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Carbamoylimidazolium and thiocarbamoylimidazolium salts: novel reagents for the synthesis of ureas, thioureas, carbamates, thiocarbamates and amides

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Dedicated to the memory of Dr. Bruce Graham, former Director of Research and Development, Crompton Chemical, Guelph, Ontario.

Abstract—Carbamoylimidazolium salts act as efficient *N*,*N*-disubstituted carbamoylating reagents. These salts are readily prepared by the sequential treatment of secondary amines with *N*,*N*′-carbonyldiimidazole (CDI) and iodomethane. The carbamoylimidazolium salts are more efficient carbamoyl transfer reagents than the intermediate carbamoylimidazoles, as a result of the 'imidazolium' effect. Kinetic studies on the base promoted hydrolysis of both carbamoylimidazoles and carbamoylimidazolium salts reveal over a hundred-fold rate acceleration. The salts react with amines, thiols, phenols/alcohols, and carboxylic acids in high yields, without the need for subsequent chromatographic purification of the products, producing ureas, thiocarbamates, carbamates, and amides, respectively. Analogous thiocarbamoylimidazolium salts were also synthesized from secondary amines and *N*,*N*′-thiocarbonyldiimidazole (TCDI), followed by methylation with iodomethane.

1. Introduction

The reaction of nucleophiles with acyl transfer reagents, such as acid chlorides, is one of the most important classes of functionalization reaction used in organic synthesis. Such reactions are also important for the generation of combinatorial libraries,[1] both using solid-phase organic synthesis (SPOS)[2] and parallel solution-phase techniques.[3] The corresponding transfer of an electrophilic carbamoyl group ($R^1R^2NC{=}O$) to nucleophiles is used in the formation of ureas, carbamates and thiocarbamates. A variety of reagents are useful synthetic equivalents to carbamoyl cations (Fig. 1). Isocyanates **1** are used as monosubstituted carbamoyl transfer reagents ($R^1NHC{=}O$), and act as synthetic equivalents to monosubstituted carbamoyl cations. Carbamoyl chlorides **2** are the most commonly used synthetic equivalents to disubstituted carbamoyl cations. Unfortunately, there are significant drawbacks associated with the use of carbamoyl chlorides. They have limited commercial availability and their synthesis requires the use of toxic phosgene. In addition, they are highly reactive, prone to hydrolysis, and their relative instability does not render them suitable for long-term storage and archiving. These considerations are particularly important where 'off the shelf' reagents or a series of combinatorial 'building blocks' are required.

As a solution to these problems, we envisaged the use of carbamoylimidazolium salts **3** as *N*,*N*′-disubstituted carbamoyl cation equivalents (Fig. 1).[4] The corresponding carbamoylimidazoles **4**, are much less reactive towards nucleophilic attack and have to be activated as carbamoylimidazolium salts. Such activation of carbonylimidazole as carbonylimidazolium salts has been demonstrated previously in a number of systems.[5,6–9] Acylimidazolium salts were shown, initially by Jencks, to be more reactive than acylimidazoles in their reactions with nucleophiles.[6]

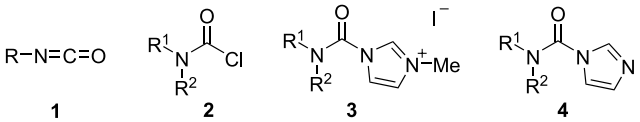

Figure 1. *N*-monosubstituted and *N*,*N*′-disubstituted carbamoyl cation equivalents.

Keywords: Carbamoylimidazolium salts; Thiocarbamoylimidazolium salts; Ureas; Thioureas; Carbamates; Thiocarbamates; Amides.
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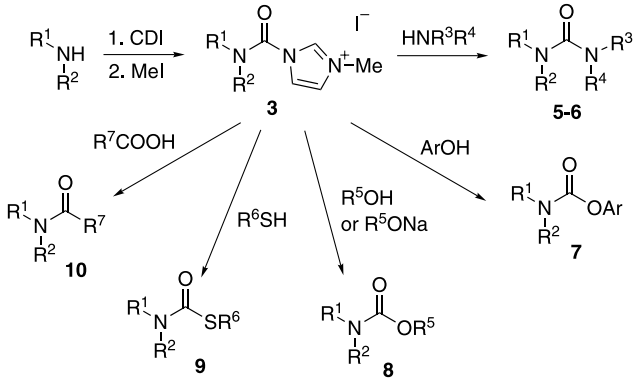
Similarly, alkoxycarbonylimidazolium salts are also activated towards nucleophilic attack by amines.[7] Rapoport has applied this strategy in the selective protection of the amino functionality in nucleosides, as amides, carbamates, and thiocarbamates.[8] Dicationic 1,1′-carbonylbis(3-methylimidazolium) ions have been used for alkoxycarbonylations of amino acids for peptide and ester bond forming reactions.[9]

We now outline a full study on the use of carbamoylimidazolium salts **3** as *N*,*N*′-disubstituted carbamoyl transfer reagents, as well as the use of the corresponding sulfur analogs. Specifically, we show their application to the synthesis of ureas, thioureas, carbamates, thiocarbamates, and amides using solution-phase methods (Scheme 1).[4] There has also been a recent application of these reagents in polymer-supported chemistry.[10]

2. Results and discussion

Carbamoylimidazolium salts **3** are readily prepared from *N*,*N*′-carbonyldiimidazole (CDI) via a two-step procedure. CDI, used as the phosgene equivalent in this synthesis, is a commercially available and easily handled crystalline solid.[5] Stable and isolable carbamoylimidazoles **4** were obtained in high yields by refluxing the secondary amines with CDI in THF for 16 h (Table 1, **4a**–**4e**). The reaction of L-proline benzylester hydrochloride, morpholine, *O*,*N*-dimethylhydroxylamine and 1,4-dioxa-8-aza-spiro[4.5]-decane with CDI under refluxing conditions afforded undesirable byproducts. However, when these reactions were stirred at rt in dichloromethane, the desired carbamoylimidazoles were cleanly formed in high yields (Table 1, **4f**–**4i**). After simple aqueous work-up, the carbamoylimidazoles **4** were reacted with MeI in acetonitrile at rt for 24 h. The carbamoylimidazolium salts **3** were obtained after evaporation of the solvent and volatile reagents.

A wide variety of carbamoylimidazolium salts **3** have been prepared for which the analogous carbamoyl chlorides are not commercially available. Since our goal was the development of carbamoyl transfer reagents suitable for a range of synthetic applications, including combinatorial library synthesis, the long-term thermal, hydrolytic and air stability of the salts is an important practical consideration.



Scheme 1.

The stability of different salts in solution and in the solid-state by using ^{1}H NMR analysis was observed. The carbamoylimidazolium salts **3a**, **3c** and **3h** derived from tetrahydroquinoline, *N*-methylaniline and *O*,*N*-dimethylhydroxylamine, respectively, were chosen as test compounds for stability studies. The stability of the compounds in the solid state was evaluated using freshly prepared salts, stored at rt without exclusion of air and moisture. The same compounds were also evaluated as stock solutions in $CDCl_3$ stored at rt. Salt **3a** is a very stable, non-hygroscopic, crystalline solid, which can be stored for extended periods of time without discoloration. There are only trace amounts of decomposition products appearing after 3 months of storage either in $CDCl_3$ solution or in solid state. Salt **3c** is a very hygroscopic yellow foam. However, NMR studies showed that the salt remained at the same purity level even after 3 months. A $CDCl_3$ solution of **3c** showed only trace amount of decomposition product after 3 months of storage. Salt **3h**, a white crystalline solid, was the least stable compound, with significant color change occurring after several days of storage in the solid state. However, decomposition can be avoided by storing the solid in a freezer at −20 °C. Decomposition was also observed in the $CDCl_3$ solution of salt **3h** after 24 h showing 12% contamination with the decomposition product. After 48 h, the decomposition caused significant color change and some precipitation.

X-ray crystallographic and IR data, clearly show the structural effects of the well-known imidazolium effect. X-ray crystallographic analysis of the salt **3b** shows a relatively short C(5)–N(3) bond (1.327(6) Å) and a longer C(5)–N(1) bond (1.466(6) Å) (Fig. 2).[11] This reflects the greater double bond character of the C(5)–N(3) bond. The C(5)–N(1) bond is longer and weaker because the lone-pair of electrons on the imidazolium nitrogen does not have a significant resonance effect with the carbonyl group, since it is part of the aromatic π-system of the imidazolium ring. These C–N bond distances compare to values of approximately 1.371–1.379 Å for simple tetrasubstituted ureas, and 1.325–1.346 Å for amides. The degree of pyramidalization of N(3) is intermediate between that of idealized sp^3 and sp^2 hybridization geometries (such as in aliphatic amines and amides, respectively). The infra-red C=O stretch absorption frequencies of the carbamoylimidazolium salts **3** usually lie in the range of 1710–1730 cm^{-1}, whereas those of the carbamoylimidazoles **4** occur some 30 cm^{-1} lower, in the range of 1680–1700 cm^{-1}, indicative of a

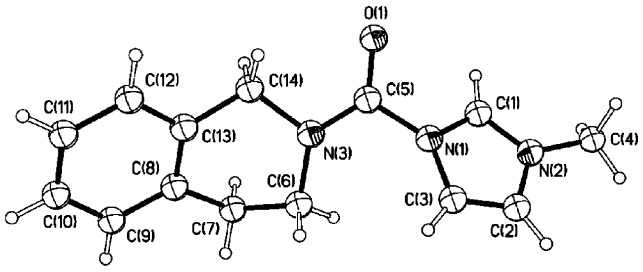
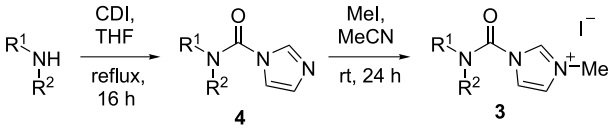
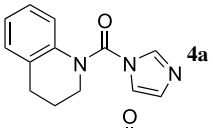
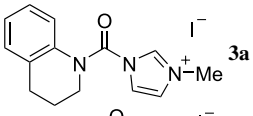
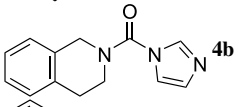
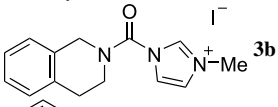
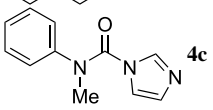
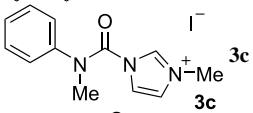
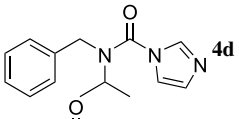
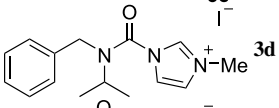
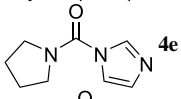
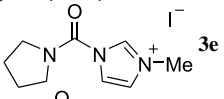
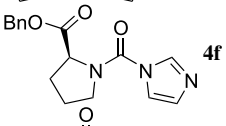
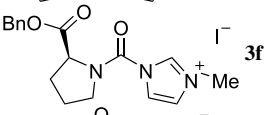
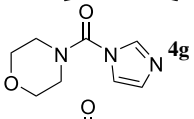
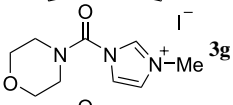
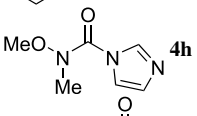
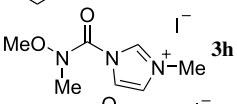
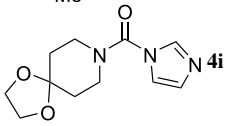
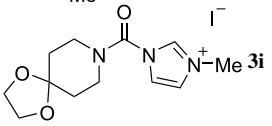


Figure 2. Solid-state structure of the carbamoylimidazolium cation of salt **3b** as determined by X-ray crystallographic analysis.[11] Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as spheres of arbitrary radii.

Table 1. Carbamoylimidazole **4**[a] and carbamoylimidazolium salt **3**[b] formation



Carbamoylimidazole	Yield (%)[c]	Carbamoylimidazole	Yield (%)[c]
 **4a**	88	 **3a**	Quant.
 **4b**	88	 **3b**	Quant.
 **4c**	87	 **3c**	Quant.
 **4d**	92	 **3d**	Quant.
 **4e**	87	 **3e**	Quant.
 **4f**	96[d]	 **3f**	98
 **4g**	90[d]	 **3g**	82
 **4h**	96[d]	 **3h**	93
 **4i**	95[d]	 **3i**	96

[a] Secondary amine (1.0 equiv) and CDI (1.1 equiv) in THF were refluxed for 16 h.
[b] Carbamoylimidazole and MeI (4.0 equiv) in acetonitrile were stirred for 24 h.
[c] Isolated yields without flash chromatography.
[d] Secondary amine (1.0 equiv), CDI (1.1 equiv) (triethylamine (1 equiv) in case of HCl salt was added) in CH_2Cl_2 were stirred at rt for 24 h.

stronger C═O bond in the **3** compared to **4**. The stronger C═O bond in the salts presumably offsets a correspondingly weaker C(═O)–N(imidazole) bond.

2.1. Reactivity studies of carbamoylimidazolium salts 3: base promoted hydrolysis

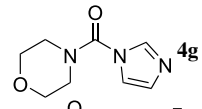
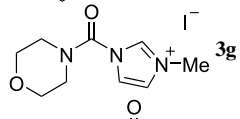
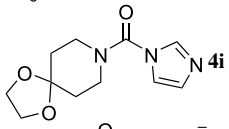
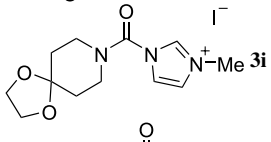
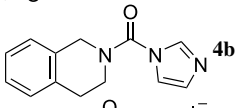
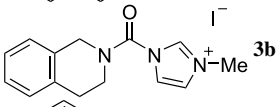
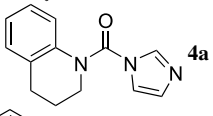
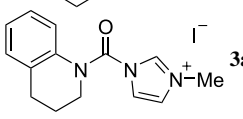
A hydrolysis study of the carbamoylimidazolium salts **3** and carbamoylimidazoles **4** was undertaken both to give a guide to their hydrolytic stability, but more importantly to provide kinetic data for their reactivity with the simple nucleophile hydroxide. Thus, second order rate constants for the hydroxide promoted hydrolysis of carbamoylimidazoles and carbamoylimidazolium salts were measured at 25 °C using UV/visible spectroscopic measurements, by observing the rate of change in absorbance at 230 nm (Table 2, Entries 1 and 2), 225 nm (Table 2, Entries 3 and 5), 235 nm (Table 2, Entries 4 and 6), 270 nm (Table 2, Entry 7) and 265 nm (Table 2, Entry 8).

The results show that hydroxide promoted hydrolysis of carbamoylimidazolium salts **3** occurs over 100-fold more rapidly than the corresponding carbamoylimidazoles. These results compare with a second order rate constant of $1.5\times 10^5\ M^{-1}\ s^{-1}$ measured for the hydroxide promoted hydrolysis of $CH_3CO–ImMe^+$ (acetylimidazolium ion), measured at $\mu=0.2$ (NaCl).[6]

2.2. H/D exchange studies of carbamoylimidazolium salts 3

The imidazolium salts **3** are very weak acids, as indicated by H/D exchange at the C-2 position of the imidazolium ring (Fig. 3). For example, compound **3i** undergoes deuterium exchange in CD_3OD, with complete exchange occurring after approximately 24 h, as measured by ^1H NMR. The addition of tertiary amine bases, such as triethylamine, to a solution of the salts **3** in CD_3OD accelerates the H/D exchange process, with full deuterium exchange occurring

Table 2. Second order rate constants for the aqueous hydroxide promoted hydrolysis of carbamoylimidazoles **4** and carbamoylimidazolium salts **3** at $T=25\,^{\circ}C$, $\mu=0.1$ (KCl)

Entry	Compounds	k_2 ($M^{-1}\,s^{-1}$)
1	 **4g**	0.34±0.14
2	 **3g**	96±13
3	 **4i**	0.11±0.04
4	 **3i**	38.0±7.9
5	 **4b**	0.094±0.037
6	 **3b**	31.1±5.3
7	 **4a**	0.038±0.008
8	 **3a**	16.0±0.9

within 1 h. The use of a triethylamine/CD_3OD combination results in the formation of the corresponding carbamates after approximately 20 h, through nucleophilic attack of CD_3OD vide infra. The H/D exchange process presumably occurs through the intermediacy of an imidazol-2-ylidene carbene (Fig. 3). The weak acidity of the salts **3** has been exploited by our laboratories for the formation of *N*-carbamoyl substituted heterocyclic carbene Pd(II) complexes.[12] Also, Hlasta has reported the nucleophilic addition reaction of these carbenes to aldehydes, via in situ generated carbamoylimidazolium salts.[13]

2.3. Synthesis of tri- and tetrasubstituted ureas 5 and 6

The initial synthetic targets that we envisaged for the reactions of the salts **3** were for the generation of ureas. There are numerous methods for the synthesis of mono-, di- and trisubstituted ureas, the most significant of which involves treatment of amines with isocyanates.[14] However, there are only a few methods for the formation of unsymmetrical tetrasubstituted ureas.[15] The most well established method involves treatment of a carbamoyl chloride with a secondary amine.[16] Katritzky has demonstrated the use of 1,1′-carbonylbisbenzotriazole[5] as a phosgene equivalent for the synthesis of unsymmetrical tetrasubstituted ureas under refluxing conditions.[17]

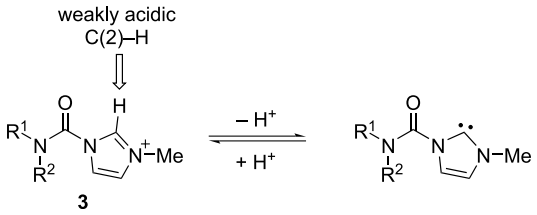


Figure 3. H/D exchange of carbamoylimidazolium salts **3** at the C-2 position via imidazol-2-ylidene carbenes.

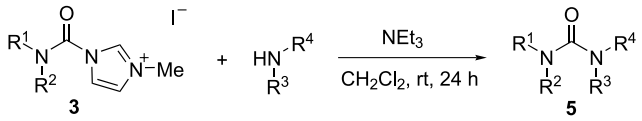
Reaction of carbamoylimidazolium salts **3** with secondary amines is an experimentally straightforward and general protocol for the synthesis of unsymmetrical tetrasubstituted ureas. Addition of secondary amines to a solution of carbamoylimidazolium salts in dichloromethane in the presence of triethylamine, afforded tetrasubstituted ureas in high yields (Table 3). A range of different secondary amines were successfully reacted forming the ureas **5a–h** in excellent yields. Similarly, the addition of primary amines to the salts **3** afforded the corresponding trisubstituted ureas **5i–l**. In most cases, the detectable byproducts, *N*-methylimidazole and triethylamine hydrochloric acid, can be removed by washing the organic phase with dilute acid. This greatly facilitates the purification protocol, and we have previously demonstrated that this method is amenable for the semi-automated solution-phase parallel synthesis of ureas.[4c] X-ray crystallographic analysis of the tetrasubstituted urea **5b** shows C(6)–N(8) and C(6)–N(1) bond distances of 1.381(3) Å and 1.354(3) Å, respectively, (Fig. 4). The preferential conjugation of N(8) with the aromatic system of the tetrahydroquinoline ring results in smaller resonance effect between the carbonyl group and N(8), which is reflected by the longer C(6)–N(8) bond distance.

Unfortunately, the experimental procedure developed for aliphatic amines is not suitable for the reaction of more weakly nucleophlic amines, such as anilines. However, reaction as the anilide anions, which are much more reactive nucleophliles, provides a convenient synthetic protocol for the formation of the corresponding ureas. Thus, pretreatment of the anilines with a strong base such as *n*-BuLi (or KHMDS), followed by addition of the salts **3** generates the corresponding ureas **6** (Table 4).

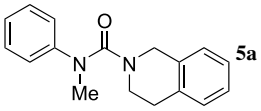
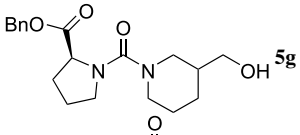
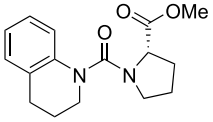
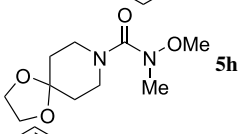
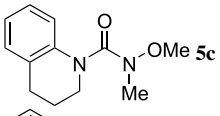
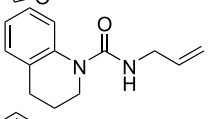
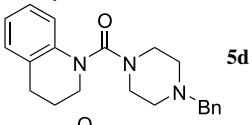
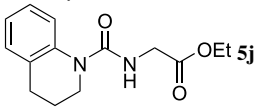
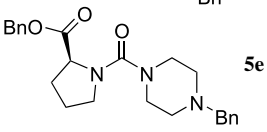
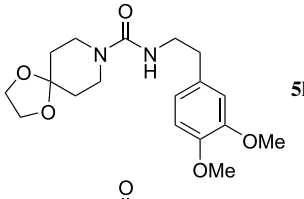
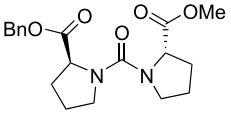
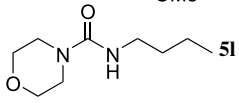
2.4. Synthesis of carbamates 7 and 8

Organic carbamates represent an important class of compounds in pharmacology, agriculture[18] and in synthetic chemistry as protecting groups for amines.[19] The standard method for their formation involves transfer of an electrophilic alkoxy carbonyl group to a nucleophilic amine. In certain cases, the alternate process of reacting a nucleophilic alcohol with an electrophilic carbamoylation reagent may be desirable. Examples of this latter process include the use of phosgene derivatives such as isocyanates or carbamoyl chlorides,[20] which upon attack by alcohols generates *N*-mono- and *N*-disubstituted carbamates, respectively. Several alternative methods that avoid the use of toxic materials have also been developed.[21] We envisaged that the salts **3**, while relatively unreactive with alcohols, would react with nucleophlic alkoxides to produce the corresponding carbamates **7/8**. In the case of phenols, tertiary amines

Table 3. Synthesis of ureas **5**[a] from carbamoylimidazolium salts **3** and amines



3 **5**

Urea	Yield (%)[b]	Urea	Yield (%)[b]
 **5a**	96	 **5g**	82
 **5b**	89	 **5h**	74
 **5c**	77	 **5i**	84
 **5d**	96	 **5j**	89
 **5e**	81	 **5k**	Quant.
 **5f**	78	 **5l**	70

[a] Imidazolium salt **3** (1.0 equiv), amine (or HCl salts) (1.0 equiv) and triethylamine (1.0 equiv, or 2.0 equiv for HCl salts) in CH_2Cl_2 were stirred at rt for 24 h.
[b] Isolated yields.

are suitable bases for the in situ generation of the reactive phenoxides. Thus, heating the substrates overnight at reflux in acetonitrile, in the presence of one molar equivalent of triethylamine, gave the corresponding carbamates **7** in excellent yields (Table 5). Again, the byproducts are easily removed by washing the organic phase with dilute acid. Using this method carbamates **7** were obtained with sufficiently high purity such that chromatographic purification was not required.

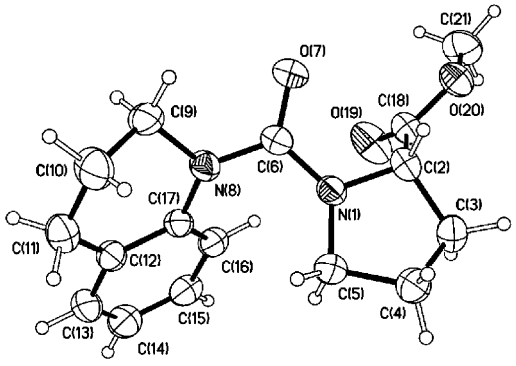
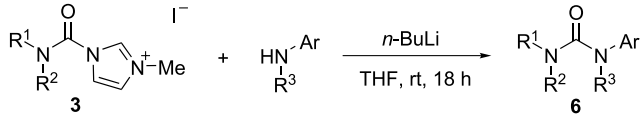


Figure 4. Solid-state structure of the tetrasubstituted urea **5b** as determined by X-ray crystallographic analysis. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as spheres of arbitrary radii.

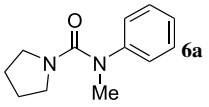
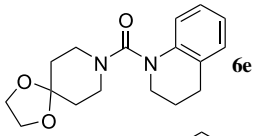
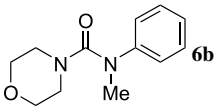
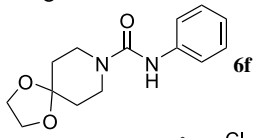
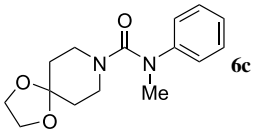
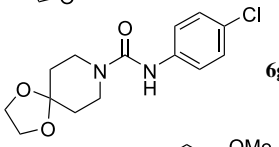
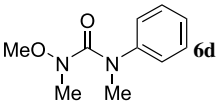
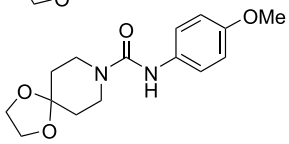
Aliphatic alcohols react slowly with carbamoylimidazolium salts even under reflux conditions in the presence of triethylamine. The lower acidity of aliphatic alcohols presumably prevents the formation of the alkoxide anion under these conditions, which would serve as the reactive nucleophile. Less acidic alcohols will react with carbamoylimidazolium salts, when first converted into more nucleophilic sodium alkoxides. Thus, formation of the alkoxides by the treatment of a mixture of the alcohol and the carbamoylimidazolium salt **3** in THF/DMF with NaH led to the formation of the desired carbamates **8** after stirring at rt for 24 h. Formation of Cbz and Alloc carbamates from amines is thus possible via the corresponding carbamoylimidazolium salts, therefore, providing another strategy for the formation of these synthetically important carbamate protecting groups.

The use of alcohols as solvents in the presence of triethylamine at rt also results in carbamate formation, as exemplified by the addition of 2,2,2-trifluoroethanol with **3i** in the presence of triethylamine at rt, to give carbamate **8b** (Table 5), as well as by the addition of CD_3OD to **3i**, vide supra. Under these conditions it is likely that base assisted

Table 4. Aryl substituted ureas **6**[a] synthesized from carbamoylimidazolium salts **3** and anilines



3 **6**

Amide	Yield (%)[b]	Amide	Yield (%)[b]
 **6a**	90	 **6e**	97
 **6b**	96	 **6f**	76
 **6c**	97	 **6g**	70
 **6d**	87	 **6h**	65

[a] Amine (1.0 equiv) and *n*-BuLi (1.5 equiv) in THF were stirred at rt for 1 h. Imidazolium salt **3** (1.2 equiv) was then added and the reaction stirred for 18 h.
[b] Isolated yields.

attack of the alcohols to **3** occurs, rather than by direct attack of alkoxides.

2.5. Synthesis of thiocarbamates 9

Thiocarbamates are generally prepared from carbamoyl chlorides and thiols,[22] chlorothiolformates and amines[23] or via the thione–carbamate rearrangement.[24] Unfortunately, the necessary intermediates are typically prepared from phosgene or thiophosgene. Now the thiocarbamates **9** can be easily synthesized in a similar manner to the carbamate analogs described above (Table 6). Addition of one equivalent of either alkylthiols or thiophenols to carbamoylimidazolium salts **3** at rt in chloroform or dichloromethane, in the presence of triethylamine, provided the desired thiocarbamates **9** in excellent yield and purity. The successful reaction of an *N*-protected cysteine (Table 6, **9e**) suggests that this reaction may be useful for the functionalization of thiol residues in peptide chemistry.

2.6. Synthesis of tertiary amides 10

The amide functional group is one of the most important functionalities in organic chemistry, due to its presence in natural products, pharmaceutical and other biologically active compounds. The most common method of synthesizing amides involves reaction of an amine with an activated derivative of a carboxylic acid, such as an acid chloride. In many cases the use of acid chlorides is not favourable, since they can be difficult to work, are not easily stored, and lead to undesirable side reactions. Thus, the more general method of combining an amine and a carboxylic acid in the presence of various coupling reagents, has grown in importance, particularly for small-scale synthesis.[25] Although these coupling reagents usually give good results, they are often expensive, some are toxic, while others are not very soluble in organic solvents, and the amide products require chromatographic purification from the coupling reagent byproducts.

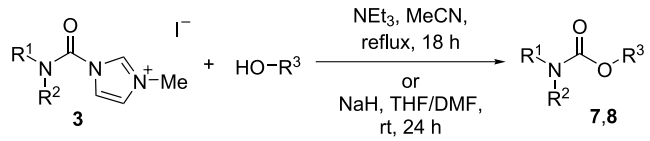
The carbamoylimidazolium salts **3** react with carboxylic acids in the presence of triethylamine, in acetonitrile at rt, to form tertiary amides **10** in excellent yields (Table 7). The desired products are of sufficient purity after aqueous work-up that chromatographic purification is not required. For example, this approach provides a very convenient approach for the synthesis of Weinreb amides **10h–l** from the corresponding imidazolium salt **3h**.[4d]

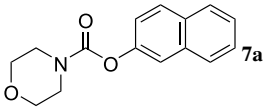
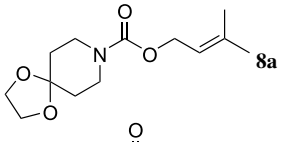
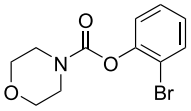
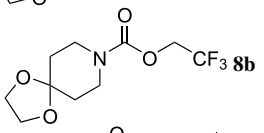
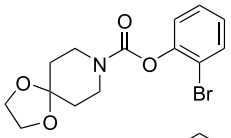
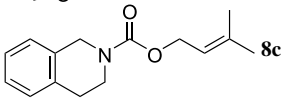
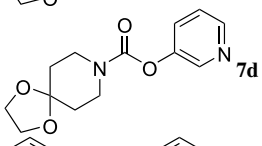
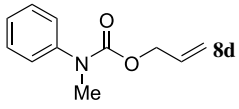
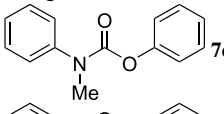
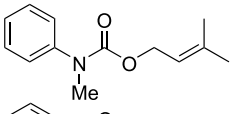
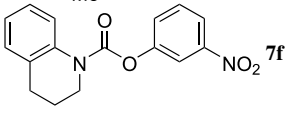
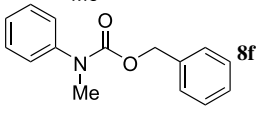
These reactions are noteworthy, in that the carbamoylimidazolium salts **3** act as coupling reagents, leading to the formation of an activated acyl transfer agent, while simultaneously generating a nucleophilic secondary amine, which then react together to form the tertiary amides **10**. In essence, the salts **3** serve as preactivated amine reagents that are capable of reacting directly with carboxylic acids, without the requirement for the introduction of additional coupling reagents. This is an unusual approach, the best analogy for which, is the reaction of carboxylic acids with isocyanates at 60 °C, to give secondary amides. The isocyanates similarly act as coupling reagent and amine source.[26]

2.7. Synthesis of thiocarbamoylimidazolium salts 12

The success of carbamoylimidazolium salts **3** as *N*,*N*-disubstituted carbamoyl transfer reagents, encouraged us to

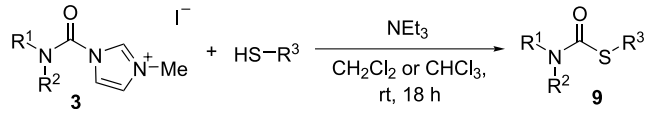
Table 5. Carbamate **7**[a] and **8**[b] synthesized from carbamoylimidazolium salts **3** and phenols or alcohols

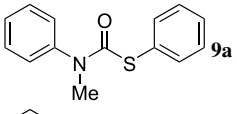
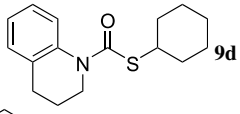
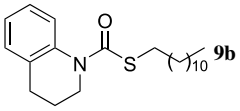
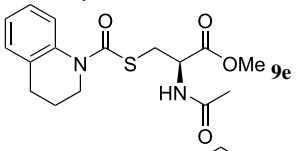
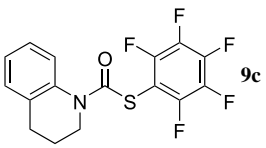
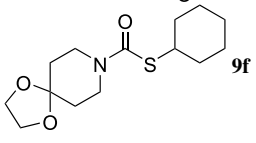


Carbamate	Yield (%)[c]	Carbamate	Yield (%)[c]
 **7a**	93	 **8a**	57
 **7b**	71	 **8b**	95[d]
 **7c**	94	 **8c**	83
 **7d**	88	 **8d**	78
 **7e**	86	 **8e**	63
 **7f**	94	 **8f**	83

[a] Imidazolium salt **3** (1.0 equiv), phenol (1.0 equiv) and triethylamine (1.0 equiv) in acetonitrile were refluxed for 18 h.
[b] Imidazolium salt **3** (1.0 equiv), alcohol (1.0 equiv) and NaH (1.0 equiv) in THF/DMF (1:1) were stirred at rt for 24 h.
[c] Isolated yields.
[d] Imidazolium salt **3** (1.0 equiv) and triethylamine (1.0 equiv) in CF_3CH_2OH were stirred at rt for 18 h.

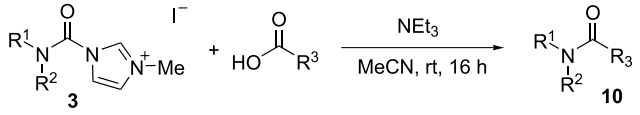
Table 6. Thiocarbamates **9**[a] synthesized from carbamoylimidazolium salts **3** and thiols



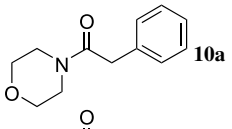
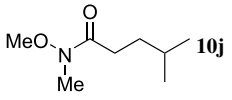
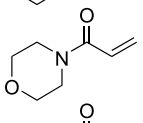
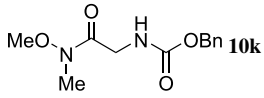
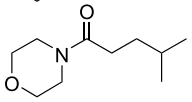
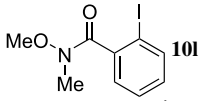
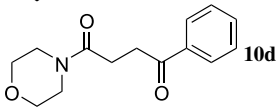
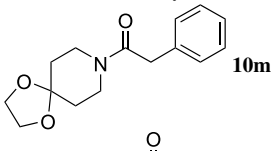
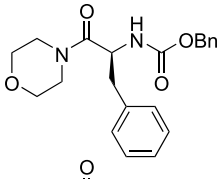
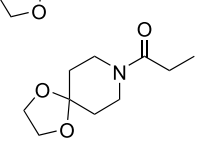
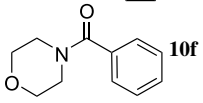
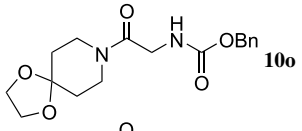
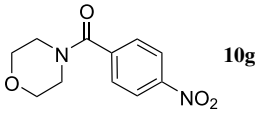
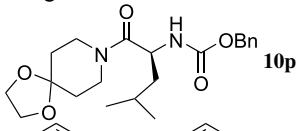
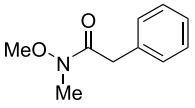
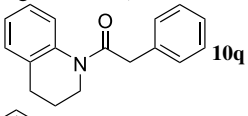
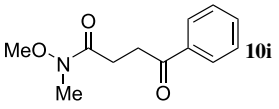
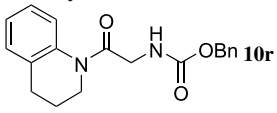
Thiocarbamate	Yield (%)[b]	Thiocarbamate	Yield (%)[b]
 **9a**	86	 **9d**	91
 **9b**	84	 **9e**	71
 **9c**	92	 **9f**	94

[a] Imidazolium salt **3** (1.0 equiv), thiol (1.0 equiv) and triethylamine (1.0 equiv) in CH_2Cl_2 or $CHCl_3$ were stirred at rt for 18 h.
[b] Isolated yield.

Table 7. Amides **10**[a] synthesized from carbamoylimidazolium salts **3** and carboxylic acids



3 **10**

Amide	Yield (%)[b]	Amide	Yield (%)[b]
 **10a**	92	 **10j**	92
 **10b**	75	 **10k**	93
 **10c**	97	 **10l**	86
 **10d**	94	 **10m**	92
 **10e**	96	 **10n**	99
 **10f**	95	 **10o**	87
 **10g**	75	 **10p**	62
 **10h**	94	 **10q**	80
 **10i**	95	 **10r**	82

[a] Imidazolium salt (1.0 equiv), carboxylic acid (1.0 equiv) and triethylamine (1.0 equiv) were stirred at rt for 16 h.
[b] Isolated yields.

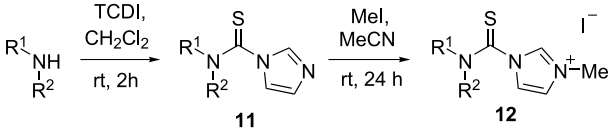
investigate the use of the analogous sulfur based thiocarbamoylimidazolium salts **12**. We anticipated that these salts would act as *N*,*N*-disubstituted thiocarbamoyl transfer reagents. The need for such reagents is particularly acute, since thiocarbamoyl chlorides are currently used for this purpose, the synthesis of which requires the use of highly toxic thiophosgene.

The thiocarbamoylimidazolium salts **12** can be readily prepared by analogous chemistry to that employed for the synthesis of **3**, using thiocarbonyldiimidazole (TCDI) as the precursor. Thus, reaction of secondary amines with TCDI proceeded in dichloromethane at rt to give thiocarbamoylimidazoles **11**, which are usually viscous yellow or brown oils. Alkylation of the unpurified thiocarbamoylimidazoles **11** with 4 equiv of MeI in acetonitrile gave the crude products **12** as brown oils. Recrystallization is required to obtain the pure products **12**. Although the compounds are not stable as oils, the recrystallized products are yellow crystals, which can be stored for extended periods of time without decomposition (Table 8).

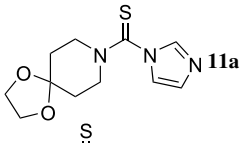
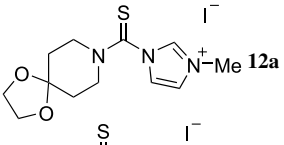
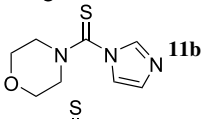
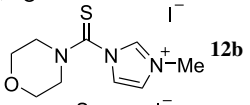
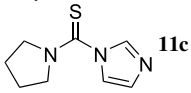
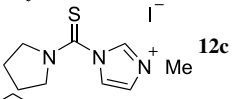
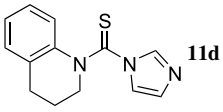
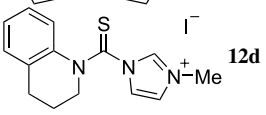
2.8. Synthesis of unsymmetrical tri- and tetrasubstituted thioureas 13

An example of the utility of thiocarbamoylimidazolium salts **12** as *N*,*N*-disubstituted thiocarbamoyl transfer reagents is exemplified by their reactivity with primary and secondary amines, to give tri- and tetrasubstituted thioureas **13**, examples of which are known to be biologically interesting. By far the most common method of preparing thioureas is the reaction of isothiocyanates with amines.[27] TCDI has also been employed in thiourea synthesis, but the addition of the second amine requires heating and the reaction most likely proceeds through

Table 8. Thiocarbamoylimidazole **11**[a] and thiocarbamoylimidazolium salt **12**[b] formation



11 **12**

Thiocarbamoylimidazole	Yield (%)[c]	Imidazolium salt	Yield (%)[c]
 **11a**	96	 **12a**	78
 **11b**	90	 **12b**	65
 **11c**	90	 **12c**	Quant.
 **11d**	Quant.	 **12d**	76

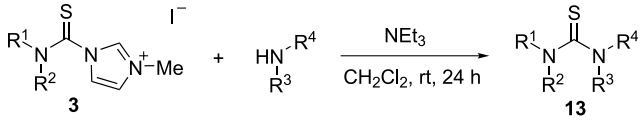
[a] Secondary amine (1.0 equiv) and TCDI (1.1 equiv) in CH_2Cl_2 were stirred at rt for 2 h.
[b] Thiocarbamoylimidazole (1.0 equiv) and MeI (4.0 equiv) in acetonitrile were stirred at rt for 24 h.
[c] Isolated yields.

an isothiocyanate.[28] Reaction of **12** with secondary amines in dichloromethane at rt results in the formation of thioureas **13** (Table 9). The salts **12** are less reactive than the salts **3**, since replacement of the oxygen by sulfur lowers their electrophilicity. This has practical implications, as demonstrated by the lower reaction yields of **13** obtained with primary amines (Table 9, compound **13f**), compared to reactions with the more nucleophilic secondary amines (Table 9, compound **13e**). Thiocarbamoylimidazolium salt **12d** was observed to show very poor reactivity with diallylamine and pyrrolidine. These results show that thiocarbamoylimidazolium salts are good thiocarbamoyl transfer reagents, offering a more practical solution than the use of thiocarbamoyl chlorides, which is particularly useful for the formation of tetrasubstituted thioureas.

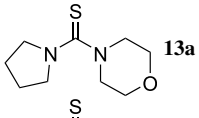
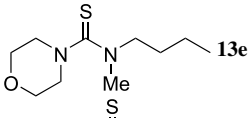
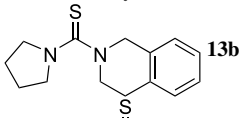
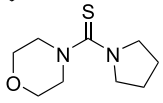
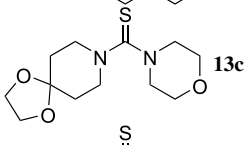
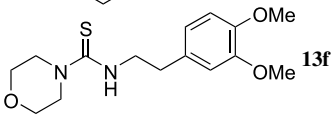
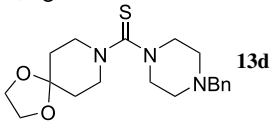
2.9. Application of carbamoylimidazolium salts 3 in target oriented synthesis

We envisaged that reaction of diethyl phosphonoacetic acid with the salts **3** would lead to the formation of diethyl phosphonoacetamides, which can then be used in

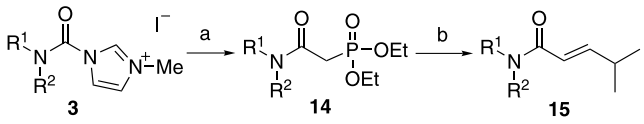
Table 9. Thioureas **13**[a] synthesized from thiocarbamoylimidazolium salts **12** and amines



3 **13**

Thiourea	Yield (%)[b]	Thiourea	Yield (%)[b]
 **13a**	Quant.	 **13e**	71
 **13b**	Quant.	 **13a**	45
 **13c**	94	 **13f**	21
 **13d**	84		

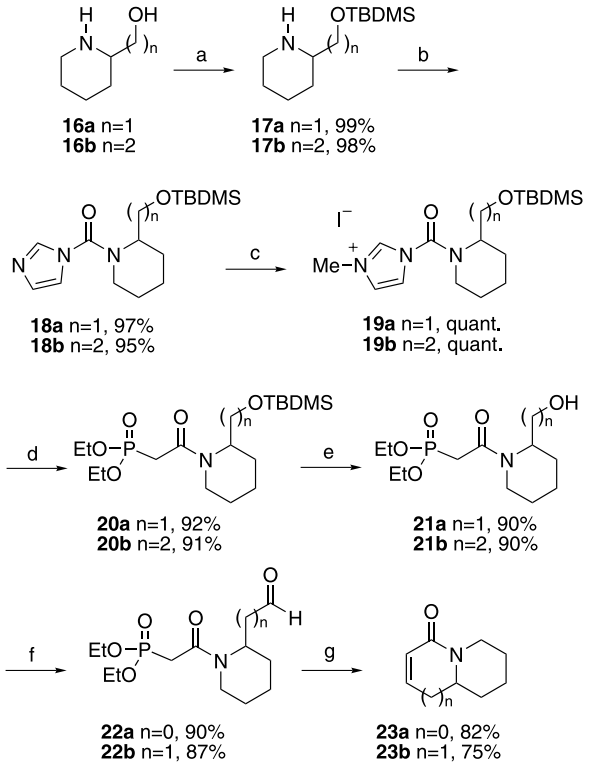
[a] Thiocarbamoylimidazolium salts **12** (1.0 equiv), secondary amines (1.2 equiv) and triethylamine (1.2 equiv) in CH_2Cl_2 were stirred at rt for 24 h.
[b] Isolated yields.



Scheme 2. (a) Diethyl phosphonoacetic acid, NEt_3, MeCN, reflux, 1 day; (b) isobutyraldehyde, LiCl, DBU, MeCN, rt, 16 h.

Wadsworth–Horner–Emmons reactions to form α,β-unsaturated amides or lactams. Reaction of the carbamoylimidazolium salts with diethyl phosphonoacetic acid in the presence of triethylamine results in the formation of diethyl phosphonoacetamides **14**, which can be used in either inter- or intramolecular Wadsworth–Horner–Emmons reactions with aldehydes and ketones (Scheme 2). For example, conversion of **3g** to the morpholine derived diethyl phosphonoacetamide **14**, followed by treatment with isobutyraldehyde yielded α,β-unsaturated amide **15** as the *E*-isomer.

A similar approach was used in a model synthesis of the fused bicyclic lactams **23a** and **23b** (Scheme 3). **23a** is an intermediate in the synthesis of indolizidines such as 2-epilentiginosine and lentiginosine,[29] while **23b** can be used in the synthesis of quinolizidine ring systems, and is an intermediate in the synthesis of leontiformine and leontiformidine.[30] The synthesis of **23a** and **23b** began with the protection of 2-piperidinemethanol or 2-piperidineethanol with TBDMSCl in 99 and 98% yield, respectively, without purification. The protected amines **17a** and **17b** were reacted with CDI in CH_2Cl_2 at rt to generate the carbamoylimidazoles in greater then 95% yield after column chromatography, which was necessary to remove some of the byproducts from the TBDMSCl protection step. **18a** and **18b** were then methylated with methyl iodide according to the standard procedure to generate the carbamoylimidazolium salts **19a** and **19b** in quantitative yields. The installation of the phosphonate moiety necessary for the Wadsworth–Horner–Emmons reaction was accomplished through the amide bond forming reaction between **19a** and **19b** and diethyl phosphonoacetic acid at 50 °C to give **20a** and **20b** in 92 and 91% yield, respectively.



Scheme 3. (a) TBDMSCl, pyr, CH_2Cl_2, rt, 4 h; (b) CDI, CH_2Cl_2, rt, 1 day; (c) MeI, MeCN, rt, 1 day; (d) Diethyl phosphonoacetic acid, NEt_3, MeCN, 50 °C, 1 day; (e) TBAF, THF, rt, 30 min; (f) *o*-$C_6H_4COOI(OAc)_2$ (i.e., Dess–Martin periodinane reagent), CH_2Cl_2, rt, overnight; (g) NaH, THF, 0 °C, 40 min.

The final fused bicycles were obtained through deprotection to the alcohols **21a** and **b** with TBAF, followed by oxidation with the Dess–Martin reagent to give aldehydes **22a** and **b**, which had to be chromatographed through a very short silica column to minimize decomposition. Oxidation using Swern conditions, TPAP/NMO, and PCC were less effective. The final cyclization was carried out with sodium hydride in THF at 0 °C to give the products **23a** and **23b** in 82 and 75% yield. Attempts to cyclize the aldehyde **22a** directly or with minimal amount of purification gave very low yields.

3. Conclusions

Carbamoylimidazolium salts behave as convenient *N*,*N*′-disubstituted carbamoyl transfer reagents, showing increased reactivity over carbamoylimidazoles as a result of the imidazolium effect. These compounds, as well as their thiocarbamoylimidazolium counterparts, are readily prepared by a simple two-step procedure from the corresponding secondary amines, and are obtained in excellent yield and purity following straightforward work-up procedures. The salts serve as useful 'building blocks' which can be utilized to generate a variety of functional groups, such as ureas, thioureas, carbamates, thiocarbamates, and amides, under mild reaction conditions. We are currently applying this methodology to the formation of combinatorial libraries.

4. Experimental

4.1. General

THF was distilled from sodium metal/benzophenone ketyl under nitrogen. CH_2Cl_2 and CH_3CN were distilled from CaH_2 under nitrogen. All other commercial reagents were used as received (Aldrich, Fischer Scientific Ltd or BDH). All glassware was flame-dried and allowed to cool under a stream of dry nitrogen. Melting points are uncorrected. ^1H and ^{13}C NMR were recorded at 400 and 100 MHz, respectively, on a Varian Unity 400 spectrometer and Gemini 200 MHz spectrometer. Proton chemical shifts were internally referenced to the residual proton resonance in $CDCl_3$ (δ 7.26) or CD_3OD (δ 3.31) or DMSO-d_6 (δ 2.50). Carbon chemical shifts were internally referenced to the deuterated solvent signals in $CDCl_3$ (δ 77.20) or CD_3OD (δ 49.00) or DMSO-d_6 (δ 39.50). Phosphorus chemical shifts were referenced to 85% phosphoric acid (external). FT-IR spectra were recorded on a Perkin-Elmer Spectrum 1000, with samples loaded as neat films on NaCl plates or as KBr

discs. Low-resolution mass spectra were recorded on a Bell and Howell 21-490 spectrometer, and high resolution spectra were recorded on an AEI MS3074 spectrometer. Specific optical rotation was determined on a Perkin-Elmer 243B Polarimeter under the conditions indicated using the sodium D line (589 nm). Analytical thin-layer chromatography (TLC) was performed on pre-coated silica gel plates, (Silicycle, Inc.), visualized with a UV254 lamp (Spectroline, Longlife Filter) and stained with 20% phosphomolybdic acid in ethanol or ninhydrin. Spectral data are provided for all new compounds and for compounds which lack full characterization in the literature.

4.2. General procedure for the preparation of carbamoylimidazoles 4a–4e

To a suspension of *N*,*N*′-carbonyldiimidazole (CDI, 60.0 mmol) in THF (100 mL) was added the amine (55.0 mmol). The mixture was refluxed for 16 h. Removal of solvent under vacuum gave a viscous oil, which was dissolved in CH_2Cl_2 (100 mL) and washed with water (2× 100 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo to yield the carbamoylimidazole **4a–e**.

4.2.1. 1-(1*H*-Imidazol-1-ylcarbonyl)-1,2,3,4-tetrahydroquinoline (3,4-dihydro-2*H*-quinolin-1-yl)-imidazol-1-ylmethanone (4a).[4a,c] Yellow solid; mp=71–73 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (1H, d, J=1.0 Hz), 7.18 (1H, m), 7.06 (1H, m), 6.98 (1H, m), 6.92 (1H, m), 6.89 (1H, m), 6.64 (1H, m), 3.86 (2H, t, J=6.5 Hz), 2.82 (2H, t, J=6.5 Hz), 2.07 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.0, 137.8, 137.5, 131.9, 129.6, 129.1, 127.1, 125.9, 123.2, 118.3, 45.9, 26.7, 24.1; IR (KBr pellet) 3122, 2958, 1691, 1578, 1492, 1396, 1215, 1100, 916 cm^{-1}; MS (EI) *m*/*z* (rel. intensity) 227 (46), 160 (94), 142 (13), 132 (100), 117 (11), 77 (17); HRMS (EI) *m*/*z* calcd (M^+) 227.1059, found 227.1051.

4.2.2. 2-(1*H*-Imidazol-1-ylcarbonyl)-1,2,3,4-tetrahydroisoquinoline (4b).[4c] Yellow solid; mp=82–83 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (1H, s), 7.26–7.08 (6H, m), 4.75 (2H, s), 3.82 (2H, t, J=6.0 Hz), 3.04 (2H, t, J=6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.8, 136.6, 133.4, 131.5, 129.5, 128.6, 127.0, 126.5, 126.0, 117.6, 48.1, 44.2, 28.3; IR (KBr pellet) 3098, 2898, 1681, 1428, 1240, 1162, 1104, 1077, 1052, 933 cm^{-1}; MS (EI) *m*/*z* (rel. intensity) 227 (69), 160 (100), 142 (49), 130 (10), 117 (36), 103 (14), 91 (12); HRMS (EI) *m*/*z* calcd (M^+) 227.1061, found 227.1059.

4.2.3. *N*-Methyl-*N*-phenyl-1*H*-imidazole-1-carboxamide (4c).[4c,31] Yellow solid; mp=62–63 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (1H, s), 7.38–7.29 (3H, m), 7.11–7.07 (2H, m), 6.81–6.76 (2H, m), 3.45 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.3, 142.0, 136.8, 129.3, 127.9, 127.1, 125.1, 117.7, 39.2; IR (KBr pellet) 3126, 2949, 1702, 1592, 1492, 1458, 1385, 1294, 1253, 1118, 1096, 1026, 983 cm^{-1}.

4.2.4. *N*-Benzyl-*N*-isopropyl-1*H*-imidazole-1-carboxamide (4d).[4c] Foamy yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (1H, s), 7.38 (2H, m), 7.31 (3H, m), 7.21 (1H, s), 7.04 (1H, s), 4.58, (2H, s), 4.16 (1H, m), 1.35 (3H, s), 1.34 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.9, 137.2, 136.9, 129.8, 129.1, 127.8, 126.8, 117.8, 51.7, 48.6, 20.6; IR (neat) 2975, 1690, 1414, 1217, 1069, 1020, 965, 754 cm^{-1}; MS (EI) *m*/*z* (rel. intensity) 243 (1), 176 (25), 92 (10), 91 (100), 85 (14), 83 (23), 68 (6), 65 (7), 51 (9); HRMS (EI) *m*/*z* Calcd (M^+) 243.1367, found 243.1372.

4.2.5. 1-(Pyrrolidin-1-ylcarbonyl)-1*H*-imidazole (4e).[32] White solid; mp 50–52 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (1H, s), 7.36 (1H, br s), 7.08 (1H, br s), 3.64–3.61 (4H, m), 2.00–1.97 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.8, 136.9, 129.6, 117.7, 48.9 (br), 25.7 (br); IR (KBr pellet) 2976, 1694, 1417, 1102, 843 cm^{-1}.

4.2.6. Benzyl 1-(1*H*-imidazol-1-ylcarbonyl)-L-prolinate (4f).[4a,c] To a solution of CDI (0.890 g, 5.50 mmol) in CH_2Cl_2 (15 mL) was added L-proline benzyl ester hydrochloride (1.21 g, 5.00 mmol) and triethylamine (0.700 mL, 5.00 mmol). The mixture was stirred for 48 h at rt, then washed with water (2×20 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered and the solvent was removed under vacuum to yield **4g** as colorless, viscous oil (1.44 g, 96%); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.02 (1H, s), 7.35 (6H, br s), 7.07 (1H, s), 5.20 (2H, m), 4.67 (1H, m), 3.76 (2H, m), 2.35 (1H, m), 2.06 (3H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.7, 149.4, 136.5, 135.1, 129.4, 128.3, 128.1, 127.8, 117.3, 66.8, 60.6, 49.5, 29.1, 24.6; IR (neat) 3583, 3469, 3122, 2980, 2957, 1746, 1682, 1417, 1171, 1100, 901 cm^{-1}; MS (EI) *m*/*z* (rel. intensity) 299 (1), 232 (12), 164 (12), 160 (6), 158 (11), 91 (100), 70 (21); HRMS (EI) *m*/*z* calcd (M^+) 299.1270, found 299.1255; $[\alpha]_D^{23}$ −61° (*c* 1.00, CH_2Cl_2).

4.3. General procedure for the preparation of carbamoylimidazoles with CH_2Cl_2 as solvent

To a cooled (cold water bath) solution of CDI (44.0 mmol) in CH_2Cl_2 (30 mL) was added the amine (40.0 mmol) dropwise. After the solids dissolved, giving a slightly yellowish clear solution, the water bath was removed, and the mixture stirred for a further 24 h. The reaction was diluted with CH_2Cl_2 (20 mL), and quenched with water (50 mL). The aqueous layer was extracted with CH_2Cl_2 (4× 50 mL), the combined organic layers dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo to yield carbamoylimidazoles **4g–4i**.

4.3.1. 4-(1*H*-Imidazol-1-ylcarbonyl)morpholine (4g).[4c,33] White solid; mp=83–84 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (1H, s), 7.17 (1H, m), 7.08 (1H, m), 3.73 (4H, m), 3.61 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.4, 136.4, 129.4, 117.5, 65.9, 46.3.

4.3.2. *N*-Methoxy-*N*-methyl-1*H*-imidazole-1-carboxamide (4h).[4d] Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (1H, s), 7.55 (1H, m), 7.03 (1H, m), 3.66 (3H, s), 3.37 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.6, 137.1, 128.6, 118.0, 60.6, 33.8; IR (neat) 3121, 2938, 1690, 1421, 1227, 1061, 965, 735 cm^{-1}; MS (EI) *m*/*z* (rel. intensity) 155 (100), 125 (34), 95 (38), 88 (55), 68 (63); HRMS (EI) *m*/*z* Calcd (M^+) 155.0695, found 155.0700.

4.3.3. 8-(1*H*-Imidazol-1-ylcarbonyl)-1,4-dioxa-8-azaspiro[4.5]decane (4i).[4c] White solid; mp=121–123 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (1H, s), 7.16 (1H, m), 7.06 (1H, m), 3.96 (4H, s), 3.65 (4H, m), 1.75 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.6, 136.7, 129.5, 117.8, 106.1, 64.4, 44.5, 34.9; IR (KBr pellet) 3112, 2869, 2855, 1700, 1464, 1427, 1361, 1243, 1098, 1026, 913 cm^{-1}; MS (EI) *m/z* (relative intensity) 237 (22), 170 (100), 142 (82), 99 (37), 98 (27), 70 (19); HRMS (EI) *m/z* Calcd (M^+) 237.1113, found 237.1111.

4.4. General procedure for the preparation of carbamoylimidazolium salts 3

To a solution of carbamoylimidazole **4** (8.00 mmol) in acetonitrile (15 mL) was added methyl iodide (32.0 mmol). The mixture was stirred at rt for 24 h. The solvent was removed under vacuum to yield the carbamoylimidazolium salt **3a–i**.

4.4.1. 1-(3,4-Dihydroquinolin-1(2*H*)-ylcarbonyl)-3-methyl-1*H*-imidazol-3-ium iodide (3a).[4a,c] Yellow solid; mp 97–99 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.90 (1H, s), 7.61 (1H, s), 7.25–7.22 (2H, m), 7.15 (1H, m), 7.08 (1H, m), 6.95 (1H, d, J=8.0 Hz), 4.12 (3H, s), 3.93 (2H, t, J=6.5 Hz), 2.93 (2H, t, J=6.5 Hz), 2.11 (2H, m); ^{13}C NMR (50 MHz, DMSO-d_6) δ 146.4, 138.3, 135.9, 132.2, 129.0, 126.3, 125.9, 123.3, 123.2, 121.2, 46.7, 36.4, 25.7, 22.9; IR (KBr pellet) 3438, 3074, 2937, 1722, 1583, 1535, 1493, 1459, 1356, 1014, 749 cm^{-1}; MS (FAB) *m/z* (relative intensity) 242 (100), 160 (40), 154 (83), 138 (29), 137 (52), 136 (61), 132 (14), 120 (12), 107 (23), 91 (12); HRMS (FAB) *m/z* Calcd (M^+-127) 242.1293, found 242.1296.

4.4.2. 1-(3,4-Dihydroisoquinolin-2(1*H*)-ylcarbonyl)-3-methyl-1*H*-imidazol-3-ium iodide (3b).[4c] Yellow solid; mp=166–168 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.63 (1H, br s), 8.09 (1H, br s), 7.89 (1H, br s), 7.22 (4H, br s), 4.75 (2H, br s), 3.94 (3H, m), 3.72 (2H, br s), 2.96 (2H, br s); ^{13}C NMR (100 MHz, DMSO-d_6) δ 146.8, 137.3, 133.9, 131.5, 128.1, 126.7, 126.4, 126.1, 123.5, 120.8, 47.5 (br), 44.2, 36.5, 27.6; IR (KBr pellet) 3144, 3078, 2968, 1711, 1408, 1354, 1150, 1132, 978 cm^{-1}; MS (FAB) *m/z* (relative intensity) 242 (100), 190 (3), 144 (5), 117 (5), 160 (39); HRMS (FAB) *m/z* calcd (M^+-127) 242.1293, found 242.1284.

4.4.3. 3-Methyl-1-{[methyl(phenyl)amino]carbonyl}-1*H*-imidazol-3-ium iodide (3c).[4a,c] Yellow solid, mp 95–98 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.71 (1H, s), 7.55 (1H, br s), 7.37–7.31 (5H, m), 7.01 (1H, br s), 4.02 (3H, s), 3.45 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.0, 139.7, 137.2, 129.8, 128.3, 125.7, 122.8, 120.2, 40.3, 37.1; IR (KBr pellet) 3457, 3076, 1732, 1594, 1494, 1372, 1271, 1152, 983, 920 cm^{-1}; MS (FAB) *m/z* (rel. intensity) 217 (20), 216 (100), 154 (14), 136 (11), 107 (6), 93 (7); HRMS (FAB) *m/z* calcd (M^+-127) 216.1137, found 216.1130.

4.4.4. 1-{[Benzyl(isopropyl)amino]carbonyl}-3-methyl-1*H*-imidazol-3-ium iodide (3d).[4c] Yellow foam; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.58 (1H, m), 7.31–7.07 (7H, m), 4.88 (2H, s), 4.44 (1H, m), 4.14 (3H, s), 1.45 (3H, s), 1.43 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.3, 136.8, 136.0, 129.3, 128.2, 126.8, 123.7, 120.4, 52.7, 49.2, 37.9, 20.6; IR (neat) 3063, 1723, 1536, 1414, 1342, 1171, 1138, 748, 617 cm^{-1}; MS (FAB) *m/z* (relative intensity) 259 (9), 258 (50), 180 (5), 176 (21), 173 (17), 132 (6), 92 (9), 91 (100), 83 (14); HRMS (FAB) *m/z* Calcd (M^+-127) 258.1621, found 258.1620.

4.4.5. 3-Methyl-1-(pyrrolidin-1-ylcarbonyl)-1*H*-imidazol-3-ium iodide (3e). White solid; mp=102–105 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.40 (1H, s), 7.83 (1H, m), 7.55 (1H, m), 4.31 (3H, s), 2.07 (4H, br m), 2.05 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.0, 136.8, 123.8, 121.2, 51.0 (br), 49.6 (br), 38.3, 26.6 (br), 34.4 (br); IR (KBr pellet) 3446, 3078, 1716, 1404, 1257, 1136, 827; MS (FAB) *m/z* (relative intensity) 180 (100), 98 (81), 83 (15); HRMS (FAB) *m/z* Calcd (M^+-127) 180.1137, found 180.1139.

4.4.6. Benzyl 1-[(3-methyl-1*H*-imidazol-3-ium-1-yl)carbonyl]-L-prolinate iodide (3f).[4a,c] Foamy yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 10.30 (1H, s), 7.78–7.32 (7H, m), 5.18 (2H, br s), 4.70 (1H, br s), 4.24 (3H, br s), 4.12–3.93 (2H, m), 2.49 (1H, br s), 2.12 (3H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 169.8, 145.1, 136.2, 134.7, 128.3, 128.1, 127.7, 123.9, 120.4, 68.0, 61.5, 51.4, 37.7, 29.9, 25.4; IR (neat) 3448, 3069, 1728, 1584, 1537, 1407, 1175, 1094 cm^{-1}; MS (FAB) (rel. intensity) 314 (100), 173 (66), 154 (11), 136 (10), 107 (6), 91 (69); HRMS (FAB) *m/z* calcd (M^+-127) 314.1505, found 134.1499; $[\alpha]_D^{23}$ −44° (*c* 1.01, CH_2Cl_2).

4.4.7. 3-Methyl-1-(morpholin-4-ylcarbonyl)-1*H*-imidazol-3-ium iodide (3g).[4c] White solid; mp=165–166 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.61 (s, 1H), 8.04 (s, 1H), 7.87 (s, 1H), 3.91 (s, 3H), 3.66 (s, 4H), 3.52 (s, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 146.5, 137.4, 123.5, 120.9, 65.3, 46.2, 36.5; IR (KBr pellet) 3115, 2862, 1718, 1437, 1244, 1145, 1117, 996; MS (FAB) *m/z* (relative intensity) 196 (100), 185 (14), 175 (5), 115 (10), 114 (50), 111 (5); HRMS (FAB) *m/z* calcd (M^+-127) 196.1086, found 196.1103.

4.4.8. 1-{[Methoxy(methyl)amino]carbonyl}-3-methyl-1*H*-imidazol-3-ium iodide (3h).[4d] White solid; mp=115–117 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.11 (1H, s), 7.88 (1H, m), 7.77 (1H, m), 4.30 (3H, s), 3.94 (3H, s), 3.43 (3H, s); ^{13}C NMR (100 MHz, DMSO-d_6) 144.6, 138.1, 123.9, 121.4, 63.6, 38.6, 35.1; IR (KBr pellet) 3063, 1714, 1459, 1385, 1160, 1085, 954, 739, 725 cm^{-1}; MS (ESI) *m/z* (rel. intensity) 170 (100), 139 (10); HRMS (ESI) *m/z* calcd (M^+-127) 170.0924, found 170.0916.

4.4.9. 1-(1,4-Dioxa-8-azaspiro[4.5]dec-8-ylcarbonyl)-3-methyl-1*H*-imidazol-3-ium iodide (3i).[4c] White solid; mp 169–172 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.58 (s, 1H), 8.03 (m, 1H), 7.87 (m, 1H), 3.91 (m, 7H), 3.54 (s, 4H), 1.76 (s, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 146.5, 137.4, 123.5, 120.9, 105.6, 63.9, 44.4 (br), 36.5, 33.8; IR (KBr pellet) 3078, 2886, 1735, 1573, 1534, 1419, 1369, 1218, 1138, 1092, 1027 cm^{-1}; MS (FAB) *m/z* (relative intensity) 252 (100), 185 (63), 170 (83), 142 (75), 126 (10); HRMS (FAB) *m/z* Calcd (M^+-127) 252.1348, found 252.1355.

4.5. Kinetics of hydroxide promoted hydrolysis of 3 and 4

Stock solutions of **3** and **4** (0.02 M in MeCN) were prepared, then sealed with rubber septa and placed in a freezer. Buffer

solutions were made using HCl (pH 2.0–3.11), EPPS (pH 7.9–8.7), CHES (pH 9.2–9.8), CAPS (pH 10.29–11.10) and NaOH (pH 11.98). Concentrations of 0.010, 0.020, and 0.030 M were used for CAPS, CHES and EPPS, and in all cases the ionic strength of the solutions was held at 0.10 by the addition of KCl.

The second order rate constants for the hydroxide promoted hydrolysis of carbamoylimidazoles and carbamoylimidazolium salts were measured at 25 °C by observing the rate of change in absorbance at 230 nm (Table 2, Entries 1 and 2), 225 nm (Table 2, Entries 3 and 5), 235 nm (Table 2, Entries 4 and 6), 270 nm (Table 2, Entry 7) and 265 nm (Table 2, Entry 8), using an OLIS modified Cary-17 UV/visible spectrophotometer. Reactions were initiated by injecting 10 μL of the substrate solution into 2.5 mL of the buffer solution, which had been thermally equilibrated in the instrument cell holder for 10 min. Absorbance versus time profiles were fit by NLLSQ methods using Prism software to give pseudo-first order rate constants. Second order rate constants were determined by dividing the pseudo-first order rate constant by the concentration of hydroxide and are given in Table 2.

4.6. General procedure for the preparation of tri- or tetrasubstituted ureas 5

To a solution of carbamoylimidazolium salt **3** (1.00 mmol) in CH_2Cl_2 (10 mL) was added the primary or secondary amine (1.00 mmol) and triethylamine (1.00 mmol). The mixture was stirred at rt for 24 h, then washed with 1.0 N HCl (2×5 mL) and brine (5 mL), the organic layer was dried ($MgSO_4$), filtered and concentrated in vacuo to yield urea **5a–l**.

4.6.1. *N*-Methyl-*N*-phenyl-3,4-dihydroisoquinoline-2(1*H*)-carboxamide (5a).[4a] Clear oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–6.91 (9H, m), 4.41 (2H, s), 3.57 (2H, t, J=6.0 Hz), 3.51 (3H, s), 2.71 (2H, t, J=6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.9, 146.6, 134.5, 133.5, 129.3, 128.4, 126.1, 126.0, 125.8, 124.4, 123.8, 47.6, 43.5, 39.5, 28.2; IR (neat) 2928, 1594, 1493, 1440, 1403, 1259, 1113, 928 cm^{-1}; MS (EI) *m*/*z* (rel. intensity) 266 (95), 235 (11), 208 (62), 189 (13), 160 (100), 142 (69), 132 (56), 117 (55), 107 (73), 91 (23); HRMS (EI) *m*/*z* calcd (M^+) 266.1419, found 26.1426.

4.6.2. Methyl 1-(3,4-dihydroquinolin-1(2*H*)-ylcarbonyl)-L-prolinate (5b).[4a,c] Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (1H, m), 7.10 (2H, m), 6.90 (1H, m), 4.56 (1H, t, J=7.5 Hz), 3.81–3.69 (4H, m), 3.42–3.36 (1H, m), 3.12–3.02 (2H, m), 2.75–2.62 (2H, m), 2.24 (1H, m), 2.00 (1H, m), 1.88–1.74 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 158.3, 140.1, 129.2, 128.3, 126.4, 122.1, 120.8, 59.8, 51.9, 48.9, 44.8, 29.5, 26.8, 25.1, 23.8; IR (neat) 2951, 2880, 1745, 1640, 1579, 1495, 1403, 1174, 1026 cm^{-1}; MS (EI) *m*/*z* (rel. intensity) 288 (49), 229 (23), 160 (37), 128 (100); HRMS (EI) *m*/*z* calcd (M^+) 288.1474, found 288.1474; $[\alpha]_D^{23}$ +125.2° (*c* 1.02, CH_2Cl_2).

4.6.3. *N*-Methoxy-*N*-methyl-3,4-dihydroquinoline-1(2*H*)-carboxamide (5c). Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25–7.23 (1H, m), 7.09–7.05 (2H, m), 6.94–6.90 (1H, m), 3.66 (2H, t, J=6.0 Hz), 3.47 (3H, s), 3.01 (3H, s), 2.73 (2H, t, J=6.5 Hz), 1.96–1.90 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.7, 139.6, 128.9, 128.5, 125.8, 122.9, 121.9, 59.5, 45.6, 35.8, 26.6, 23.6; IR (neat) 2932, 1663, 1493, 1374, 965 cm^{-1}; MS (EI) *m*/*z* (rel. intensity) 220 (42), 160 (91), 142 (16), 132 (100), 117 (19), 77 (19); HRMS (EI) *m*/*z* calcd (M^+) 220.1212, found 220.1220.

4.6.4. 1-[(4-Benzylpiperazin-1-yl)carbonyl]-1,2,3,4-tetrahydroquinoline (5d).[4a,c] White solid; mp 171–173 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.55–6.90 (9H, m), 4.02 (2H, br s), 3.67–3.57 (6H, m), 2.88–2.70 (6H, m), 2.01–1.88 (2H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 159.1, 139.6, 130.7, 129.6, 129.2, 128.9, 128.7, 128.3, 126.4, 122.7, 119.9, 60.7, 50.9, 45.2, 42.9, 26.5, 23.3; IR (KBr pellet) 2940, 1640, 1578, 1492, 1300, 1260, 1202, 1176 cm^{-1}; MS (EI) *m*/*z* (rel. intensity) 335 (15), 203 (26), 160 (22), 146 (24), 132 (37), 91 (100); HRMS (EI) *m*/*z* calcd (M^+) 335.1998, found 335.1990.

4.6.5. Benzyl 1-[(4-benzylpiperazin-1-yl)carbonyl]-L-prolinate (5e).[4a] Yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.66–7.29 (10H, m), 5.30–5.02 (2H, m), 4.69–4.57 (1H, m), 4.11–3.68 (6H, m), 3.46–3.21 (4H, m), 2.95–2.30 (3H, m) 2.00–1.78 (3H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.4, 160.8, 135.5, 131.3, 130.0, 129.1, 128.5, 128.3, 128.2, 127.9, 66.6, 61.0, 59.8, 50.4, 49.6, 42.5, 29.2, 25.5; IR (neat) 2950, 2451, 1741, 1634, 1418, 1276, 1174, 1081, 1031, 957, 922, 734, 700, 644 cm^{-1}; MS (EI) *m*/*z* (relative intensity) 407 (25), 275 (15), 203 (16), 159 (26), 146 (35), 134 (34), 132 (39), 120 (12), 108 (16), 91 (100); HRMS (EI) *m*/*z* calcd (M^+) 407.2209, found 407.2199; $[\alpha]_D^{23}$ −24.0° (*c* 1.01, CH_2Cl_2).

4.6.6. Benzyl 1-{[(2*S*)-2-(methoxycarbonyl)pyrrolidin-1-yl]carbonyl}-L-prolinate (5f). Yellow oil; ^{1}H NMR (200 MHz, MeOH-d_4) δ 7.34–7.23 (5H, m), 5.21–5.04 (2H, m), 4.83–4.37 (3H, m), 3.69 (3H, m), 3.58–3.53 (3H, m), 2.29–2.18 (2H, m), 1.98–1.71 (6H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 173.3, 172.6, 158.4, 136.2, 128.5, 127.7, 126.5, 65.6, 63.0, 60.1, 60.0, 51.6, 48.2, 28.9, 28.9, 24.9; IR (neat) 2953, 2880, 1740, 1616, 1438, 1343, 1279, 1173, 1096, 1042, 1004, 914, 752, 699 cm^{-1}; MS (EI) *m*/*z* (relative intensity) 360 (5), 301 (20), 225 (77), 160 (30), 156 (35), 142 (15), 128 (100), 108 (41), 91 (76); HRMS (EI) *m*/*z* calcd (M^+) 360.1685, found 360.1682; $[\alpha]_D^{23}$ −25.8° (*c* 1.00, MeOH).

4.6.7. Benzyl 1-{[3-(hydroxymethyl)piperidin-1-yl]carbonyl}-L-prolinate (5g). Yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$) (rotamers) δ 7.35–7.28 (5H, m), 5.24–5.06 (2H, m), 4.71–4.59 (2H, m), 3.61–3.05 (8H, m), 2.30 (1H, m), 2.08–1.25 (8H, m); ^{13}C NMR (50 MHz, DMSO-d_6) (rotamers) δ 172.5, 172.5, 161.2, 142.4, 136.1, 128.3, 127.9, 127.5, 126.5, 126.3, 65.4, 63.6, 63.6, 62.8, 59.9, 59.8, 49.5, 49.2, 49.2, 49.1, 46.5, 46.2, 38.5, 38.2, 29.0, 27.0, 24.9, 24.8, 24.4, 24.1; IR (neat) 3406, 2931, 2820, 1735, 1615, 1435, 1353, 1303, 1169, 1082, 1028, 748, 699 cm^{-1}; MS (EI) *m*/*z* (rel. intensity) 347 (6), 212 (88), 204 (7), 142 (100), 114 (33), 98 (17), 91 (57), 81 (18), 70 (92); HRMS (EI) *m*/*z* Calcd (M^+) 346.1893, found 346.1904.

4.6.8. *N*-Methoxy-*N*-methyl-1,4-dioxa-8-azaspiro[4.5] decane-8-carboxamide (5h). Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.87 (4H, s), 3.47 (3H, s), 3.43 (4H, t, J=6.0 Hz), 2.84 (3H, s), 1.60 (4H, t, J=6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.6, 106.9, 64.2, 58.5, 43.4, 36.3, 34.9; IR (neat) 2959, 1648, 1473, 1437, 1260, 1099 cm^{-1}; MS (EI) *m/z* (rel. intensity) 230 (9), 170 (100), 142 (98), 99 (29); HRMS (EI) *m/z* calcd (M^+) 230.1267, found 230.1255.

4.6.9. *N*-Allyl-3,4-dihydroquinoline-1(2*H*)-carboxamide (5i).[4a,4c,34] White solid; mp=55–57 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.12 (4H, m), 5.84 (1H, m), 5.18 (2H, m), 3.92 (2H, d, J=5.0 Hz), 3.81 (2H, t, J=6.0 Hz), 2.73 (2H, t, J=6.5 Hz), 2.01–1.88 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.6, 139.4, 135.4, 132.5, 129.7, 126.7, 124.4, 123.4, 115.9, 43.6, 43.5, 27.2, 24.0; IR (neat) 3325, 2947, 1654, 1512, 1321, 1202, 912 cm^{-1}.

4.6.10. Ethyl *N*-(3,4-dihydroquinolin-1(2*H*)-ylcarbonyl) glycinate (5j). White solid; mp=49–50 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (1H, m), 7.26–7.14 (2H, m), 7.06 (1H, m), 5.67 (1H, br m), 4.20 (2H, q, J=7.0 Hz), 4.05 (2H, d, J=5.5 Hz), 3.78 (2H, t, J=6.0 Hz), 2.77 (2H, t, J=6.5 Hz), 1.94 (2H, m), 1.29 (3H, t, J=7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 156.5, 139.1, 132.6, 129.7, 126.9, 124.7, 123.4, 61.5, 43.7, 42.9, 27.2, 24.1, 14.4; IR (KBr pellet) 3385, 2983, 1751, 1643, 1507, 1395, 1195, 1034 cm^{-1}; MS (EI) *m/z* (relative intensity) 262 (84), 217 (8), 189 (10), 160 (18), 133 (100), 118 (17), 103 (5); HRMS (EI) *m/z* calcd (M^+) 262.1317, found 262.1328.

4.6.11. *N*-[2-(3,4-Dimethoxyphenyl)ethyl]-1,4-dioxa-8-azaspiro[4.5]decane-8-carboxamide (5k).[4c,35] Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (1H, m), 6.63 (2H, m), 4.76 (1H, t, J=5.5 Hz), 3.86 (4H, s), 3.76 (6H, s), 3.33 (6H, m), 2.67 (2H, t, J=7.0 Hz), 1.55 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.0, 148.4, 147.0, 131.6, 120.3, 111.6, 110.9, 106.6, 63.9, 55.4, 55.3, 42.0, 41.6, 35.6, 34.3; IR (neat) 3334, 2960, 1614, 1515, 1232, 1142, 1030 cm^{-1}.

4.7. General procedure for the preparation of tri- or tetrasubstituted ureas 6

To a solution of amine (1.00 mmol) in THF (6 mL) was added *n*-BuLi (1.50 mmol), and the reaction was stirred for 1 h. Then the carbamoylimidazolium salt **3** (1.20 mmol) was added. The mixture was stirred at rt for 18 h, then diluted with CH_2Cl_2 (20 mL) and washed with 0.2 N HCl (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3×25 mL). The combined organic layers were washed with 0.2 N HCl (2×20 mL) and brine (15 mL), the organic layer dried ($MgSO_4$), filtered and concentrated in vacuo. The products were obtained following column chromatography.

4.7.1. *N*-Methyl-*N*-phenylpyrrolidine-1-carboxamide (6a). Peach solid; mp=64–66 °C; R_f=0.5 (100% EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31–7.26 (2H, m), 7.10–7.07 (3H, m), 3.21 (3H, s), 3.04 (4H, t, J=6.5 Hz), 1.69–1.64 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.7, 146.4, 129.3, 125.0, 124.6, 48.1, 39.9, 25.7; IR (KBr pellet) 2972, 2875, 1638, 1594, 1499, 1431, 1383, 1248, 1106, 764, 703 cm^{-1}; MS (EI) *m/z* (rel. intensity) 204 (100), 173 (17), 106 (27), 98 (86), 55 (54); HRMS (EI) *m/z* Calcd (M^+) 204.1263, found 204.1258.

4.7.2. *N*-Methyl-*N*-phenyl-1,4-dioxa-8-azaspiro[4.5] decane-8-carboxamide (6c). Yellow oil; R_f=0.55 (1:9 Hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30–7.25 (2H, m), 7.07–7.04 (3H, m), 3.85 (4H, s), 3.25 (4H, t, J=6.0 Hz), 3.17 (3H, s), 1.45 (4H, t, J=6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.1, 147.2, 129.7, 124.7, 123.9, 107.3, 64.5, 43.9, 39.8, 34.7; IR (KBr pellet) 2960, 2880, 1648, 1595, 1496, 1432, 1254, 1109, 1033, 945, 761 cm^{-1}; MS (EI) *m/z* (rel. intensity) 276 (73), 170 (65), 142 (100), 106 (32), 77 (37); HRMS (EI) *m/z* calcd (M^+) 276.1474, found 276.1471.

4.7.3. *N*-Methoxy-*N*,*N*′-dimethyl-*N*′-phenylurea (6d). Yellow oil; R_f=0.5 (6:4 Hexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35–7.28 (2H, m), 7.16–7.12 (3H, m), 3.19 (3H, s), 2.90 (3H, s), 2.82 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.7, 145.8, 129.0, 126.0, 126.0, 58.0, 40.3, 34.0; IR (KBr pellet) 2934, 1669, 1596, 1497, 1465, 1371, 1122, 1054, 764, 697 cm^{-1}; MS (EI) *m/z* (relative intensity) 194 (25), 163 (27), 134 (100), 106 (59), 77 (31); HRMS (EI) *m/z* calcd (M^+) 194.1058, found 194.1058.

4.7.4. 1-(1,4-Dioxa-8-azaspiro[4.5]dec-8-ylcarbonyl)-1,2,3,4-tetrahydroquinoline (6e). Yellow oil; R_f=0.45 (1:9 Hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01–6.92 (3H, m), 6.80 (1H, t, J=7.0 Hz), 3.84 (4H, s), 3.50 (2H, t, J=6.0 Hz), 3.31 (4H, t, J=6.0 Hz), 2.67 (2H, t, J=6.5 Hz), 1.90–1.83 (2H, m), 1.58 (4H, t, J=5.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.8, 140.8, 129.0, 127.4, 126.3, 121.8, 119.5, 106.9, 64.2, 45.5, 43.7, 34.7, 26.9, 23.4; IR (KBr pellet) 2955, 2880, 1649, 1493, 1417, 1246, 1096, 946, 754 cm^{-1}; MS (EI) *m/z* (rel. intensity) 302 (95), 170 (81), 142 (100), 132 (42), 98 (26); HRMS (EI) *m/z* calcd (M^+) 302.1630, found 302.1632.

4.7.5. *N*-Phenyl-1,4-dioxa-8-azaspiro[4.5]decane-8-carboxamide (6f). White solid; mp=138–139 °C; R_f=0.3 (4:6 Hexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33–7.18 (4H, m), 7.00–6.92 (2H, m), 3.94 (4H, s), 3.53 (4H, t, J=5.5 Hz), 1.67 (4H, t, J=5.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.9, 139.2, 128.6, 122.8, 120.2, 106.9, 64.5, 42.6, 35.1; IR (KBr pellet) 3319, 2958, 1638, 1535, 1445, 1240, 1111, 945, 753 cm^{-1}; MS (EI) *m/z* (rel. intensity) 262 (77), 217 (15), 170 (54), 142 (100), 119 (16); HRMS (EI) *m/z* calcd (M^+) 262.1317, found 262.1314.

4.7.6. *N*-(4-Chlorophenyl)-1,4-dioxa-8-azaspiro[4.5] decane-8-carboxamide (6g). Peach solid; mp=199–201 °C; R_f=0.35 (4:6 Hexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29–7.19 (4H, m), 6.56 (1H, s), 3.98 (4H, s), 3.56 (4H, t, J=6.0 Hz), 1.74 (4H, t, J=6.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.4, 137.7, 128.8, 128.0, 121.2, 106.9, 64.7, 42.9, 35.2; IR (KBr pellet) 3341, 1639, 1534, 1494, 1240, 1116, 1089, 946 cm^{-1}; MS (EI) *m/z* (relative intensity) 296 (59), 251 (9), 170 (73), 153 (23), 142 (100), 98 (28); HRMS (EI) *m/z* calcd (M^+) 296.0928, found 296.0921.

4.7.7. *N*-(4-Methoxyphenyl)-1,4-dioxa-8-azaspiro[4.5] decane-8-carboxamide (6h). Beige solid; mp=154–156 °C;

R_f=0.2 (1:1 Hexane/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17 (2H, d, J=9.0 Hz), 6.75 (2H, d, J=9.0 Hz), 6.72 (1H, s), 3.93 (4H, s), 3.72 (3H, s), 3.45 (4H, t, J=5.5 Hz), 1.65 (4H, t, J=5.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.6, 155.3, 132.1, 122.6, 113.9, 107.0, 64.5, 55.6, 42.6, 35.1; IR (KBr pellet) 3318, 2958, 1634, 1513, 1421, 1235, 1109, 1034, 946, 822 cm^{-1}; MS (EI) *m/z* (rel. intensity) 292 (100), 247 (13), 170 (33), 149 (68), 142 (98), 98 (30); HRMS (EI) *m/z* calcd (M^+) 292.1423, found 292.1422.

4.8. General procedure for the preparation of carbamate 7 from phenols

To a solution of carbamoylimidazolium salt **3** (1.00 mmol) in acetonitrile (6 mL) was added the phenol (1.00 mmol) and triethylamine (1.00 mmol). The reaction was refluxed overnight. The solvent was removed under vacuum and the residue was dissolved in CH_2Cl_2 (15 mL) and 0.1 M HCl (15 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3×15 mL). The combined organic layers were washed with water (20 mL) and brine (20 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated in vacuo to yield carbamate **7a–f**.

4.8.1. 2-Naphthyl morpholine-4-carboxylate (7a).[4b] Clear oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85–7.78 (3H, m), 7.58 (1H, m), 7.49–7.42 (2H, m), 7.29–7.26 (1H, m), 3.77–3.74 (4H, m), 3.71 (2H, br s), 3.59 (2H, br s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.5, 148.6, 133.5, 131.0, 129.0, 127.5, 127.3, 126.2, 125.3, 121.2, 118.2, 66.3, 66.2, 44.6, 43.9; IR (KBr pellet) 2956, 2853, 1722, 1418, 1230, 1161, 1115, 1063 cm^{-1}; MS (EI) *m/z* (relative intensity) 257 (71), 144 (11), 127 (14), 114 (100), 70 (51); HRMS (EI) *m/z* Calcd (M^+) 257.1052, found 257.1045.

4.8.2. 2-Bromophenyl morpholine-4-carboxylate (7b).[4b] ^{1}H White solid, mp 62–63 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57–7.05 (4H, m), 3.74 (6H, m), 3.56 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.4, 148.4, 133.0, 128.3, 126.9, 124.0, 116.3, 66.5, 45.0, 44.2; IR (KBr pellet) 2917, 1715, 1214, 763 cm^{-1}; MS (EI) *m/z* (relative intensity) 206 (89), 156 (8), 114 (100), 70 (59); HRMS (EI) *m/z* calcd (M^+) 286.0079, found 286.0083.

4.8.3. 2-Bromophenyl 1,4-dioxa-8-azaspiro[4.5]decane-8-carboxylate (7c).[4b] Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54–7.52 (1H, m), 7.29–7.02 (3H, m), 3.94 (4H, s), 3.78–3.63 (4H, m), 1.79–1.74 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.2, 148.4, 132.8, 128.2, 126.6, 124.0, 116.3, 106.5, 64.2, 42.7, 42.4, 35.0, 34.5; IR (neat) 2960, 1732, 1423, 1214, 1104, 945, 750 cm^{-1}; MS (EI) (rel. intensity) 341 (5), 262 (15), 170 (77), 142 (100), 99 (38); HRMS (EI) *m/z* calcd (M^+) 341.0263, found 341.0270.

4.8.4. Pyridin-3-yl 1,4-dioxa-8-azaspiro[4.5]decane-8-carboxylate (7d).[4b] White solid; mp=102–103 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36–8.33 (2H, m), 7.47–7.44 (1H, m), 7.27–7.23 (1H, m), 3.87 (4H, s), 3.83–3.52 (4H, m), 1.87–1.28 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.3, 147.6, 145.8, 143.2, 128.9, 123.3, 106.1, 64.1, 42.3, 42.1, 34.6, 34.2; IR (KBr pellet) 2892, 1723, 1219, 1108, 958 cm^{-1}; MS (EI) *m/z* (rel. intensity) 264 (3), 170 (100), 142 (76), 99 (25), 70 (14); HRMS (EI) *m/z* calcd (M^+) 264.1110, found 264.1110.

4.8.5. Phenyl methyl(phenyl)carbamate (7e).[4b,36] White solid; mp=56–58 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70–7.20 (10H, m), 3.48 (3H. s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.1, 151.5, 143.1, 129.4, 129.2, 126.7, 126.0, 125.5, 121.8, 38.3; IR (KBr pellet) 1735, 1600, 1560, 1260, 1239, 1233 cm^{-1}.

4.8.6. 3-Nitrophenyl 3,4-dihydroquinoline-1(2*H*)-carboxylate (7f).[4b] Yellow solid; mp=78–80 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08–8.04 (2H, m), 7.74 (1H, br s), 7.55–7.51 (2H, m), 7.24–7.06 (3H, m), 3.93 (2H, m), 2.85 (2H, t, J=6.5 Hz), 2.05 (2H, t, J=6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.1, 151.3, 148.5, 137.1, 130.5, 129.7, 128.6, 128.1, 126.0, 124.4, 123.7, 120.2, 117.3, 45.3, 27.0, 23.3; IR (KBr pellet) 2949, 1725, 1493, 1349, 1117, 991 cm^{-1}; MS (EI) *m/z* (rel. intensity) 298 (41), 160 (100), 142 (13), 132 (78), 117 (10), 77 (10); HRMS (EI) *m/z* calcd (M^+) 298.0954, found 298.0944.

4.9. General procedure for the preparation of carbamate 8 from alcohols

To a solution of carbamoylimidazolium salt **3** (2.00 mmol) and alcohol (2.00 mmol) in THF/DMF (2:1, 12 mL) was added portionwise NaH (2.20 mmol, 80% in mineral oil). The solution was stirred at rt for 1 day. H_2O (10 mL) and Et_2O (20 mL) were added, and the organic layer was washed with H_2O (2×10 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated in vacuo. The oil was purified by flash column chromatography (CH_2Cl_2) to yield carbamate **8e–f**.

4.9.1. 3-Methylbut-2-en-1-yl 1,4-dioxa-8-azaspiro[4.5]decane-8-carboxylate (8a).[4b] Yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.30–5.27 (1H, m), 4.52 (2H, d, J=7.0 Hz), 3.90 (4H, s), 3.49–3.47 (4H, m), 1.69 (3H, s), 1.64 (3H, s), 1.61–1.58 (4H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 155.3, 137.9, 119.4, 106.9, 64.3, 62.2, 41.8, 34.7, 25.6, 17.9; IR (neat) 2961, 2879, 1694, 1428, 1231, 1112 cm^{-1}; MS (EI) *m/z* (rel. intensity) 255 (37), 196 (16), 186 (3), 170 (19), 142 (27), 99 (41); HRMS (EI) *m/z* calcd (M^+) 255.1471, found 255.1468.

4.9.2. 2,2,2-Trifluoroethyl 1,4-dioxa-8-azaspiro[4.5]decane-8-carboxylate (8b).[4b] Yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.42 (2H, q, J=8.5 Hz), 3.91 (4H, s), 3.53–3.52 (4H, m), 1.64–1.63 (4H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 153.1, 123.1 (q, J=277.5 Hz), 106.5, 64.3, 61.3 (q, J=54.0 Hz), 42.4, 42.1, 34.8, 34.5; IR (neat) 2966, 1714, 1474, 1232, 1166, 962 cm^{-1}; MS (EI) *m/z* (rel. intensity) 269 (74), 210 (19), 186 (100), 170 (23), 99 (65); HRMS (EI) *m/z* calcd (M^+) 269.0875, found 269.0873.

4.9.3. 3-Methylbut-2-en-1-yl 3,4-dihydroisoquinoline-2(1*H*)-carboxylate (8c).[4b] Yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.24–7.14 (4H, m), 5.40–5.33 (1H, m), 4.63–4.60 (4H, m), 3.71–3.65 (2H, m), 2.86–2.80 (2H, m), 1.75 (3H, s), 1.71 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 155.6, 137.8, 134.4, 133.2, 128.5, 126.2, 126.1, 125.9, 119.4, 62.2, 45.5, 41.3, 28.7, 25.6, 17.8; IR (neat) 2930,

1703, 1428, 1227, 1118, 984 cm^{-1}; MS (EI) *m/z* (relative intensity) 245 (5), 176 (47), 132 (36), 104 (19), 69 (100); HRMS (EI) *m/z* Calcd (M^+) 245.1416, found 245.1415.

4.9.4. 3-Methylbut-2-en-1-yl methyl(phenyl)carbamate (8e).[4b] Clear oil; ^1H NMR (200 MHz, $CDCl_3$) δ 7.25 (5H, m), 5.33 (1H, m), 4.61 (2H, d, $J=7.0$ Hz), 3.30 (3H, s), 1.73 (3H, s), 1.68 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 155.6, 143.3, 137.8, 128.6, 125.6, 125.4, 119.3, 62.4, 37.4, 25.5, 17.8; IR (neat) 2934, 1707, 1598, 1498, 1386, 1353, 1298, 1277, 1153 cm^{-1}; MS (EI) *m/z* (rel. intensity) 219 (3), 175 (3) 160 (9), 151 (24) 107 (59), 69 (100); HRMS (EI) *m/z* calcd (M^+) 219.1259, found 219.1251.

4.9.5. Benzyl methyl(phenyl)carbamate (8f).[4b,37] Yellow oil; ^1H NMR (200 MHz, $CDCl_3$) δ 7.40–7.20 (10H, m), 5.20 (2H, s), 3.35 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.6, 143.5 (d), 136.8, 129.0, 128.6, 128.0, 127.8, 126.3, 125.9, 67.4, 37.9; IR (neat) 2950, 1705, 1596, 1496, 1387, 1348, 1152 cm^{-1}.

4.10. General procedure for the preparation of thiocarbamate 9

To a suspension of carbamoylimidazolium salt **3** (1.00 mmol) in CH_2Cl_2 (6 mL) was added the thiol (1.00 mmol) and triethylamine (1.00 mmol). After stirring at rt overnight, the reaction was diluted with CH_2Cl_2 (5 mL) and 0.1 M HCl (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3×10 mL) and the combined organic layers were washed with H_2O (10 mL) and brine (15 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated in vacuo. The crude material was purified by flash column chromatography (98:2 Hexane: ethyl acetate) to yield the thiocarbamate **9a–f**.

4.10.1. *S*-Phenyl methyl(phenyl)thiocarbamate (9a).[4b,38] White solid; mp = 66–67 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 7.60–7.40 (10H, m), 3.37 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 167.4, 141.8, 135.4 (d), 129.5 (d), 129.4, 129.0 (d), 128.8 (d), 128.6 (d), 128.2 (d), 38.5; IR (neat) 2950, 1666, 1592, 1484, 1443, 1341, 1272, 1106 cm^{-1}.

4.10.2. *S*-Dodecyl 3,4-dihydroquinoline-1(2*H*)-carbothioate (9b).[4b] Clear oil; ^1H NMR (200 MHz, $CDCl_3$) δ 7.72–7.70 (1H, m), 7.17–7.06 (3H, m), 3.78 (2H, t, $J=6.0$ Hz), 2.90 (2H, t, $J=7.0$ Hz), 2.75 (2H, t, $J=6.5$ Hz), 2.00–1.94 (2H, m), 1.63–1.58 (2H, m), 1.39–1.24 (18H, m), 0.86 (3H, t, $J=7.0$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 168.6, 138.1, 131.3, 125.8, 125.8, 124.9, 124.7, 45.0, 31.8, 30.8, 29.9, 29.5, 29.5, 29.4, 29.4, 29.2, 29.1, 28.9, 26.8, 23.6, 22.6, 14.0; IR (neat) 2852, 1661, 1489, 1295, 1194, 1090, 937 cm^{-1}; MS (EI) *m/z* (relative intensity) 361 (79), 193 (12), 160 (100), 132 (50), 118 (6); HRMS (EI) *m/z* Calcd (M^+) 361.2439, found 361.1444.

4.10.3. *S*-(Pentafluorophenyl) 3,4-dihydroquinoline-1(2*H*)-carbothioate (9c).[4b] White solid; mp = 78–79 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.70–7.66 (1H, m), 7.23–7.18 (3H, m), 3.85 (2H, t, $J=6.5$ Hz), 2.81 (2H, t, $J=6.5$ Hz), 2.11–1.98 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2, 150.3 (m), 145.3 (m), 140.2 (m), 137.2, 135.1 (m), 132.5, 128.9, 126.3, 124.5, 45.9, 26.6, 23.6 (1 missing signal); ^{19}F NMR (376 MHz, $CDCl_3$) δ −131 (2F, m), −150 (1F, m), −161 (2F, m); IR (KBr pellet) 1664, 1517, 1470, 1295, 1094, 976 cm^{-1}; MS (EI) *m/z* (relative intensity) 359 (17), 199 (24), 160 (100), 132 (78), 118 (19); HRMS (EI) *m/z* calcd (M^+) 359.0403, found 359.0419.

4.10.4. *S*-Cyclohexyl 3,4-dihydroquinoline-1(2*H*)-carbothioate (9d).[4b] Clear oil; ^1H NMR (200 MHz, $CDCl_3$) δ 7.72 (1H, d, $J=8.0$ Hz), 7.20–7.02 (3H, m), 3.76 (2H, tr, $J=6.0$ Hz), 3.49 (1H, m), 2.75 (2H, tr, $J=6.5$ Hz), 2.07–1.15 (12H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 168.3, 138.1, 131.3, 128.6, 125.8, 124.9, 124.8, 45.0, 44.2, 33.5, 26.9, 26.2, 25.6, 23.6; IR (neat) 2930, 1646, 1580, 1488, 1446, 1362, 1295, 1197, 1162, 1089 cm^{-1}; MS (EI) *m/z* (rel. intensity) 275 (89), 193 (25), 172 (47), 160 (69), 133 (100), 83 (37); HRMS (EI) *m/z* calcd (M^+) 275.1344, found 275.1335.

4.10.5. Methyl *N*-acetyl-*S*-(3,4-dihydroquinolin-1(2*H*)-ylcarbonyl)-L-cysteinate (9e).[4b] Yellow foam; ^1H NMR (200 MHz, $CDCl_3$) δ 7.61–7.59 (1H, m), 7.15–7.06 (3H, m), 6.73 (1H, d, $J=5.5$ Hz), 4.73–4.69 (1H, m), 3.78–3.69 (5H, m), 3.33 (2H, d, $J=6.0$ Hz), 2.72 (2H, t, $J=6.5$ Hz), 1.97–1.91 (5H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.7, 169.9, 167.8, 137.4, 131.7, 128.6, 125.9, 125.5, 124.5, 52.9, 52.4, 45.4, 32.0, 26.6, 23.5, 22.9; IR (neat) 3290, 2950, 1760, 1682, 1647, 1372, 1296, 1090 cm^{-1}; MS (EI) *m/z* (rel. intensity) 336 (44), 277 (19), 193 (6), 160 (100), 144 (13), 132 (93); HRMS (EI) *m/z* calcd (M^+) 336.1144, found 336.1140.

4.10.6. *S*-Cyclohexyl 1,4-dioxa-8-azaspiro[4.5]decane-8-carbothioate (9f).[4b] White solid; mp = 56–57 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 3.87 (4H, s), 3.51–3.34 (5H, m), 1.91–1.88 (2H, m), 1.63–1.37 (7H, m), 1.34–1.16 (5H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 166.7, 106.8, 64.3, 44.7, 43.6, 41.4, 34.7, 33.5, 25.9, 25.4; IR (KBr pellet) 2931, 1644, 1447, 1263, 1033, 914 cm^{-1}; MS (EI) *m/z* (rel. intensity) 285 (18), 252 (20), 204 (66), 170 (100), 142 (80), 99 (32); HRMS (EI) *m/z* calcd (M^+) 285.1399, found 285.1408.

4.11. General procedure for the preparation of amides 10 from carboxylic acids

To a suspension of **3** (1.00 mmol) in acetonitrile (6 mL) were added the carboxylic acid (1.00 mmol) and triethylamine (1.00 mmol). The reaction was stirred at rt overnight. The solvent was removed in vacuo and the residue dissolved in CH_2Cl_2 (15 mL) and 0.2 N HCl (15 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3×15 mL). The combined organic layers were washed with 0.2 N HCl (15 mL), 0.5 M K_2CO_3 (25 mL), and brine (20 mL), dried ($MgSO_4$), filtered and concentrated in vacuo to give the amide **10a–l**.

4.11.1. 4-(4-Methylpentanoyl)morpholine (10c).[4d,39] Yellow oil; ^1H NMR (300 MHz, $CDCl_3$) δ 3.60–3.37 (8H, m), 2.25–2.20 (2H, m), 1.55–1.39 (3H, m), 0.83 (6H, d, $J=6.5$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2, 67.1, 66.8, 46.2, 42.0, 34.2, 31.3, 28.0, 22.5; IR (neat) 2956, 1651, 1429, 1273, 1116, 1030, 851 cm^{-1}; MS (EI) *m/z* (rel. intensity) 170 (10), 142 (15), 129 (100), 114 (30), 86 (41),

57 (63); HRMS (EI) *m/z* calcd (MH+) 186.1494, found 186.1495.

4.11.2. Benzyl [(1*S*)-1-benzyl-2-morpholin-4-yl-2-oxoethyl]carbamate (10e).[4d,40] Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32–7.17 (10H, m), 6.17 (1H, d, J=8.5 Hz), 5.12–5.01 (2H, m), 4.89–4.81 (1H, m), 3.66–3.22 (6H, m), 3.07–2.82 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.2, 156.0, 136.6, 136.5, 129.8, 128.8, 128.7, 128.3, 128.2, 127.4, 67.0, 66.6, 66.2, 51.6, 46.2, 42.5, 40.4; IR (neat) 3289, 1716, 1636, 1528, 1455, 1231, 1114, 751 cm^{-1}; MS (EI) *m/z* (rel. intensity) 368 (3), 254 (60), 217 (53), 210 (62), 91 (100); HRMS (EI) *m/z* calcd (M^+) 368.1736, found 368.1726.

4.11.3. *N*-Methoxy-*N*-methyl-4-oxo-4-phenylbutanamide (10i).[4d,41] Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (2H, d, J=7.0 Hz), 7.49–7.36 (3H, m), 3.70 (3H, s), 3.27 (2H, t, J=6.5 Hz), 3.14 (3H, s), 2.84 (2H, t, J=6.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.1, 173.4, 137.0, 133.2, 128.7, 128.2, 61.4, 33.2, 32.4, 26.3.

4.11.4. *N*-{2-[Methoxy(methyl)amino]-2-oxoethyl}-4-methylpentanamide (10j).[4d] Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.62 (3H, s), 3.11 (3H, s), 2.35 (2H, t, J=7.5 Hz), 1.60–1.40 (3H, m), 0.85 (6H, d, J=6.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.0, 61.4, 33.7, 32.4, 30.1, 28.0, 22.5; IR (neat) 2957, 1669, 1467, 1345, 1177, 1001 cm^{-1}; MS (EI) *m/z* (rel. intensity) 144 (12), 103 (48), 99 (79), 81 (100), 61 (99); HRMS (EI) *m/z* calcd (M^+) 159.1259, found 159.1253.

4.11.5. 2-Iodo-*N*-methoxy-*N*-methylbenzamide (10l).[4d,42] White solid; mp=55–58 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 50 °C) δ 7.83–7.80 (1H, m), 7.38–7.34 (1H, m), 7.26–7.24 (1H, m), 7.09–7.05 (1H, m), 3.51 (3H, br s), 3.31 (3H, br s); ^{13}C NMR (100 MHz, $CDCl_3$, 50 °C) δ 141.7, 139.1, 130.4, 127.8, 127.4, 92.5, 61.2, 32.7 (1 missing signal); MS (EI) *m/z* (rel. intensity) 291 (18), 231 (100), 203 (31), 104 (8), 76 (26); HRMS (EI) *m/z* Calcd (M^+) 290.9756, found 290.9760.

4.11.6. 8-(Phenylacetyl)-1,4-dioxa-8-azaspiro[4.5]decane (10m).[4d] Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25–7.16 (5H, m), 3.85 (4H, d, J=2.0 Hz), 3.68 (2H, s), 3.65 (2H, t, J=6.0 Hz), 3.43 (2H, t, J=6.0 Hz), 1.58 (2H, t, J=6.0 Hz), 1.37 (2H, t, J=5.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.5, 135.3, 128.9, 128.7, 127.0, 107.0, 64.6, 44.4, 41.3, 40.1, 35.4, 34.8; IR (neat) 2962, 2878, 1630, 1440, 1360, 1250, 1097, 1029 cm^{-1}; MS (EI) *m/z* (rel. intensity) 261 (73), 170 (100), 142 (80), 118 (37), 91 (77); HRMS (EI) *m/z* calcd (M^+) 261.1365, found 261.1368.

4.11.7. 8-Propionyl-1,4-dioxa-8-azaspiro[4.5]decane (10n).[4d] White solid; mp 59–60 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.86 (4H, s), 3.58 (2H, t, J=6.0 Hz), 3.41 (2H, t, J=6.0 Hz), 2.25 (2H, m), 1.56 (4H, m), 1.03 (3H, t, J=7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2, 107.0, 64.6, 43.5, 39.8, 35.7, 34.9, 26.6, 9.7; IR (KBr pellet) 2961, 2873, 1648, 1419, 1226, 1075, 928, 816 cm^{-1}; MS (EI) *m/z* (rel. intensity) 199 (72), 142 (35), 99 (100), 86 (35), 57 (53); HRMS (EI) calcd (M^+) 199.1208, found 199.1214.

4.11.8. Benzyl [2-(1,4-dioxa-8-azaspiro[4.5]dec-8-yl)-2-oxoethyl]carbamate (10o).[4d] White solid; mp=84–86 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30–7.24 (5H, m), 5.90 (1H, s), 5.06 (2H, s), 3.97 (2H, d, J=4.0 Hz), 3.90 (4H, s), 3.64 (2H, t, J=5.5 Hz), 3.37 (2H, t, J=5.5 Hz), 1.65–1.60 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.0, 156.0, 136.3, 128.3, 127.8, 127.8, 106.4, 66.6, 64.3, 42.4, 42.2, 40.0, 35.0, 34.4; IR (KBr pellet) 3306, 2962, 2878, 1717, 1635, 1520, 1443, 1218, 1058, 734 cm^{-1}; MS (EI) *m/z* (rel. intensity) 334 (24), 243 (27), 170 (41), 142 (84), 108 (38), 99 (100); HRMS (EI) *m/z* calcd (M^+) 334.1529, found 334.1529.

4.11.9. Benzyl [(1*S*)-1-(1,4-dioxa-8-azaspiro[4.5]dec-8-ylcarbonyl)-3-methylbutyl]carbamate (10p). Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33–7.26 (5H, m), 5.74 (1H, d, J=9.0 Hz), 5.06 (2H, s), 4.80–4.72 (1H, m), 3.95 (4H, s), 3.76–3.53 (4H, m), 1.76–1.65 (5H, m), 1.51–1.38 (2H, m), 0.99 (3H, d, J=6.5 Hz), 0.91 (3H, d, J=6.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5, 156.0, 136.3, 128.3, 127.9, 127.9, 106.7, 66.9, 64.6, 64.6, 49.2, 43.6, 43.1, 40.5, 35.7, 34.9, 24.9, 23.6, 22.2; IR (thin film) 3293, 2958, 1715, 1640, 1531, 1454, 1231, 1100, 1044, 945 cm^{-1}; MS (EI) *m/z* (rel. intensity) 390 (2), 334 (3), 220 (24), 176 (45), 142 (28), 91 (100); HRMS (EI) *m/z* calcd (M^+) 390.2155, found 390.2168.

4.11.10. 1-(Phenylacetyl)-1,2,3,4-tetrahydroquinoline (10q).[43] Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27–7.12 (9H, m), 3.87 (2H, s), 3.80 (2H, t, J=6.5 Hz), 2.60 (2H, br s), 1.89 (2H, t, J=6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 139.3, 135.5, 128.9, 128.6, 128.5, 126.8, 126.2, 125.7, 124.9, 43.2, 41.4, 26.6, 24.1 (1 carbon missing); IR (thin film) 3029, 2946, 1652, 1580, 1492, 1383, 1165, 1074, 760, 719 cm^{-1}; MS (EI) *m/z* (rel. intensity) 251 (95), 160 (26), 133 (100), 117 (18), 91 (60); HRMS (EI) *m/z* calcd (M^+) 251.1310, found 251.1310.

4.11.11. Benzyl [2-(3,4-dihydroquinolin-1(2*H*)-yl)-2-oxoethyl]carbamate (10r). Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35–7.13 (9H, m), 5.78 (1H, s), 5.10 (2H, s), 4.15 (2H, d, J=4.5 Hz), 3.76 (2H, br s), 2.72 (2H, br m), 2.00–1.92 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1, 156.4, 137.8, 136.6, 129.0, 128.6, 128.2, 128.2, 126.6, 126.1, 124.3, 67.0, 44.0, 43.6, 26.8, 23.7 (1 carbon missing); IR (thin film) 3326, 2947, 1722, 1660, 1492, 1404, 1237, 1048, 759 cm^{-1}; MS (EI) *m/z* (rel. intensity) 324 (42), 216 (18), 160 (27), 133 (100), 91 (60); HRMS (EI) *m/z* calcd (M^+) 324.1474, found 324.1479.

4.12. General procedure for the preparation of thiocarbamoylimidazoles

To a suspension of *N*,*N*′-thiocarbonyldiimidazole (5.50 mmol) in CH_2Cl_2 (5 mL) was added amine (5.00 mmol). The mixture was stirred at rt for 2 h. The reaction mixture was then diluted with CH_2Cl_2 (100 mL) and washed with water (3×20 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated in vacuo to yield the product thiocarbamoylimidazole **11a–d**.

4.12.1. 8-(1*H*-Imidazol-1-ylcarbonothioyl)-1,4-dioxa-8-azaspiro[4.5]decane (11a). Beige solid; mp=89–92 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.81–7.80 (1H, m), 7.14–7.13

(1H, m), 7.02 (1H, m), 3.95–3.94 (8H, m), 1.80 (4H, br s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 178.2, 137.0, 129.4, 119.0, 105.6, 64.3, 49.4, 34.6; IR (KBr pellet) 3114, 1507, 1362, 1238, 1079, 935 cm^{-1}; MS (EI) *m/z* (rel. intensity) 253 (97), 186 (100), 158 (91), 142 (27), 99 (66); HRMS (EI) *m/z* calcd (M^+) 253.0885, found 253.0876.

4.12.2. 4-(1*H*-Imidazol-1-ylcarbonothioyl)morpholine (11b). White solid; mp = 84–90 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.78 (1H, s), 7.10–7.09 (1H, m), 6.98–6.97 (1H, m), 3.82–3.67 (8H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 178.4, 137.1, 129.8, 118.9, 66.0, 51.7; IR (KBr pellet) 2975, 1487, 1436, 1362, 1304, 1239, 1115, 1029, 962 cm^{-1}; MS (EI) *m/z* (rel. intensity) 197 (80), 130 (100), 111 (7), 86 (89); HRMS (EI) *m/z* calcd (M^+) 197.0623, found 197.0625.

4.12.3. 1-(Pyrrolidin-1-ylcarbonothioyl)-1*H*-imidazole (11c). Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97–7.96 (1H, m), 7.33–7.32 (1H, m), 7.07–7.06 (1H, m), 3.91 (2H, br m), 3.65 (2H, br m), 2.05 (4H, br m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.7, 137.0, 129.6, 118.9, 54.9, 53.7, 26.7, 24.6; IR (neat) 3114, 2975, 1694, 1495, 1358, 1281, 1043, 954, 825, 746 cm^{-1}; MS (EI) *m/z* (rel. intensity) 181 (81), 114 (100), 84 (12), 72 (59), 55 (33); HRMS (EI) *m/z* calcd (M^+) 181.0674, found 181.0677.

4.12.4. 1-(1*H*-Imidazol-1-ylcarbonothioyl)-1,2,3,4-tetrahydroquinoline (11d). Beige solid; mp = 75–77 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (1H, s), 7.74 (1H, s), 7.26–7.23 (2H, m), 7.12 (3H, br m), 4.96 (2H, s), 4.03 (2H, m), 3.08 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.0, 139.1, 137.3, 132.6, 129.2, 128.4, 127.0, 126.4, 122.3, 119.3, 52.2, 26.4, 24.2; IR (KBr pellet) 3118, 1652, 1471, 1233, 1062, 928 cm^{-1}; MS (EI) *m/z* (rel. intensity) 143 (100), 215 (17), 176 (55), 142 (33), 117 (48); HRMS (EI) *m/z* calcd (M^+) 243.0830, found 243.0831.

4.13. General procedure for the preparation of thiocarbamoylimidazolium salts 12

To a solution of thiocarbamoylimidazole (8.00 mmol) in acetonitrile (15 mL) was added methyl iodide (32.0 mmol). The mixture was stirred at rt for 24 h. The solvent was removed under vacuum to yield the thiocarbamoyl imidazolium salt **12a–d** as a yellow viscous oil. Recrystalization in methanol/ethyl acetate gave yellow crystals.

4.13.1. 1-(1,4-Dioxa-8-azaspiro[4.5]dec-8-ylcarbonothioyl)-3-methyl-1*H*-imidazol-3-ium iodide (12a). Yellow solid; mp = 192–196 °C; ^{1}H NMR (200 MHz, DMSO-d_6) δ 9.62 (1H, s), 8.09–80.8 (1H, m), 7.86–7.84 (1H, m), 4.17 (2H, br s), 3.93 (4H, s), 3.90 (3H, s), 3.63 (2H, br s), 1.89–1.80 (4H, br m); ^{13}C NMR (50 MHz, DMSO-d_6) δ 172.0, 137.2, 123.7, 121.2, 105.2, 64.0, 50.0, 36.4, 34.0 (br); IR (KBr pellet) 2962, 1639, 1457, 1236, 1097, 906 cm^{-1}; MS (FAB) *m/z* (rel. intensity) 268 (59), 227 (6), 186 (100), 158 (31), 142 (13); HRMS (EI) *m/z* calcd ($M^+ - 127$) 268.1120, found 268.1136.

4.13.2. 3-Methyl-1-(morpholin-4-ylcarbonothioyl)-1*H*-imidazol-3-ium iodide (12b). Yellow solid; mp = 205–210 °C; ^{1}H NMR (200 MHz, DMSO-d_6) δ 9.65 (1H, s), 8.10–8.09 (1H, m), 7.88–7.87 (1H, m), 4.13–3.99 (2H, br s), 3.91 (3H, s), 3.87–3.67 (6H, br m); ^{13}C NMR (50 MHz, DMSO-d_6) δ 171.9, 137.5, 123.8, 121.2, 65.4 (br), 52.0, 36.6; IR (KBr pellet) 3065, 1507, 1437, 1242, 1052, 963 cm^{-1}; MS (FAB) *m/z* (rel. intensity) 121 (51), 185 (100), 175 (12), 130 (45).

4.13.3. 3-Methyl-1-(pyrrolidin-1-ylcarbonothioyl)-1*H*-imidazol-3-ium iodide (12c). Yellow solid; mp = 178–180 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.25 (1H, br m), 7.91 (1H, br m), 7.60 (1H, br m), 4.25 (3H, s), 4.07 (2H, br m), 3.89–3.86 (2H, m), 2.18–2.11 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) 168.6, 136.1, 123.7, 121.9, 56.2, 55.4, 38.2, 26.8, 24.7; IR (KBr pellet) 3064, 1579, 1516, 1447, 1331, 1193, 956, 855 cm^{-1}; MS (FAB) *m/z* (rel. intensity) 196 (92), 114 (100); HRMS (FAB) *m/z* calcd ($M^+ - 127$) 196.0908, found 196.0908.

4.13.4. 1-(3,4-Dihydroquinolin-1(2*H*)-ylcarbonothioyl)-3-methyl-1*H*-imidazol-3-ium iodide (12d). Yellow solid; mp = 199–204 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.65 (1H, s), 7.65 (1H, s), 7.59 (1H, s), 7.36 (1H, d, J = 9.0 Hz), 7.23 (1H, m), 7.06 (1H, m), 6.91 (1H, d, J = 8.0 Hz), 4.20 (2H, t, J = 6.5 Hz), 3.86 (3H, s), 2.88 (2H, t, J = 6.0 Hz), 2.09–2.06 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) 171.6, 138.4, 137.6, 134.6, 128.8, 127.6, 127.0, 123.4, 123.1, 121.6, 53.6, 36.5, 25.8, 23.7; MS (FAB) *m/z* (rel. intensity) 258 (45), 236 (20), 176 (100), 160 (29), 146 (35).

4.14. General procedure for the synthesis of thioureas 13

To a solution of thiocarbamoylimidazolium salt **12** (0.50 mmol) in CH_2Cl_2 (1.0 mL) was added a primary or secondary amine (0.600 mmol) and triethylamine (0.60 mmol). The reaction was stirred at rt for 2 h, and diluted with CH_2Cl_2 (10 mL). The mixture was washed with 1N HCl solution (2×5 mL) and brine. The aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were washed with H_2O (10 mL) and brine (10 mL), dried ($MgSO_4$), filtered and concentrated in vacuo to afford thiourea **13a–e**.

4.14.1. 4-(Pyrrolidin-1-ylcarbonothioyl)morpholine (13a). Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.75 (4H, t, J = 4.5 Hz), 3.67–3.63 (4H, m), 3.46 (4H, t, J = 4.5 Hz), 1.94–1.91 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.7, 66.8, 53.2, 51.4, 25.6; IR (neat) 2965, 2854, 1434, 1346, 1269, 1215, 1115, 1030, 872 cm^{-1}; MS (EI) *m/z* (rel. intensity) 200 (100), 167 (37), 143 (30), 130 (11), 114 (61), 96 (10), 86 (53), 70 (45); HRMS (EI) *m/z* calcd (M^+) 200.0983, found 200.0992.

4.14.2. 2-(Pyrrolidin-1-ylcarbonothioyl)-1,2,3,4-tetrahydroisoquinoline (13b). Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19–7.10 (4H, m), 4.65 (2H, s), 3.73–3.66 (6H, m), 3.00 (2H, t, J = 6.0 Hz), 1.94–1.91 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.8, 134.6, 133.7, 128.6, 126.6, 126.4, 126.3, 53.2, 53.0, 49.0, 29.0, 25.6; IR (neat) 2967, 1667, 1435, 1207, 1107, 920, 751 cm^{-1}; MS (EI) *m/z* (rel. intensity) 246 (73), 161 (22), 147 (20), 132 (100), 117 (41), 103 (17), 90 (18), 83 (17), 70 (42); HRMS (EI) *m/z* calcd (M^+) 246.1192, found 246.1191.

4.14.3. 8-(Morpholin-4-ylcarbonothioyl)-1,4-dioxa-8-azaspiro[4.5]decane (13c). White solid; mp = 94–96 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.86 (4H, s), 3.61–3.55 (8H, m), 3.45–3.43 (4H, m), 1.67–1.64 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.5, 106.6, 66.1, 64.2, 51.8, 49.0, 34.5; IR (neat) 2849, 1644, 1427, 1232, 1094, 854, 754 cm^{-1}; MS (EI) *m/z* (rel. intensity) 272 (100), 239 (29), 215 (17), 186 (34), 154 (22), 142 (19), 127 (11), 99 (22), 86 (56), 72 (11); HRMS (EI) *m/z* calcd (M^+) 272.1204, found 272.1195.

4.14.4. 8-[(4-Benzylpiperazin-1-yl)carbonothioyl]-1,4-dioxa-8-azaspiro[4.5]decane (13d). White foam; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31–7.24 (5H, m), 3.94 (4H, s), 3.65–3.58 (8H, m), 3.53 (2H, s), 2.52–2.50 (4H, m), 1.75–1.73 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.2, 136.9, 129.1, 128.2, 127.3, 106.8, 64.3, 62.6, 52.4, 51.2, 49.2, 34.7; IR (neat) 2955, 1883, 1475, 1422, 1357, 1236, 1138, 1086, 1034 cm^{-1}; MS (EI) *m/z* (rel. intensity) 361 (42), 328 (20), 238 (33), 229 (76), 215 (36), 186 (56), 159 (58), 146 (42), 99 (28), 91 (100); HRMS (EI) *m/z* calcd (M^+) 361.1830, found 361.1824.

4.14.5. *N*-Butyl-*N*-methylmorpholine-4-carbothioamide (13e). Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.72–3.66 (4H, m), 3.56 (2H, t, J=7.5 Hz), 3.38–3.35 (4H, m), 3.03 (3H, s), 1.60–1.53 (2H, m), 1.24 (2H, sextet, J=7.5 Hz), 0.87 (3H, t, J=7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.6, 66.4, 54.6, 51.9, 40.4, 29.1, 19.8, 13.7; IR (neat) 2928, 1495, 1455, 1392, 1248, 1116, 1029, 875 cm^{-1}; MS (EI) *m/z* (rel. intensity) 216 (67), 183 (23), 159 (18), 130 (48), 98 (37), 86 (100), 74 (35), 57 (29); HRMS (EI) *m/z* calcd (M^+) 216.1301, found 216.1296.

4.14.6. *N*-[2-(3,4-Dimethoxyphenyl)ethyl]morpholine-4-carbothioamide (13f). Yellow solid, mp 79–81 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.78–6.76 (1H, m), 6.70–6.68 (2H, m), 5.52 (1H, br m), 3.88 (2H, td, J=7.0 Hz, J=5.5 Hz), 3.83 (3H, s), 3.82 (3H, s), 3.65 (8H, br s), 2.85 (2H, t, J=7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.4, 149.0, 147.7, 131.1, 120.5, 111.7, 111.2, 66.0, 55.8, 55.8, 47.2, 46.8, 34.5; IR (KBr pellet) 3373, 2932, 1515, 1261, 1235, 1141, 1025 cm^{-1}; MS (EI) *m/z* (rel. intensity) 310 (10), 223 (27), 164 (99), 151 (100), 107 (8), 87 (6), 72 (7); HRMS (EI) *m/z* calcd (M^+) 310.1362, found 310.1351.

4.14.7. Diethyl (2-morpholin-4-yl-2-oxoethyl)phosphonate (14).[44] To a suspension of **3f** (4.00 mmol) in dry MeCN (24.0 mL) were added diethyl phosphonoacetic acid (4.00 mmol) and triethylamine (4.00 mmol). The reaction mixture was refluxed for 24 h. The solvent was removed in vacuo and the residue was dissolved in CH_2Cl_2 and washed with 0.2 N HCl. The aqueous layer was extracted with CH_2Cl_2 (×3). The combined organic layers were washed with 0.2 N HCl, 0.5 M K_2CO_3, and brine, dried ($MgSO_4$), and concentrated in vacuo. Product **14** was obtained without further purification as a yellow oil (76%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.11–4.07 (4H, m), 3.66–3.49 (8H, m), 2.98 (2H, d, J=22.0 Hz), 1.26 (6H, t, J=7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.5 (d, J=6.0 Hz), 66.9, 66.8, 62.8 (d, J=7.0 Hz), 47.5, 42.5, 33.4 (d, J=132.0 Hz), 16.5 (d, J=7.0 Hz); ^{31}P (121 MHz, $CDCl_3$) δ 22.11; IR (thin film) 2981, 2859, 1644, 1442, 1258, 1115, 1032, 970, 788 cm^{-1}; MS (EI) *m/z* (relative intensity) 235 (64), 179 (92), 125 (66), 86 (89), 57 (100); HRMS (EI) *m/z* Calcd (MH^+) 266.1157, found 266.1155.

4.14.8. 4-[(2*E*)-4-Methylpent-2-enoyl]morpholine (15). To a suspension of LiCl (1.24 mmol) in acetonitrile (15 mL) was added **14** (1.24 mmol) followed by 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 1.04 mmol) and isobutyrylaldehyde (1.04 mmol). The reaction was stirred at rt for 16 h. The solvent was then removed in vacuo and the crude product dissolved in CH_2Cl_2 and washed with 0.1 N HCl, brine, dried ($MgSO_4$), and concentrated in vacuo. The crude product was purified by column chromatography (100% EtOAc) to give a yellow oil (85%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.75 (1H, dd, J=15.0 Hz, J=7.0 Hz), 6.05 (1H, dd, J=15.0 Hz, J=1.5 Hz), 3.57–3.47 (8H, br m), 2.39–2.32 (1H, m), 0.96 (6H, d, J=6.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.7, 153.2, 116.5, 66.8, 46.1, 42.3, 31.2, 21.6; IR (thin film) 2961, 2857, 1658, 1620, 1432, 1270, 1229, 1116, 975, 846 cm^{-1}; MS (EI) *m/z* (rel. intensity) 183 (25), 168 (18), 140 (68), 97 (100), 86 (30); HRMS (EI) *m/z* calcd (M^+) 183.1259, found 183.1264.

4.15. General procedure for TBDMS protection of alcohol 16

To a solution of 2-piperidinemethanol (17.3 mmol) in CH_2Cl_2 (35 mL) was added imidazole (34.7 mmol). After stirring for 5 min., *t*-butyldimethylsilyl chloride (19.1 mmol) was added and the reaction mixture was stirred at rt for 4.5 h. The reaction mixture was diluted with CH_2Cl_2 and saturated aqueous $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (×4). The combined organic layers were washed once with H_2O, dried ($MgSO_4$), filtered and concentrated in vacuo to give **17**.

4.15.1. 2-(*tert*-Butyldimethylsilanyloxymethyl)piperidine (17a).[4d] Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.51–3.47 (1H, m), 3.38–3.34 (1H, m), 3.06–3.02 (1H, m), 2.62–2.52 (2H, m), 1.76–1.72 (1H, m), 1.57–1.24 (4H, m), 1.09–0.90 (1H, m), 0.85 (9H, s), 0.01 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 68.1, 58.4, 46.8, 28.6, 26.6, 26.1, 24.6, 18.4, −5.2; IR (thin film) 3343, 2931, 1472, 1463, 1330, 1089, 930, 837, 777 cm^{-1}; MS (EI) *m/z* (rel. intensity) 230 (3), 214 (7), 172 (27), 84 (100), 73 (8); HRMS (EI) *m/z* calcd (MH^+) 230.1940, found 230.1947.

4.16. General procedure for formation of carbamoylimidazole 18

To a solution of **17** (13.9 mmol) in CH_2Cl_2 (28 mL) was added CDI (15.2 mmol). The reaction mixture was stirred at rt for 1 day, diluted with H_2O and the aqueous layer was extracted with CH_2Cl_2 (×3). The combined organic layers were washed with H_2O (×2), dried ($MgSO_4$), filtered and concentrated in vacuo. The product was obtained following column chromatography.

4.16.1. [2-(*tert*-Butyldimethylsilanyloxymethyl)piperidin-1-yl]imidazol-1-yl-methanone (18a).[4d] Pale yellow oil; R_f=0.5 (3:7 Hexane/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (1H, s), 7.25 (1H, s), 7.02 (1H, m), 5.26 (1H, br s), 3.94 (1H, t, J=10.0 Hz), 3.58–3.55 (1H, m), 3.07–3.02 (1H, m), 1.74–1.55 (6H, m), 0.84 (9H, s), 0.03 (3H, s), 0.02 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.2, 137.2, 129.4, 118.3, 61.0, 55.7, 41.8, 26.0, 25.8, 25.5, 19.7, 18.4, −5.3; IR (thin film) 3120, 2931, 1694, 1422, 1385, 1249,

1103, 1003, 839, 779 cm^{-1}; MS (EI) *m/z* (relative intensity) 323 (1), 308 (6), 266 (100), 256 (27), 178 (58), 73 (44); HRMS (EI) *m/z* Calcd (M^+) 323.2029, found 323.2035.

4.16.2. {2-[2-(*tert*-Butyldimethylsilanyloxy)ethyl]piperidin-1-yl}imidazol-1-yl-methanone (18b).[4d] Pale yellow oil; R_f=0.55 (3:7 Hexane/EtOAc); ^1H NMR (500 MHz, $CDCl_3$) δ 7.87 (1H, s), 7.22 (1H, s), 7.06 (1H, s), 4.44 (1H, br s), 3.90–3.87 (1H, m), 3.67–3.62 (2H, m), 3.13 (1H, t, J= 12.5 Hz), 2.04–1.98 (1H, m), 1.87–1.83 (1H, m), 1.75–1.67 (5H, m), 1.57–1.54 (1H, m), 0.86 (9H, s), −0.01 (6H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.3, 137.1, 129.6, 118.1, 60.3, 51.5, 42.4, 33.2, 28.7, 26.1, 26.0, 19.1, 18.5, −5.1, −5.2; IR (thin film) 3117, 2856, 1682, 1472, 1246, 1201, 1099, 989, 828, 775 cm^{-1}; MS (EI) *m/z* (rel. intensity) 322 (5), 280 (100), 270 (22), 198 (11), 184 (20), 73 (27); HRMS (EI) *m/z* calcd ($M-H^+$) 336.2107, found 336.2115.

4.17. General procedure for formation of carbamoylimidazolium salts 19

To a solution of **18** (27.7 mmol) in MeCN (55 mL) was added MeI (110.8 mmol) and the reaction mixture was stirred at rt for 1 day. The solvent was evaporated in vacuo to give the product.

4.17.1. 3-[2-(*tert*-Butyldimethylsilanyloxymethyl)piperidine-1-carbonyl]-1-methyl-3*H*-imidazol-1-ium iodide (19a).[4d] Foamy yellow solid; very hygroscopic; ^1H NMR (400 MHz, $CDCl_3$) δ 9.97 (1H, s), 7.69 (1H, s), 7.67 (1H, s), 4.39–4.37 (1H, m), 4.24 (3H, s), 4.07–4.02 (1H, m), 3.95 (1H, t, J=10.5 Hz), 3.63–3.59 (1H, m), 3.12–3.05 (1H, m), 2.20–2.10 (1H, m), 1.70–1.46 (5H, m), 0.84 (9H, s), 0.058 (3H, s), 0.054 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.3, 136.3, 123.8, 120.7, 60.2, 55.8 (br), 41.7 (br), 37.6, 25.4, 25.0, 24.2, 18.6, 17.8, −5.8, −5.9; IR (thin film) 3076, 2951, 1723, 1537, 1418, 1252, 1150, 1100, 1004, 839, cm^{-1}; MS (ESI) *m/z* (rel. intensity) 338 (9), 270 (7), 256 (100), 197 (31); HRMS (ESI) *m/z* calcd (M^+-127) 338.2258, found 338.2265.

4.17.2. 3-{2-[2-(*tert*-Butyldimethylsilanyloxy)-ethyl]piperidine-1-carbonyl}-1-methyl-3*H*-imidazol-1-ium iodide (19b).[4d] Foamy light yellow solid; very hygroscopic; ^1H NMR (400 MHz, $CDCl_3$) δ 10.06 (1H, s), 7.72 (1H, s), 7.66 (1H, s), 4.62 (1H, br s), 4.25 (3H, s), 3.85 (1H, br s), 3.67–3.64 (2H, m), 3.34 (1H, br s), 2.07–1.61 (8H, m), 0.82 (9H, s), −0.01 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.5, 137.1, 124.2, 121.1, 60.2, 52.6 (br), 44.0 (br), 38.2, 32.8, 28.5 (br), 26.0, 25.8, 18.5, 18.3, −5.2; IR (thin film) 2930, 2857, 1720, 1639, 1420, 1255, 1098, 836, 776 cm^{-1}; MS (ESI) *m/z* (rel. intensity) 352 (11), 271 (27), 270 (100); HRMS (ESI) *m/z* calcd (M^+-127) 352.2414, found 352.2427.

4.18. General procedure for formation of amide 20

To a solution of **19** (6.29 mmol) in MeCN (38 mL) were added diethylphosphonoacetic acid (6.92 mmol) and Et_3N (6.92 mmol). The reaction mixture was stirred at 50 °C for 1 day. The solvent was removed in vacuo and the crude product was partitioned between CH_2Cl_2 and H_2O. The aqueous layer was extracted with CH_2Cl_2 (×4). The combined organic layers were washed with H_2O, 0.5 M K_2CO_3, brine, dried ($MgSO_4$), filtered and concentrated in vacuo. The product was obtained following column chromatography.

4.18.1. Diethyl {2-[2-(*tert*-Butyldimethylsilanyloxymethyl)piperidin-1-yl]-2-oxoethyl}phosphonate (20a).[4d] Yellow oil; R_f=0.2 (100% EtOAc); ^1H NMR (400 MHz, $CDCl_3$) (rotamers) δ 4.55–4.50 (1H, m), 4.25–4.07 (4H, m), 3.88–3.81 (1H, m), 3.56–3.46 (2H, m), 3.08–2.79 (2H, m), 2.59–2.51 (1H, m), 1.78–1.35 (6H, m), 1.33–1.28 (6H, m), 0.85 (2.67H, s), 0.83 (6.33H, s), 0.02 (4.2H, s), −0.01 (1.8H, s); ^{13}C NMR (100 MHz, $CDCl_3$) (rotamers) δ 164.7 (d, J=5.5 Hz), 163.7 (d, J=5.0 Hz), 62.6 (d, J=6.0 Hz), 62.5 (d, J=6.0 Hz), 62.4 (d, J=7.0 Hz), 62.0 (d, J= 6.0 Hz), 61.4, 60.7, 44.0, 37.0, 33.8 (d, J=133.0 Hz), 33.8 (d, J=133.0 Hz), 25.8, 25.8, 25.8, 25.6, 25.2, 24.3, 19.8, 19.0, 18.1, 16.3 (d, J=6.0 Hz), 16.3 (d, J=6.0 Hz), −5.5, −5.6; ^{31}P NMR (121 MHz, $CDCl_3$) (rotamers) δ 23.68, 22.78; IR (thin film) 2932, 2858, 1638, 1443, 1254, 1102, 1027, 969, 838, 779 cm^{-1}; MS (EI) *m/z* (rel. intensity) 409 (5), 350 (46), 322 (19), 262 (100), 172 (38), 84 (90); HRMS (EI) *m/z* calcd (MH^+) 408.2335, found 408.2332.

4.18.2. Diethyl (2-{2-[2-(*tert*-butyldimethylsilanyloxy)ethyl]piperidin-1-yl}-2-oxoethyl)phosphonate (20b).[4d] Yellow oil; R_f=0.5 (95:5 EtOAc/MeOH); ^1H NMR (300 MHz, $CDCl_3$) (rotamers) δ 4.79 (0.3H, br s), 4.54–4.48 (0.7H, br m), 4.33–4.27 (0.7H, br m), 4.18–4.04 (3.3H, m), 3.62–3.42 (3H, m), 3.05–2.79 (2H, m), 2.54–2.44 (1H, m), 1.86–1.81 (2H, m), 1.73–1.50 (6.3H, m), 1.36–1.24 (5.7H, m), 0.86 (6.3H, s), 0.84 (2.7H, s), 0.02 (1.8H, s), 0.00 (4.2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) (rotamers) δ 163.8 (d, J=5.0 Hz), 162.9 (d, J=5.0 Hz), 62.7 (d, J=6.0 Hz), 62.6, 62.5 (d, J=6.5 Hz), 62.0 (d, J=6.5 Hz), 61.1, 59.1, 50.4, 46.5, 43.0, 37.1, 34.0 (d, J=132.0 Hz), 33.6 (d, J= 133.5 Hz), 33.3, 33.2, 29.5, 28.8, 26.4, 26.2, 25.8, 19.5, 19.2, 18.5, 16.7 (d, J=6.0 Hz), 16.7 (d, J=6.5 Hz), −5.9, −5.0; ^{31}P NMR (121 MHz, $CDCl_3$) (rotamers) δ 23.55, 22.84; IR (thin film) 2931, 2858, 1640, 1444, 1255, 1095, 1024, 967, 835, 777 cm^{-1}; MS (EI) *m/z* (rel. intensity) 422 (8), 365 (81), 336 (100), 308 (27), 243 (39); HRMS (EI) *m/z* calcd (MH^+) 422.2492, found 422.2480.

4.19. General procedure for TBDMS deprotection to alcohol 21

To a solution of **20** (14.7 mmol) in THF (70 mL) was added tetrabutylammonium fluoride (17.7 mmol). The reaction mixture was stirred at rt for 30 min, quenched with H_2O and extracted with CH_2Cl_2 (×4), dried ($MgSO_4$), filtered and concentrated in vacuo. The product was obtained following column chromatography.

4.19.1. Diethyl {2-[2-(hydroxymethyl)piperidin-1-yl]-2-oxoethyl}phosphonate (21a).[4d] Yellow oil; yield: 94%; R_f=0.3 (9:1 EtOAc/MeOH); ^1H NMR (400 MHz, $CDCl_3$) (rotamers) δ 4.51 (1H, br s), 4.23 (1H, br d, J=13.5 Hz), 3.91–3.84 (4H, m), 3.65 (1H, br t, J=10.5 Hz), 3.52–3.14 (2.6H, m), 2.96–2.68 (1.7H, m), 2.43 (0.7H, br t, J= 12.5 Hz), 1.56–1.22 (6H, m), 1.19–1.02 (6H, m); ^{13}C NMR (125 MHz, $CDCl_3$) (rotamers) δ 164.8 (d, J=5.5 Hz), 164.1 (d, J=5.5 Hz), 62.9 (d, J=6.0 Hz), 62.8 (d, J=6.5 Hz),

62.5 (d, J=6.5 Hz), 62.5 (d, J=6.0 Hz), 60.8, 60.5, 55.9, 50.9, 43.4, 37.2, 33.8 (d, J=132.0 Hz), 33.6 (d, J=132.0 Hz), 26.1, 25.7, 25.3, 24.9, 19.6, 19.3, 16.4, 16.3; ^{31}P NMR (121 MHz, $CDCl_3$) (rotamers) δ 23.72, 23.00; IR (thin film) 3412, 2939, 2869, 1624, 1446, 1245, 1025, 972, 787 cm^{-1}; MS (EI) m/z (rel. intensity) 294 (8), 263 (72), 262 (100), 248 (16), 84 (92); HRMS (EI) m/z calcd (MH^+) 294.1470, found 294.1461.

4.19.2. Diethyl {2-[2-(2-hydroxyethyl)piperidin-1-yl]-2-oxoethyl}phosphonate (21b).[4d] Yellow oil; R_f=0.3 (9:1 EtOAc/MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) (rotamers) δ 4.89–4.86 (0.7H, m), 4.56–4.52 (0.3H, br m), 4.37–4.4.36 (0.3H, br m), 4.22–4.11 (3.7H, m), 3.82–3.70 (1.7H, m), 3.65–3.58 (1.3H, m), 3.43–3.01 (3.7H, m), 2.63–2.56 (0.3H, br m), 2.09–1.94 (1.3H, m), 1.78–1.46 (7H, m), 1.40–1.30 (5.7H, m); ^{13}C NMR (75 MHz, $CDCl_3$) (rotamers) δ 165.4 (d, J=6.0 Hz), 63.1 (d, J=6.5 Hz), 62.8 (d, J=3.5 Hz), 62.7 (d, J=3.5 Hz), 62.4 (d, J=6.0 Hz), 58.2, 58.0, 50.6, 45.6, 43.2, 37.2, 33.7 (d, J=132.0 Hz), 32.9 (d, J=134.0 Hz), 32.6, 32.4, 29.2, 29.0, 25.9, 25.6, 19.3, 16.4 (d, J=6.5 Hz); ^{31}P NMR (121 MHz, $CDCl_3$) (rotamers) δ 23.83, 22.31; IR (thin film) 3441, 2942, 1626, 1448, 1247, 1025, 975, 788 cm^{-1}; MS (EI) m/z (rel. intensity) 308 (14), 307 (10), 262 (78), 179 (20), 128 (100), 84 (65); HRMS (EI) m/z calcd (MH^+) 308.1623, found 308.1638.

4.20. General procedure for oxidation of alcohol to the aldehyde 22

To a solution of **21** (3.75 mmol) in CH_2Cl_2 (37 mL) was added 1,1,1-tris(acetyloxy)-1,1-dihydro-1,2-benziodoxol-3-(1*H*)-one (Dess–Martin reagent, 4.50 mmol). The reaction mixture was stirred at rt for 16 h. The reaction mixture was filtered through Celite, and the filtrate diluted with 0.5 M K_2CO_3 and extracted with CH_2Cl_2 (×4). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated in vacuo. The product was obtained after column chromatography.

4.20.1. Diethyl [2-(2-formylpiperidin-1-yl)-2-oxoethyl] phosphonate (22a).[4d] Yellow oil; R_f=0.14 (100% EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) (rotamers) δ 9.66 (0.2H, s), 9.51 (0.8H, s), 5.18 (0.7H, br d, J=5.5 Hz), 4.73–4.61 (0.3H, br m), 4.24–4.08 (4H, m), 3.93–3.89 (1H, br m), 3.23–2.94 (3H, m), 2.64–2.57 (0.2H, m), 2.42–2.25 (0.8H, br m), 1.83–1.47 (4H, m), 1.39–1.25 (7H, m); ^{13}C NMR (100 MHz, $CDCl_3$) (rotamers) δ 200.9, 200.0, 165.2, 165.1, 63.6, 62.8 (d, J=6.5 Hz), 62.7 (d, J=6.5 Hz), 59.3, 45.8, 40.5, 33.9 (d, J=131.0 Hz), 33.5 (d, J=133.0 Hz), 25.2, 24.7, 24.6, 23.4, 20.9, 20.8, 16.4 (d, J=6.5 Hz); ^{31}P NMR (121 MHz, $CDCl_3$) δ 20.65; IR (thin film) 2940, 2866, 1731, 1639, 1444, 1249, 1025, 972, 833, 787 cm^{-1}; MS (EI) m/z (rel. intensity) 292 (5), 262 (49), 179 (9), 151 (8), 123 (12), 84 (100); HRMS (EI) m/z calcd (M^+) 291.1236, found 291.1230.

4.20.2. Diethyl {2-oxo-2-[2-(2-oxoethyl)piperidin-1-yl] ethyl}phosphonate (22b).[4d] Yellow oil; R_f=0.15 (100% EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) (rotamers) δ 9.63 (0.3H, s), 9.54 (0.7H, s), 5.22–5.16 (0.6H, m), 4.61–4.55 (0.2H, br m), 4.44–4.38 (0.2H, br m), 4.06–3.96 (4H, m), 3.69–3.64 (0.7H, br m), 3.37–3.25 (0.3H, m), 3.06–2.85 (3H, m), 2.67–2.39 (2H, m), 1.75–1.34 (7H, m), 1.18 (6H, t, J=7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) (rotamers) δ 200.3, 199.5, 163.8 (d, J=5.5 Hz), 163.2 (d, J=5.5 Hz), 62.5 (d, J=6.5 Hz), 62.3 (d, J=6.5 Hz), 48.4, 44.5, 44.2, 43.8, 42.8, 37.2, 33.5 (d, J=132.5 Hz), 33.3 (d, J=132.5 Hz), 29.3, 28.2, 25.5, 25.2, 18.9, 18.5, 16.2 (d, J=6.5 Hz); ^{31}P NMR (121 MHz, $CDCl_3$) (rotamers) δ 21.63, 20.92; IR (thin film) 2939, 2867, 1721, 1631, 1250, 1024, 970 cm^{-1}; MS (EI) m/z (rel. intensity) 305 (9), 179 (17), 150 (28), 126 (100), 98 (74), 84 (80); HRMS (EI) m/z calcd (M^+) 305.1392, found 305.1396.

4.21. General procedure for the Wadsworth–Horner–Emmons reaction

To a solution of **22** (0.515 mmol) in THF (10 mL) at 0 °C was added NaH (0.515 mmol) and the reaction mixture was stirred at 0 °C for 40 min. The crude reaction mixture was diluted with CH_2Cl_2 and H_2O and the aqueous layer was extracted with CH_2Cl_2 (×5). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated in vacuo. The product was obtained following column chromatography.

4.21.1. 6,7,8,8a-Tetrahydroindolizin-3(5*H*)-one (23a).[4d,29] Yellow oil; R_f=0.3 (100% EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00–6.96 (1H, m), 6.13–6.01 (1H, m), 4.27–4.23 (1H, m), 3.86–3.82 (1H, m), 2.84–2.77 (1H, m), 2.10–2.06 (1H, m), 1.92–1.87 (1H, m), 1.74–1.70 (1H, m), 1.54–1.43 (1H, m), 1.36–1.20 (1H, m), 1.05–0.94 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0, 147.1, 127.5, 61.5, 39.4, 30.8, 25.4, 23.6.

4.21.2. 1,6,7,8,9,9a-Hexahydro-4*H*-quinolizin-4-one (23b).[4d,30] Yellow oil; R_f=0.48 (100% EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.46–6.42 (1H, m), 5.88–5.85 (1H, m), 4.50–4.46 (1H, m), 3.45–3.38 (1H, m), 2.55–2.45 (2H, m), 2.22–2.13 (1H, m), 1.83–1.78 (1H, m), 1.74–1.70 (2H, m), 1.52–1.35 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 138.2, 124.7, 54.9, 43.1, 33.5, 31.2, 24.9, 24.1; IR (thin film) 2934, 2856, 1667, 1613, 1429, 1321, 1272, 1154, 826, 814 cm^{-1}; MS (EI) m/z (rel. intensity) 151 (67), 136 (9), 122 (30), 84 (100), 68 (27); HRMS (EI) m/z calcd (M^+) 151.0997, found 151.0994.

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References and notes

1. For recent reviews on combinatorial chemistry, see: (a) Dolle, R. E. *J. Comb. Chem.* **2001**, *3*, 477–517. (b) Dolle, R. E. *J. Comb. Chem.* **2000**, *2*, 383–433.
2. For recent reviews on solid-phase organic synthesis, see: (a) Krchnák, V.; Holladay, M. W. *Chem. Rev.* **2002**, *102*, 61–91. (b) Lorsbach, B. A.; Kurth, M. J. *Chem. Rev.* **1999**, *99*, 1549–1581. (c) Brown, A. R.; Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. C. *Synlett* **1998**, 817–827. (d) Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. *Tetrahedron* **1996**, *52*, 4527–4554. (e) Nefzi, A.; Ostresh, J. M.; Houghten, R. A. *Chem. Rev.* **1997**, *97*, 449–472.
3. For recent reviews on solution-phase organic synthesis, see: (a) An, H.; Cook, P. D. *Chem. Rev.* **2000**, *100*, 3311–3340. (b) Merritt, A. T. *Comb. Chem. High Throughput Screen.* **1998**, *1*, 57–72.
4. (a) Batey, R. A.; Santhakumar, V.; Yoshina-Ishii, C.; Taylor, S. D. *Tetrahedron Lett.* **1998**, *39*, 6267–6270. (b) Batey, R. A.; Yoshina-Ishii, C.; Taylor, S. D.; Santhakumar, V. *Tetrahedron Lett.* **1999**, *40*, 2669–2672. (c) Batey, R. A.; Shen, M.; Santhakumar, V.; Yoshina-Ishii, C. *Comb. Chem. High Throughput Screen.* **2002**, *5*, 219–232. (d) Grzyb, J. A.; Batey, R. A. *Tetrahedron Lett.* **2003**, *44*, 7485–7488.
5. Staab, K. M.; Bauer, H.; Schneider, K. M. *Azolides in organic synthesis and biochemistry*; Wiley-VCH: Weinheim, 1998.
6. Oakenfull, D. G.; Salvesen, K.; Jencks, W. P. *J. Am. Chem. Soc.* **1971**, *93*, 188–194 and references cited.
7. Guibé-Jampel, E.; Bram, G.; Wakselman, M.; Vilkas, M. *Synth. Commun.* **1973**, *3*, 111–114.
8. Watkins, B. E.; Rapoport, H. *J. Org. Chem.* **1982**, *47*, 4471–4477.
9. (a) Guibé-Jampel, E.; Bram, G.; Wakselman, M.; Vilkas, M. *Bull. Soc. Chim. Fr.* **1973**, 1021–1027. (b) Saha, A. K.; Schultz, P.; Rapoport, H. *J. Am. Chem. Soc.* **1989**, *111*, 4856–4859. (c) Kamijo, T.; Yamamoto, R.; Harada, H.; Iizuka, K. *Chem. Pharm. Bull.* **1982**, *30*, 4242–4244.
10. Zheng, C.; Combs, A. P. *J. Comb. Chem.* **2002**, *4*, 38–43.
11. Batey, R. A.; Yoshina-Ishii, C.; Lough, A. J. *Acta Crystallogr. Sect. C* **1999**, *55*, 615–618.
12. Batey, R. A.; Shen, M.; Lough, A. J. *Org. Lett.* **2002**, *4*, 1411–1414.
13. (a) Hlasta, D. J. *Org. Lett.* **2001**, *3*, 157–159. (b) Deng, Y.; Hlasta, D. J. *Tetrahedron Lett.* **2002**, *43*, 189–192.
14. Ozaki, S. *Chem. Rev.* **1972**, *72*, 457–496.
15. Peterson, U. In *Houben-Weyl, Methoden der Organische Chemie*, *Vol. 4*; Thieme: Stuttgart, 1983; pp 335–367.
16. See for example: Settepani, J. A.; Pettit, G. R. *J. Org. Chem.* **1970**, *35*, 843–844.
17. Katritzky, A. R.; Pleynet, D. P. M.; Yang, B. *J. Org. Chem.* **1997**, *62*, 4155–4158.
18. (a) Adams, P.; Baron, F. A. *Chem. Rev.* **1965**, *65*, 567–602. (b) Mateen, A.; Chapalamadugu, S.; Kaskar, B.; Bhatti, A. R.; Chaudhry, G. R. *Biol. Degrad. Biorem. Toxicol. Chem.* **1994**, 198–233.
19. Greene, T. W.; Wuts, P. G. M. *Protective groups in organic synthesis*, 2nd ed.; Wiley: New York, 1991; pp 315–348.
20. For example see: (a) Babad, H.; Zeiler, A. C. *Chem. Rev.* **1973**, *73*, 75–91. (b) Toda, N.; Tago, K.; Marumoto, S.; Takami, K.; Ori, M.; Yamada, N.; Koyama, K.; Naruto, S.; Abe, K.; Yamazaki, R.; Hara, T.; Aoyagi, A.; Abe, Y.; Kaneko, T.; Kogen, H. *Bioorg. Med. Chem.* **2003**, *11*, 1935–1955. (c) Kamila, S.; Mukherjee, C.; Mondal, S. S.; De, A. *Tetrahedron* **2003**, *59*, 1339–1348. (d) Mongin, F.; Trécourt, F.; Gervais, B.; Mongin, O.; Quéguiner, G. *J. Org. Chem.* **2002**, *67*, 3272–3276. (e) Tarzia, G.; Duranti, A.; Tontini, A.; Piersanti, G.; Mor, M.; Rivara, S.; Plazzi, P. V.; Park, C.; Kathuria, S.; Piomelli, D. *J. Med. Chem.* **2003**, *46*, 2352–2360.
21. For example see: (a) Salvatore, R. N.; Shin, S. I.; Nagle, A. S.; Jung, K. W. *J. Org. Chem.* **2001**, *66*, 1035–1037. (b) Inesi, A.; Mucciante, V.; Rossi, L. *J. Org. Chem.* **1998**, *63*, 1337–1338. (c) Mulla, S. A. R.; Gupte, S. P.; Chaudhari, R. V. *J. Mol. Catal.* **1991**, *67*, L7–L10. (d) Ohta, A.; Inagawa, Y.; Mitsugi, C. *J. Heterocycl. Chem.* **1985**, *22*, 1643–1646. (e) Raucher, S.; Jones, D. S. *Synth. Commun.* **1985**, *15*, 1025–1031.
22. (a) Wuest, H. M.; Sakal, E. H. *J. Am. Chem. Soc.* **1951**, *73*, 1210–1216. (b) Weijlard, J.; Tishler, M. *J. Am. Chem. Soc.* **1951**, *73*, 1497–1500. (c) Johnson, D. E.; DeLane, J. C.; Wisted, E. E. *J. Org. Chem.* **1987**, *52*, 3688–3690. (d) Marr, F.; Hoppe, D. *Org. Lett.* **2002**, *4*, 4217–4220.
23. (a) Overberger, C. G.; Ringsdorf, H.; Weinshenker, N. *J. Org. Chem.* **1962**, *27*, 4331–4337. (b) Marchand-Brynaert, J.; Laub, R.; De Meester, F.; Frêre, J.-M. *Eur. J. Med. Chem.* **1988**, *23*, 561–571.
24. (a) Newman, M. S.; Karnes, H. A. *J. Org. Chem.* **1966**, *31*, 3980–3984. (b) Kwart, H.; Evans, E. R. *J. Org. Chem.* **1966**, *31*, 410–413. (c) Nishide, K.; Miyamoto, T.; Kumar, K.; Ohsugi, S.-I.; Node, M. *Tetrahedron Lett.* **2002**, *43*, 8569–8573.
25. For examples of some coupling methods see: (a) Sheehan, J. C.; Hess, G. P. *J. Am. Chem. Soc.* **1955**, *77*, 1067–1068. (b) Padwa, A.; Reger, T. S. *Can. J. Chem.* **2000**, *78*, 749–756. (c) Bald, E.; Saigo, K.; Mukaiyama, T. *Chem. Lett.* **1975**, 1163–1166. (d) Frérot, E.; Coste, J.; Pantaloni, A.; Dufour, M.-N.; Jouin, P. *Tetrahedron* **1991**, *47*, 259–270. (e) Coste, J.; Le-Nguyen, D.; Castro, B. *Tetrahedron Lett.* **1990**, *31*, 205–208. (f) Cabré, J.; Palomo, A. L. *Synthesis* **1984**, 413–417. (g) Masaguer, C. F.; Raviña, E.; Fontenla, J. A.; Brea, J.; Tristán, H.; Loza, M. I. *Eur. J. Med. Chem.* **2000**, *35*, 83–95.
26. Blagbrough, I. S.; Mackenzie, N. E.; Ortiz, C.; Scott, A. I. *Tetrahedron Lett.* **1986**, *27*, 1251–1254.
27. (a) Katritzky, A. R.; Cai, X.; Rogovoy, B. V. *J. Comb. Chem.* **2003**, *5*, 392–399. (b) Brewer, M. D.; Dorgan, R. J. J.; Manger, B. R.; Mamalis, P.; Webster, R. A. B. *J. Med. Chem.* **1987**, *30*, 1848–1853. (c) Yoon, J. W.; Choi, H.-Y.; Lee, H. J.; Ryu, C. H.; Park, H.-G.; Suh, Y.-G.; Oh, U.; Jeong, Y. S.; Choi, J. K.; Park, Y.-H.; Kim, H.-D. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1549–1552.
28. Goud, P. M.; Venkatachalam, T. K.; Uckun, F. M. *Synth. Commun.* **2003**, *33*, 1185–1193.
29. (a) Rasmussen, M. O.; Delair, P.; Greene, A. E. *J. Org. Chem.* **2001**, *66*, 5438–5443. (b) Lim, S. H.; Ma, S.; Beak, P. *J. Org. Chem.* **2001**, *66*, 9056–9062.
30. Takatsu, N.; Ohmiya, S.; Otomasu, H. *Chem. Pharm. Bull.* **1987**, *35*, 891–894.
31. Staab, H. A.; Benz, W. *Angew. Chem., Int. Ed. Engl.* **1961**, *73*, 66.
32. Groutas, W. C.; Abrams, W. R.; Theodorakis, M. C.; Kasper, A. M.; Rude, S. A.; Badger, R. C.; Ocain, T. D.; Miller, K. E.; Moi, M. K.; Brubaker, M. J.; Davis, K. S.; Zandler, M. E. *J. Med. Chem.* **1985**, *28*, 204–209.
33. Iguchi, S.; Iwamura, H.; Nishizaki, M.; Hayashi, A.; Senokuchi, K.; Kobayashi, K.; Sakaki, K.; Hachiya, K.; Ichioka, Y.; Kawamura, M. *Chem. Pharm. Bull.* **1992**, *40*, 1462–1469.
34. Mazza, M.; Montanari, L.; Pavanetto, F. *Farmaco Ed. Sci.* **1977**, *32*, 270–277.

35. Arya, V. P.; David, J.; Grewal, R. S. *Indian J. Chem. Sect. B* **1977**, 635–640.
36. Tokitoh, N.; Okazaki, R. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 3291–3297.
37. (a) Löcsei, V.; Facsko, O.; Chirilâ, T. *J. Prakt. Chem.* **1983**, *325*, 49–54. (b) Ben-Ishai, D.; Berger, A. *J. Org. Chem.* **1952**, *17*, 1564–1570.
38. Chen, C.-C.; Chen, S.-T.; Chuang, T.-H.; Fang, J.-M. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2217–2221.
39. Ito, K.; Iida, T.; Fujita, T.; Tsuji, S. *Synthesis* **1981**, 287.
40. Douat, C.; Heitz, A.; Martinez, J.; Fehrentz, J.-A. *Tetrahedron Lett.* **2000**, *41*, 37–40.
41. Raghuram, T.; Vijaysaradhi, S.; Singh, I.; Singh, J. *Synth. Commun.* **1999**, *29*, 3215–3219.
42. Brunette, S. R.; Lipton, M. A. *J. Org. Chem.* **2000**, *65*, 5114–5119.
43. Turbanti, L.; Cerbai, G.; Bramanti, G.; Bianchini, P.; Tellini, N. *Chim. Ther.* **1967**, *2*, 354–365.
44. Janecki, T.; Bodalski, R.; Wieczorek, M.; Bujacz, G. *Tetrahedron* **1995**, *51*, 1721–1740.