecting groups using WET at 150 °C has also been investigated. The Boc derivatives of *N*-(4-aminophenyl)acetamide and *N*-(4-aminophenyl)pivalamide were used in exploring the competitive cleavage of the *N*-Boc protecting group in the presence of an amide protecting group (Table 4). The yields as a function of time for each of these reactions are graphically displayed in Fig. 7. The rates of hydrolysis of the *N*-Boc-(4-aminophenyl)acetamide is greater than that of *N*-Boc-(4-aminophenyl)pivalamide; the former was completed in 20 minutes while the latter required approximately 75 minutes. The rate profile for the pivalamide derivative exhibits the S-shaped curve reminiscent of the Boc derivatives of aniline and *p*-methoxyaniline. In this particular case, however, it is conjectured that the rate profile differences as well as the overall rates are attributed to differences in solubility. The pivalamide (*N*-Piv) derivative is more hydrophobic and therefore less soluble than the corresponding acetamide (*N*-Ac) derivative. Indeed, solubility estimates using COSMOtherm software package indicate that the acetamide substrate is fifteen times more soluble in water at room temperature than the pivalamide[16] substrate (see ESI†). It is projected that this difference should also be reflected at the higher temperatures. Solubilities and rate profiles aside, in both cases, the *N*-Boc groups were cleaved selectively to the corresponding amines in excellent yields with the amide groups remaining intact.

The selective removal of the *N*-Boc group in the presence of an alcohol protecting group, *O*-acetyl (O-Ac), was also

Table 3 Summary of experimental and calculated solubilities

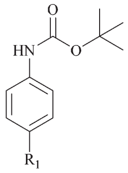
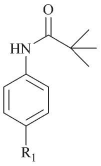
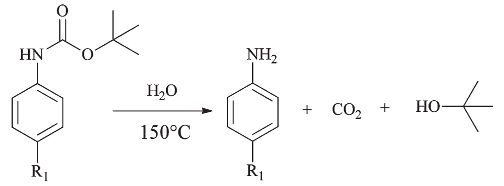
	Boc substrates			Analogous model substrates (amide)	
					
	Experimental solubility at 25 °C	Estimated by COSMO-RS at 25 °C	Estimated by ACD software at 25 °C	Experimental solubility at 22 °C	Estimated with experimental data at 150 °C
R_1	Solubility ($g\ L^{-1}$)				
H	0.22	0.12	0.33	0.363	5.84
OCH_3	—	0.12	0.31	0.437	8.44
Cl	0.12	0.03	0.06	0.061	1.70

Table 4 Selective WET hydrolysis of the Boc group in the presence of an amide protecting group[a]



Entry	R_1	Time (min)	Yield[b] (%)
4	N-Ac[c]	20	100 ± 0
5	N-Piv[d]	75	97 ± 1

[a] Reactions were conducted with 0.05 mmol of substrate in 1.5 mL deionized water at 150 °C in a closed vessel (see Experimental section). [b] Yield was calculated using the HPLC data and calibration curves. [c] Ac = acetyl (C=O)CH_3. [d] Piv = pivaloyl (C=O)C$(CH_3)_3$.

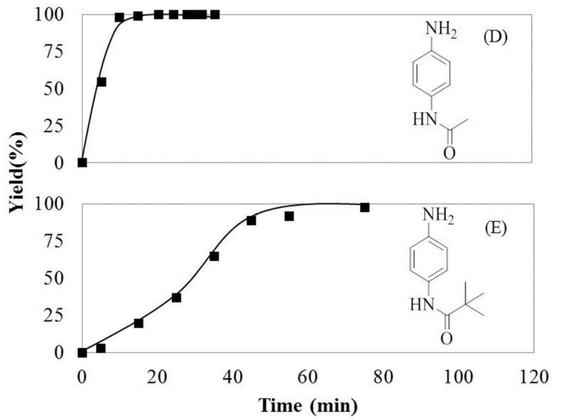


Fig. 7 WET hydrolysis of N-Boc group of different protected anilines containing a second amine-protecting group as a function of time at 150 °C: (D) yield of N-(4-aminophenyl) acetamide (entry 4), (E) yield of N-(4-aminophenyl) pivalamide (entry 5).

investigated. 4-((*tert*-Butoxycarbonyl)amino)phenyl acetate was subject to WET at 150 °C. A 96% conversion after 40 minutes with an accompanying 70% yield of 4-aminophenyl acetate (desired product) was achieved. Under these conditions, however, the side products *N*-(4-hydroxyphenyl)acetamide, 4-acetamidophenyl acetate and 4-aminophenol were also formed (see Fig. 8). At still higher temperatures (200 °C) the amounts of these side products dramatically increased. It is believed that these side products arose from acyl transfer processes between the free amino nitrogen on one molecule with the acyl ester on another molecule. Clearly, the reaction conditions were too severe. In addition, the desired product itself was not stable over time. Indeed, it was observed that over a period of a week the isolated product, 4-aminophenyl acetate, slowly underwent acyl transfer to form these same side products. Milder conditions and subsequent derivatization of the product would be necessary in order to employ this deprotection protocol. As a consequence a lower WET reactions temperature of 125 °C was investigated (Table 5). It was found that 100% conversion could be achieved over a 150 minute time period with a yield of 90%. Less than 10% of the side products were detected. The yields of 4-aminophenylacetate as function of time at 125 °C are displayed in Fig. 9. By tuning the temperature, we were able to selectively remove the *N*-Boc group while leaving the *O*-Ac group intact. The lower reaction temperature was necessary to maintain high selectivity toward the removal of the *N*-Boc group.

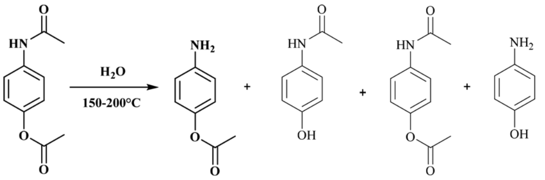
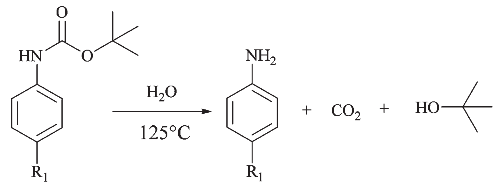


Fig. 8 Formation of desired product along with side products such as *N*-(4-hydroxyphenyl)acetamide, 4-acetamidophenyl acetate, and 4-aminophenyl at higher temperatures due to acyl migration.

Table 5 WET hydrolysis of the Boc group in the presence of an acetate group[a]



Entry	R_1	Time (min)	Yield[b] (%)
6	*O*-Ac[c]	150	90

[a] Reactions were conducted with 0.05 mmol of substrate in 1.5 mL de-ionized water at 150 °C in a closed vessel (see Experimental section). [b] Yield was calculated using the HPLC data and calibration curves. [c] Ac = acetyl (C=O)CH_3.

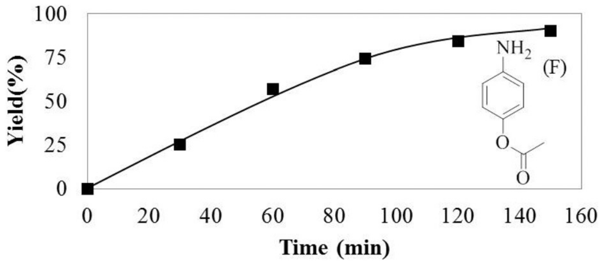
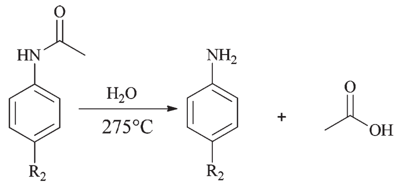


Fig. 9 Removal of *N*-Boc group of a protected aniline containing a second alcohol-protecting group as a function of time at 125 °C: (F) yield of 4-aminophenyl acetate (entry 6).

WET hydrolysis of amides. Another common protecting group for amines is the acetyl derivative (*N*-Ac). Removal of this protecting group usually requires strongly acidic or basic conditions. For example, *N*-Ac group could be hydrolyzed using a hydrochloric acid–water solution at reflux temperatures for one hour.[18] This procedure, of course, must be accompanied by the subsequent neutralization of the acid in order to isolate the amine products. To investigate the use of WET, where the neutralization step is not needed, model substrates were employed. Acetanilide and 4-methoxyacetanilide were subject to WET at 275 °C. The results are summarized in Table 6 and the yields of products as a function of time are illustrated in Fig. 10. In previous reactions with Boc protected substrates no precautions were made to exclude air from the closed vessels. Under these conditions, the yields of aniline and 4-methoxyaniline were 35% (entry 7) and 46% (entry 9), respectively. The major side products were phenazine derivatives – the products from an oxidative coupling of the aryl amine products (Fig. 11). These side products were identified by means of LC-MS analyses. When the same reactions were conducted in the absence of oxygen, the desired hydrolysis products were obtained in near quantitative yields (entries 8 and 10). Under these conditions only trace quantities of the phenazines were detected. It was concluded that high temperature deprotection procedures forming easily oxidized products

Table 6 WET hydrolysis of amide groups[a]



Entry	R_2	Time (min)	Yield[b] (%)
7	H	250	35
8[c]	H	250	97
9	OMe	400	46
10[c]	OMe	400	92

[a] All reactions were conducted with 0.05 mmol of substrate in 1.5 mL de-ionized water at 275 °C in a closed vessel (see Experimental section). [b] Yield was calculated using the HPLC data and calibration curves. [c] Reaction conducted with degassed water and under nitrogen atmosphere.

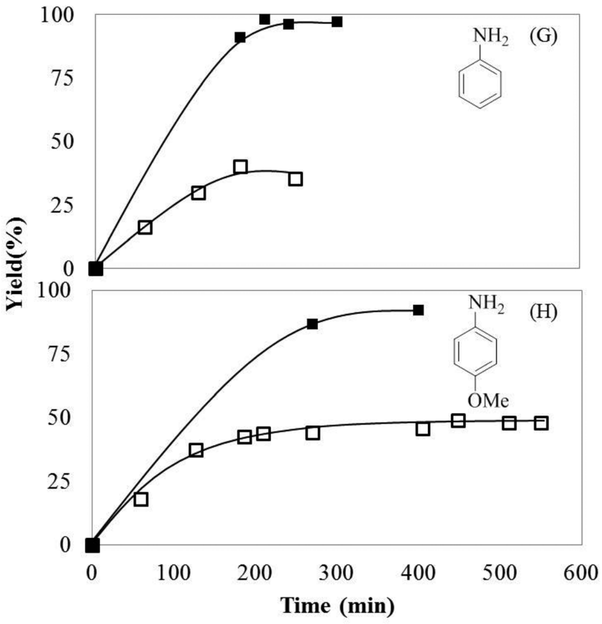


Fig. 10 Removal an amide protecting group from different protected anilines as a function of time: (G) yield of aniline (entries 7 and 8) under air atmosphere (□) and under N_2 atmosphere (■), (H) yield of 4-aminophenol (entries 9 and 10) under air atmosphere (□) and under N_2 atmosphere (■).

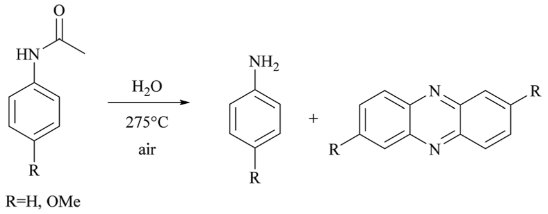
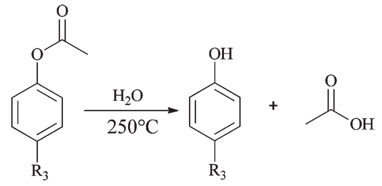


Fig. 11 Formation of phenazine derivatives in the presence of air at high temperature.

must be conducted in the absence of air. It is interesting to note that the methoxy substituent is stable under the conditions of amide hydrolysis.

WET hydrolysis of esters. Acetate esters are often used as protecting groups for alcohol functionalities. Generally, acetate esters can be hydrolyzed under acidic or basic conditions.[11] Neutralization of the acid or base, however, must also precede the isolation of the alcohol product – an additional process step which produces waste salts. We previously reported that *meta*- and *para*-substituted methyl and ethyl benzoate esters are hydrolyzed using WET at temperatures greater than 250 °C.[5c] In contrast, no phenyl esters have yet to be subjected to WET conditions. Since the phenol products are electron-rich aromatics which can be easily oxidized and since the temperatures for ester hydrolysis are near of those for hydrolysis of amides, the WET procedure was conducted under a nitrogen atmosphere. Phenyl acetate and 4-acetamidophenyl acetate were investigated as substrates for this process. The latter substrate was chosen in order to determine if the ester functionality could be hydrolyzed in the presence of the amide. The deprotection of the phenyl acetate derivatives to their corresponding phenols was conducted in WET at 250 °C. The results are summarized in Table 7. Fig. 12 shows the yields as a function of time for *N*-(4-hydroxyphenyl)acetamide (entry 12). The reactions proceeded rapidly in less than 30 minutes. In the case of the phenyl acetate (entry 11), the deprotection was achieved in 20 minutes and 92% yield was obtained. In the case of the acetamide (*N*-Ac) substituted ester (entry 12), complete and selective deprotection of the *O*-Ac was obtained in 30 minutes at 250 °C, leaving the acetamide group intact.

Table 7 WET hydrolysis of esters[a]



Entry	R_3	Time (min)	Yield[b] (%)
11	H	20	92
12	*N*-Ac	30	99

[a] Reactions were conducted with 0.05 mmol of substrate in 1.5 mL deionized water at 250 °C in a closed vessel (see Experimental section). [b] Yield was calculated using the HPLC data and calibration curves.

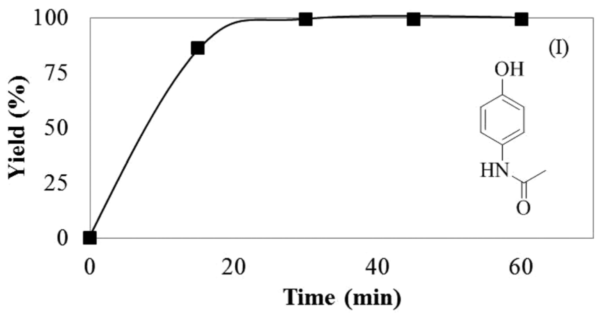


Fig. 12 WET hydrolysis of an acetate ester group from a molecule containing an alcohol and an amine-protecting group as a function of time: (I) yield of *N*-(4-hydroxyphenyl)acetamide (entry 12).

Conclusions

The Boc derivatives of anilines and substituted anilines were fully deprotected under relatively mild conditions (125 °C to 150 °C) and short reaction times (less than 2 hours). Acetamides (*N*-Ac) and acetates (*O*-Ac) were also successfully hydrolyzed at higher temperatures, 275 °C and 250 °C, respectively. Excellent yields were achieved in all cases. It was demonstrated that the reaction selectivity can be tuned by simply adjusting the temperature of the WET system. Several scenarios were explored for proof of concept: (1) selective removal of a carbamate group (*i.e. N*-Boc) in the presence of amides and acetate (*i.e. N*-Ac, *N*-Piv, *O*-Ac); (2) selective deprotection of an acetate (*i.e. O*-Ac) group in the presence of an amide (*i.e. N*-Ac) and (3) removal of an acetamide (*N*-Ac) derivative. In all cases, selective and near quantitative deprotection of the targeted functional group was achieved. *It should be emphasized, however, that the protocols discussed here may not be applicable to substrates which cannot tolerate high temperatures*. Nevertheless this study demonstrates that WET can be an attractive alternative solvent vehicle for the development of sustainable, environmentally greener processes.

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Notes and references

1 (*a*) P. E. Savage, A perspective on catalysis in sub- and supercritical water, *J. Supercrit. Fluids*, 2009, **47**(3), 407–414; (*b*) M. Siskin and A. R. Katritzky, A review of the reactivity of organic compounds with oxygen-containing functionality in superheated water, *J. Anal. Appl. Pyrolysis*, 2000, **54** (1–2), 193–214; (*c*) G. Brunner, Near critical and supercritical water. Part I. Hydrolytic and hydrothermal processes, *The J. Supercrit. Fluids*, 2009, **47**(3), 373–381; (*d*) A. G. Carr, R. Mammucari and N. R. Foster, A review of subcritical water as a solvent and its utilisation for the processing of hydrophobic organic compounds, *Chem. Eng. J.*, 2011, **172** (1), 1–17; (*e*) B. Kuhlmann, E. M. Arnett and M. Siskin, Classical Organic-Reactions in Pure Superheated Water, *J. Org. Chem.*, 1994, **59**(11), 3098–3101; (*f*) A. R. Katritzky, S. M. Allin and M. Siskin, Aquathermolysis: Reactions of organic compounds with superheated water, *Acc. Chem.*

Res., 1996, **29**(8), 399–406; (*g*) C. L. Liotta, C. A. E. P. Pollet and J. Hallett, Reactions in Near-critical Water, in *Organic Reactions in Water: Principles, Strategies, and Applications*, ed. U. Lindström, Blackwell Publishing, 2007.

2 M. Uematsu and E. U. Franck, Static dielectric-constant of water and steam, *J. Phys. Chem. Ref. Data*, 1980, **9**(4), 1291–1306.

3 W. L. Marshall and E. U. Franck, Ion product of water substance, 0-degrees-C-1000-degrees-C-, 1–10,000 bars – new international formulation and its background, *J. Phys. Chem. Ref. Data*, 1981, **10**(2), 295–304.

4 (*a*) M. M. Hoffmann and M. S. Conradi, Are there hydrogen bonds in supercritical water?, *J. Am. Chem. Soc.*, 1997, **119** (16), 3811–3817; (*b*) A. H. Harvey, *Thermodynamics Properties of Water*, NIST, Boulder, Colorado, October 2008 edn, 1998.

5 (*a*) J. Wang, Y. L. Liang and J. Qu, Boiling water-catalyzed neutral and selective N-Boc deprotection, *Chem. Commun.*, 2009 (34), 5144–5146; (*b*) H. R. Patrick, K. Griffith, C. L. Liotta, C. A. Eckert and R. Glaser, Near-critical water: A benign medium for catalytic reactions, *Ind. Eng. Chem. Res.*, 2001, **40**(26), 6063–6067; (*c*) H. P. Lesutis, R. Glaser, C. L. Liotta and C. A. Eckert, Acid/base-catalyzed ester hydrolysis in near-critical water, *Chem. Commun.*, 1999 (20), 2063–2064; (*d*) G. Wang, C. J. Li, J. Li and X. S. Jia, Catalyst-free water-mediated N-Boc deprotection, *Tetrahedron Letters*, 2009, **50**(13), 1438–1440.

6 S. A. Nolen, C. L. Liotta, C. A. Eckert and R. Glaser, The catalytic opportunities of near-critical water: a benign medium for conventionally acid and base catalyzed condensations for organic synthesis, *Green Chem.*, 2003, **5**(5), 663–669.

7 K. Chandler, F. H. Deng, A. K. Dillow, C. L. Liotta and C. A. Eckert, Alkylation reactions in near-critical water in the absence of acid catalysts, *Ind. Eng. Chem. Res.*, 1997, **36** (12), 5175–5179.

8 J. P. Hallett, *Enhanced recovery of homogeneous catalysts through manipulation of phase behavior*, Dissertation, Georgia Institute of Technology, Atlanta, GA, 2008.

9 P. Anastas and N. Eghbali, Green Chemistry: Principles and Practice, *Chem. Soc. Rev.*, 2010, **39**(1), 301–312.

10 (*a*) J. S. Carey, D. Laffan, C. Thomson and M. T. Williams, Analysis of the reactions used for the preparation of drug candidate molecules, *Org. Biomol. Chem.*, 2006, **4**(12), 2337–2347; (*b*) M. Karpf and R. Trussardi, New, azide-free transformation of epoxides into 1,2-diamino compounds: Synthesis of the anti-influenza neuraminidase inhibitor oseltamivir phosphate (Tamiflu), *J. Org. Chem.*, 2001, **66**(6), 2044–2051.

11 P. G. M. Wuts and T. W. Greene, *Protective groups in organic synthesis*, John Wiley & Sons, Inc., 4th edn, 2007.

12 *tert*-Butyl (4-methoxyphenyl)carbamate: *p*-methoxyaniline (0.82 g, 6.7 mmol) and di-*tert*-butyl dicarbonate (Boc_2O, 2.2 g, 10 mmol) were stirred in 25 mL absolute ethanol overnight at room temperature. The solvent was removed by rotary evaporation. The resulting solid was dissolved in diethyl ether (Et_2O, 30 mL) and washed three times with water (H_2O, 30 mL). The organic layer was dried over magnesium sulfate ($MgSO_4$), filtered, and the solvent was removed on the rotovap. White solid, mp = 95–96 °C. ^1H NMR (400 MHz, DMSO-d_6): δ 9.11 (s, 1H), 7.33 (d, 2H), 6.81 (d, 2H), 3.68 (s, 3H), 1.44 (s, 9H). ^{13}C NMR: 153.96, 152.44, 132.09, 119.16, 113.30, 78.14, 54.52, 27.67.

13 *tert*-Butyl (4-chlorophenyl)carbamate: *p*-chloroaniline (0.85 g, 6.7 mmol) and di-*tert*-butyl dicarbonate (Boc_2O, 2.2 g, 10 mmol) were stirred in 25 mL absolute ethanol overnight at room temperature. The solvent was removed by rotary evaporation. The resulting solid was dissolved in diethyl ether (Et_2O, 30 mL) and washed three times with water (H_2O, 30 mL). The organic layer was dried over magnesium sulfate ($MgSO_4$), filtered, and the solvent was removed on the rotovap. White solid, mp = 102–103 °C. ^1H NMR (400 MHz, DMSO-d_6): δ 9.49 (s, 1H), 7.46 (d, 2H), 7.27 (d, 2H), 1.45 (s, 9H). ^{13}C NMR: 152.18, 138.04, 128.00, 125.09, 119.03, 78.84, 27.58.

14 O. Levenspiel, *Chemical Reaction Engineering*, John Wiley & Sons, Inc., New York, 2nd edn, 1995.

15 J. M. Prausnitz, R. N. Lichtenthaler and E. Gomes de Azevedo, *Molecular Thermodynamics of Fluid-Phase Equilibria*, Prentice Hall, New Jersey, 3rd edn, 1999.

16 *COSMOtherm, C2.1 Release 01.11*, COSMOlogic GmbH & Co. KG, Leverkusen, Germany, 2010; http://www.cosmologic.de (accessed September 2012).

17 Advanced Chemistry Development (ACD/Labs) Software V11.02 (© 1994–2013 ACD/Labs).

18 J. C. Sheehan and D. D. H. Yang, The use of N-formyll-amino acids in peptide synthesis, *J. Am. Chem. Soc.*, 1958, **80**(5), 1154–1158.