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Synthetic Methods

The Urea Renaissance

*Nicole Volz and Jonathan Clayden**

amination · hydrogen bonds · palladium · rearrangement · urea

Over the last decade the use of urea derivatives as useful reagents, catalysts, and structural features in organic chemistry has increased rapidly. They now find utility as hydrogen-bond donors in organocatalysts and anion transporters, as important scaffolds in supramolecular chemistry, as lithiation directors, amination substrates, and promoters of metalation, and as substrates for novel rearrangement reactions. Highlighted herein is the remarkably rapid and recent development of the chemistry of ureas, which for many years had been considered unreactive, intractable, and of little value.

1. Introduction

The synthesis of urea by Wöhler in 1828[1a] marks the foundation of the science of synthesis—the beginning of classical organic chemistry. Wöhler's synthesis opened the first direct line of communication between chemistry and biology, thus paving the way for the work of Berthelot, Fischer, and Perkin, and leading to the golden age of natural product synthesis in the 20th century.[1b]

Urea and its derivatives were, however, largely bypassed by the major developments of organic chemistry in the 20th century. With a few exceptions, for example, the urea/hydrogen peroxide complex (UHP),[2] or the cyclic urea cosolvent 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU),[3] ureas rarely featured as tools or targets in organic synthesis. Ureas lacked the natural ubiquity of amides, the reactivity of esters, and the versatility of carbamates, and therefore languished on the dark fringes of the carbonyl functional world. They gained a reputation for unreactivity and intractability, and as a functional class were largely ignored. And within peptide chemistry they remained firmly typecast as waste products generated from diimide coupling reagents.

But since the beginning of the 21st century, ureas have staged a remarkable re-emergence in several fields of chemistry. The structural properties of ureas are now regularly exploited as scaffolds in supramolecular chemistry, and their ability to act as powerful hydrogen-bond donors has earned them a role in foldamer structures, ion transporters, and (along with their thiourea cousins) as functional components of important organocatalysts. In the last five to ten years new and unique urea reactivity has been uncovered too: ureas are now used as amination substrates, promoters of metalation, or as substrates for remarkable rearrangement reactions, and their reputation for being unreactive is being overturned by the discovery of mild solvolysis methods for their cleavage.

This Minireview summarizes these developments by taking examples to illustrate each of the new themes associated with this renaissance of urea chemistry—the simple neoclassicism of ureas as lithiation directors; the baroque designs of urea-based catalysts and supramolecular structures; the postmodern unexpected increase in reactivity that is characteristic of more hindered ureas, and the electrophilicity disguised within electron-rich aromatic ureas.

[*] Dr. N. Volz, Prof. J. Clayden
School of Chemistry, University of Manchester
Oxford Road, Manchester, M13 9PL (United Kingdom)
E-mail: j.p.clayden@man.ac.uk

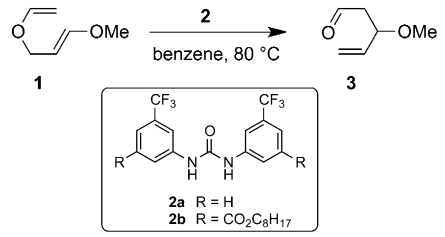
2. Conformational Properties of Ureas

The planarity of the urea linkage leads to the well-defined organization of its four N substituents, and the directionality of these substituents has been exploited in a number of ways.

2.1. Ureas as Hydrogen-Bond Donors

The two parallel NH bonds of ureas (RNHCONHR′) are perfectly suited for coordination to the two lone pairs of a carbonyl group. This ability to bind carbonyl groups selectively in a well-defined orientation makes ureas ideal components of catalyst structures.

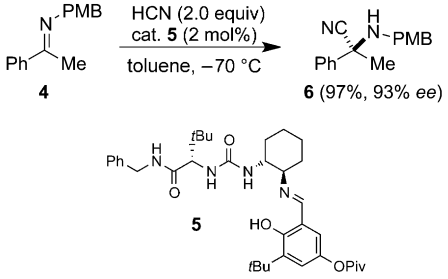
The basis for the development of urea-based organocatalysts was provided by the observation of Etter and Panunto in 1988: the *N*,*N*′-diarylurea **2a** (R = H; Scheme 1) co-crystallized with ketones through the donation of two hydrogen bonds to the carbonyl Lewis base.[4] Only a few years later Curran and Kuo reported the first example of urea catalysis, that is, the diarylurea **2b** increased both the yield



Scheme 1. Diarylurea catalysis of the Claisen rearrangement.

and the diastereoselectivity of the allylation of cyclic α-sulfinyl radicals with allyltributylstannane.[5] In 1995, the same group found that catalytic amounts of this urea promoted the Claisen rearrangement.[6]

During the last few years, the importance of ureas as components in hydrogen-bonding organocatalysts has increased rapidly.[7] Several groups have pushed forward the development of chiral ureas for asymmetric organocatalysis. For example Jacobsen et al. developed an efficient and highly enantioselective chiral bifunctional urea catalyst (**5**; Scheme 2) for the asymmetric Strecker reaction.[8,9] This

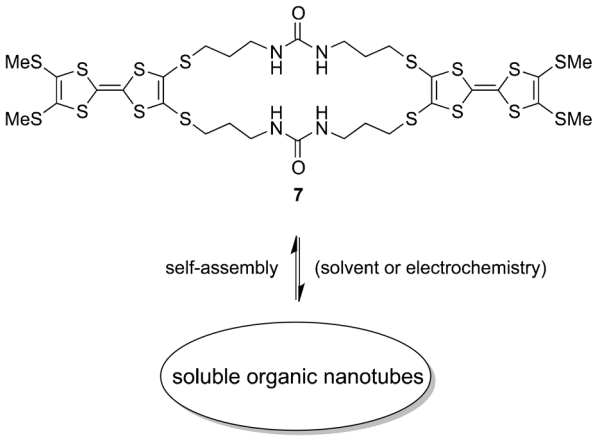


Scheme 2. Urea-catalyzed asymmetric Strecker reactions. PMB = *para*-methoxybenzyl.

method allows the preparation of optically pure quaternary amino acids and is the first example for a catalytic enantioselective addition of HCN to ketimines.

In 2002 Schreiner and Wittkopp reported that the simple 1,3-bis(3,5-bis(trifluoromethyl)phenyl)urea acts as a catalyst for Diels–Alder reactions.[10] This was an attractive starting point for further catalyst design because of the many advantages of thioureas; for example, their higher acidity, higher solubility, and easier preparation.

The parallel hydrogen bonding in ureas makes them well suited as key linking components of supramolecular assemblages. Besides the use of ureas as hydrogen-bonding organocatalysts, ureas were recently investigated as new materials for optoelectronic applications through self-assembly. Ortí, Martín, and co-workers obtained soluble self-assembled nanotubes with electron-donor di(methylthio)tetrathiafulvalene groups by employing a combination of urea–urea hydrogen bonds and π–π stacking interactions.[11] The self-assembly of macrocycle **7** into soluble organic nanotubes (Scheme 3) is solvent and redox controlled, which makes them good candidates for their incorporation into optoelectronic devices.



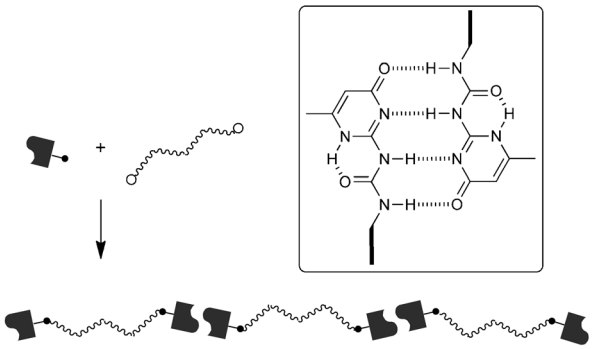
Scheme 3. Self-assembly of the bisurea macrocycle **7**.

N,*N*′-Disubstituted ureas are often used in the construction of hydrogen-bonded supramolecular polymers,[12] organogelators,[13] foldamers,[14] and novel crystalline frameworks.[15] One example is the family of telechelic polymers developed by Meijers et al.[16] Those polymers are functionalized with ureidopyrimidinone units that can dimerize because of the formation of quadruple hydrogen bonding without formation of crystalline domains (Scheme 4). Hence, polymer networks with thermodynamically controlled architectures can be obtained for use in, for example, coatings and hot melts, where a reversible, strongly temperature-dependent rheology is highly advantageous.

Another area where hydrogen bonds play an important structural role is in anion recognition, and ureas have been

Jonathan Clayden was born in Uganda in 1968. In 1992 he completed a PhD at the University of Cambridge with Dr. Stuart Warren. After postdoctoral work with Prof. Marc Julia at the École Normale Supérieure, he moved in 1994 to Manchester and in 2001 was promoted to a chair in organic chemistry. His research interests include synthesis and stereochemistry, with a focus on conformation: asymmetric synthesis, atropisomerism, organolithium chemistry, dearomatization, conformational control, and remote stereocontrol.

Nicole Volz was born in 1983 in Neuenbürg, Germany. She graduated from the University of Karlsruhe (TH) in 2007. Under the guidance of Prof. Dr. S. Bräse she earned her PhD in chemistry from the Karlsruhe Institute of Technology (KIT) in 2010. She is now conducting postdoctoral studies in the group of Prof. Dr. J. Clayden at the University of Manchester.



Scheme 4. Schematic drawing of functionalization of telechelic polymers with quadruple hydrogen-ureidopyrimidinone units.

widely studied as artificial host molecules (receptors).[17] They are attractive building blocks for designing those receptors because they possess two NH fragments: They can bind either a single acceptor atom (e.g. halides), thus forming a six-membered chelate ring, or two adjacent oxygen atoms of an oxoanion, thus forming an eight-membered chelate ring. A great number of cyclic and acyclic receptors that contain two or more urea moieties have been synthesized. For example Davis et al. recently reported the diaxial diureido decalin **8** (Figure 1) having four hydrogen-bond donors;[18] **8** is a synthetic anionophore of potential use in the treatment of defects in natural anion channels.

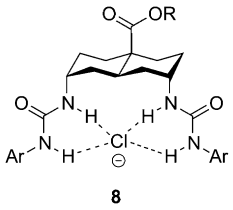


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Figure 1. Diaxial diureido decalin **8** as an anion transporter.

2.2. Conformation of Substituted Ureas

Ureas carrying aromatic substituents have long been known to adopt a conformation in which the aryl rings adopt a *cis* conformation.[19] Shudo and co-workers,[20] and later Clayden et al.[21] exploited this preference in the design of the helical oligourea foldamers **9** (Figure 2) whose helicity can be controlled over one or two turns of the helix in solution,[22] thus allowing relayed remote stereochemical control.[23] Slow rotation in a *N*,*N*′-diaryl urea[24] generates atropisomeric structures.[25] The assumption that π-stacking interactions govern the conformation in *N*,*N*′-diaryl ureas has been probed by DFT calculations.[26]

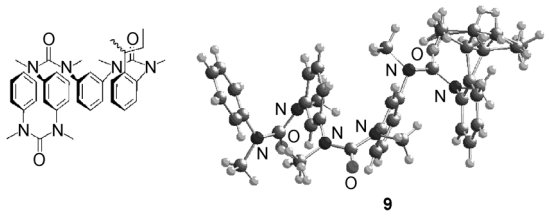

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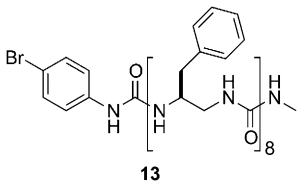
Figure 2. A stacked helical oligourea foldamer.

Conformational preferences in substituted ureas have also been exploited by Baell et al. who made use of the acylureas **10** as masked cisoid secondary amides (Scheme 5). The urea substituent facilitates the formation of the macrocyclic lactams **11**, thus promoting rapid and high yielding ring-closing metathesis, and it can be easily removed.[27]

N,*N*′-Linked oligoureas with proteinogenic side chains (**13**, Figure 3) are mimics of peptides whose preferred helical conformation results from intramolecular hydrogen bonds.[28,29] Those foldamers are unique scaffolds for potential use in a range of biological and biomedical applications.[30]

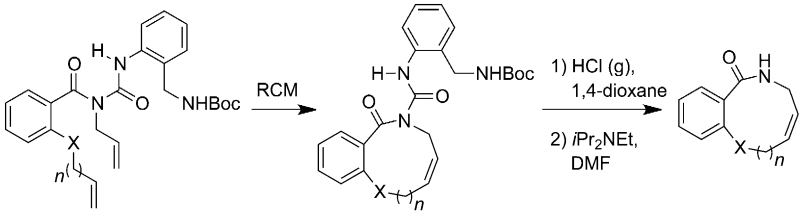


13

Figure 3. *N*,*N*′-linked oligourea (**13**) forming a helix.[29]

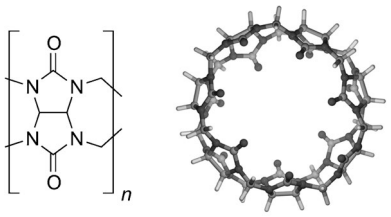
Glycoluril and formaldehyde condense under acidic conditions to deliver the cucurbit[*n*]urils **14** (Figure 4), which consist of *n* glycoluril units that are joined to the next one by two methylene bridges to form a closed band in which the urea oxygen atoms are tilted inwards, thus forming a partly enclosed cavity. These compounds are particularly interesting because they are capable of binding other molecules within these cavities. The first preparation was reported by Behrend et al. in the beginning of the 20th century,[31] but their structure was not published until 1981;[32] subsequently the cucurbiturils have been isolated in various ring sizes.[33]

The host–guest properties of cucurbiturils have been explored for drug-delivery vehicles. For example cucurbit-[7]uril (**14a**) forms an inclusion compound with oxaliplatin, an important drug in the treatment of cancer.[34] Cucurbit-



10 **11** **12**

Scheme 5. Acylurea-induced ring-closing metathesis (RCM) and release of auxiliary. Boc = *tert*-butoxycarbonyl, DMF = *N*,*N*′-dimethylformamide.



14 14a

Figure 4. Cucurbit[*n*]urils. Cucurbit[*n*]uril (**14**) and cucurbit[7]uril (**14a**).

[7]uril (**14a**) can also take up guest molecules like Thioflavin T,[35] an important fluorescent dye molecule in medicinal chemistry that is used for diagnosing neurodegenerative diseases such as Alzheimer's and Parkinson's.[36] It can be taken up by, or released from **14a** through the addition of metal cations to the solution.

3. Coordinative Properties of the Urea Carbonyl Group

The urea carbonyl oxygen atom is remarkably electron rich, a feature that has been exploited in the use of the cyclic urea DMPU as a metal-coordinating cosolvent, particularly in organolithium (and organocopper)[37] chemistry. The metal-coordinating properties of the urea oxygen atom also mean that ureas turn out to be excellent promoters of metalation chemistry, both with main-group and transition metals.[38]

3.1. Palladium-Directed Carbonylation

Ureas are highly efficient directing groups for palladium-catalyzed *ortho* carbonylation at room temperature (see **18** and **19**; Scheme 6).[39] The reaction proceeds by a urea-directed C–H insertion into **15** to give the reactive Pd–Ar complex **16**, which also shows reactivity towards a range of additional coupling partners and reagents (Scheme 6).

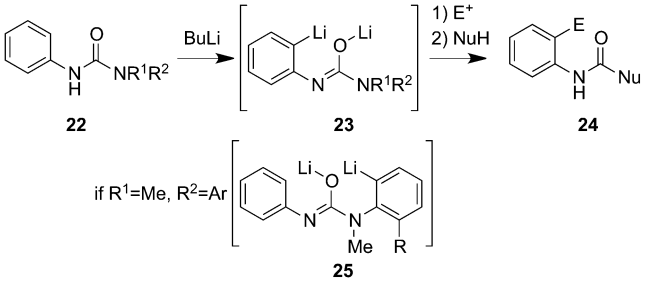
The related Pd^{II}-catalyzed 1,2-carboamination reaction of dienes, involving an *ortho* C–H insertion/carbopalladation/cyclization sequence, enabled the generation of functionalized indolines **17** from readily available *N*-aryl ureas in a single step.[40]

3.2. Directed ortho and Lateral Metalation

Directed metalation is a powerful way of functionalizing aromatic systems regioselectively.[41] Ureas are potent metalation directing groups as a result of their electron-rich carbonyl group and electron-deficient nitrogen atoms; however, until recently[42] they remained largely unused in the regioselective synthesis of aromatic compounds.

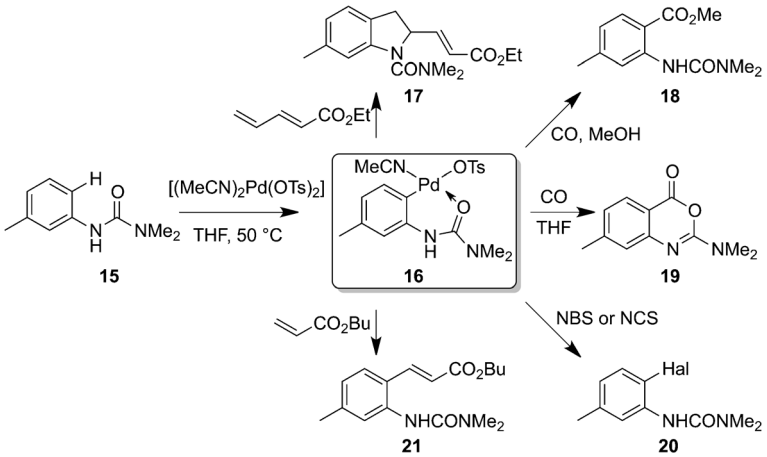
Double lithiation of highly hindered *N*,*N*-dialkyl-*N*′-aryl ureas allows *ortho* functionalization of aniline derivatives.[43] Hindered ureas in particular show a surprisingly facile tendency to eliminate an amino group (see below), and therefore exhibit isocyanate-like reactivity, thus allowing a range of *ortho*-functionalized aniline derivatives to be made.

In the double lithiation of unsymmetrical *N*,*N*′-diarylureas (**22**→**23**; Scheme 7),[44] the presence of an *N*-alkyl group (**25**) is sufficient to direct the regioselectivity of the *ortho* lithiation to the ring adjacent to the alkylated nitrogen atom, irrespective of the substitution pattern of the rings. Lateral lithiation of benzylic sites adjacent to a urea is preferred to *ortho* lithiation (Scheme 8),[45] and double lithiation of *N*′-aryl-*N*,*N*-dimethyl ureas[46] has been used to make several classes of products,[47] including the one-pot synthesis of substituted



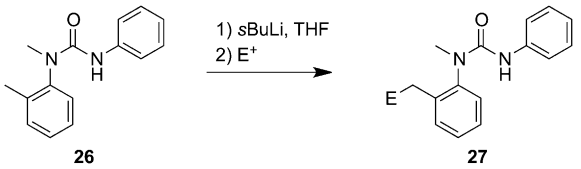
22 23 24 25

Scheme 7. Double lithiation of an *N*,*N*′-dialkyl-*N*′-aryl urea **22**.



15 16 17 18 19 20 21

Scheme 6. Reactivity of Pd^{II} complex **16**. Ts = 4-toluenesulfonyl.



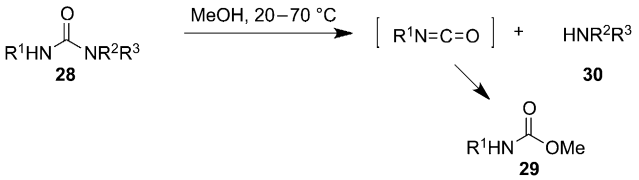
Scheme 8. Efficient lateral lithiation of urea **26**. THF = tetrahydrofuran.

isoindolin-1-ones[48] and the synthesis of tetrahydroisoquinolines[49] and isatins.[50,51]

4. New Reactivity from Ureas

4.1. Solvolysis of Hindered Ureas

Ureas have not enjoyed the general utility of carbamates as protecting groups because of the perception that they are unreactive towards acids, bases, and nucleophiles. However, in 2008 and 2009 Clayden and Hennecke[52] and Lloyd-Jones, Booker-Milburn, and co-workers[53] reported the instability of the trisubstituted ureas **28** (Scheme 9), especially hindered ones, towards mild solvolysis conditions. The products of the



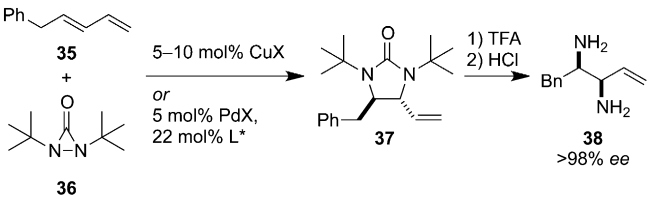
Scheme 9. Solvolysis of ureas under neutral conditions.

attack by a wide range of O, N, and S nucleophiles onto the urea may be obtained, thus providing both a means of deprotection where the urea has been used as a protecting group, and of transformation of the products where other reactivity (e.g. ability to direct metalation or rearrangement) has been exploited.

4.2. Palladium-Directed Amination with Ureas

The catalytic asymmetric diamination of conjugated dienes and trienes[54] exploits the reactivity of an *N*,*N*′-disubstituted urea. In 2005 Lloyd-Jones, Booker-Milburn, and Bar reported the first palladium-catalyzed intermolecular 1,2-diamination of the diene **32** (Scheme 10),[54a] which proceeded in good to excellent yield, with greater than 95% regioselectivity for diamination at the least-substituted alkene terminus (**33** versus **34**).

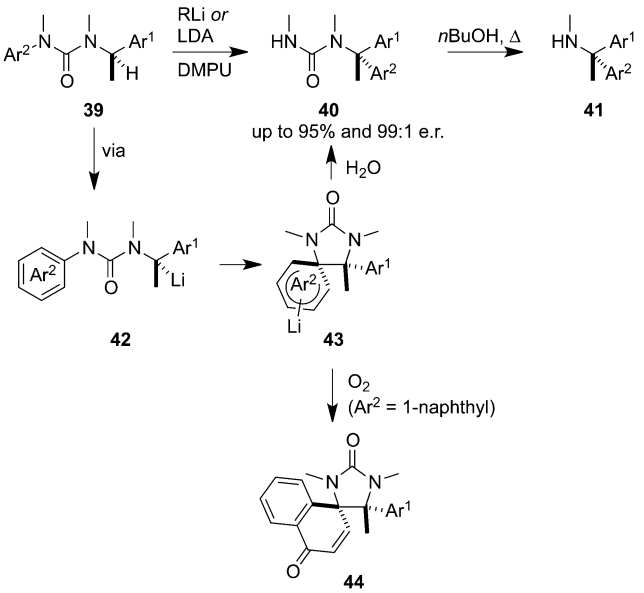
Shi et al. developed a reaction of the diene **35** with di-*tert*-butyldiaziridinone (**36**) as a nitrogen source and different catalysts to give the diamination product **37** in good yield with high regio-, diastereo-, and enantioselectivity (Scheme 11).[54b–f] Those products are potentially valuable intermediates for the synthesis of various optically active compounds such as the diamine **38** or 2,3-diamino acids.



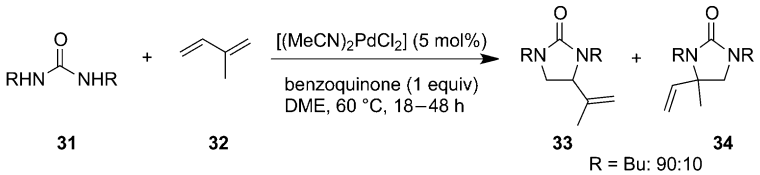
Scheme 11. Catalytic asymmetric diamination of conjugated diene **35**. Bn = benzyl, TFA = trifluoroacetic acid.

4.3. Electrophilicity of Aryl and Vinyl Ureas

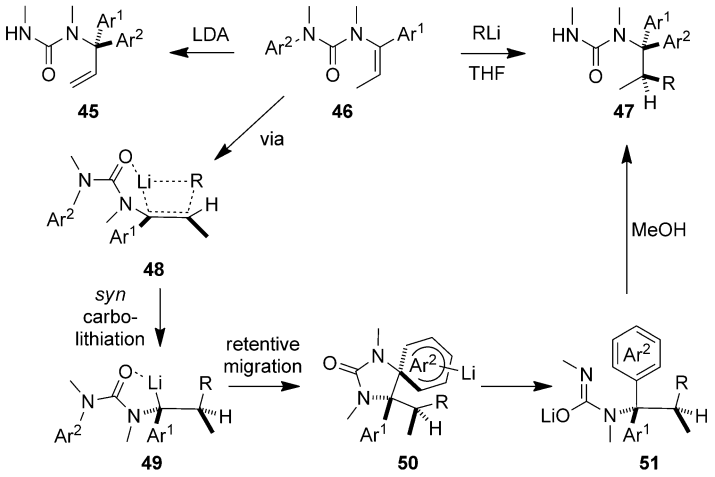
The benzylic deprotonation of the *N*-benzyl-*N*′-aryl ureas **39** (Scheme 12) promotes an unexpected migration of Ar^2 from the nitrogen to carbon atom, thus yielding the rear-



Scheme 12. N-to-C aryl migration in lithiated *N*-benzyl-*N*′-aryl ureas.



Scheme 10. Pd^{II}-catalyzed diamination of isoprene with *N*,*N*′-dialkyl ureas. DME = dimethyl ether.



Scheme 13. N-to-C aryl migration (left) and carbolithiation/rearrangement (right) of vinyl ureas **46**. LDA = lithium diisopropylamine.

ranged diphenylmethylureas **40**.[55] This reaction, which bears similarities to the Truce–Smiles rearrangement, lay unexploited until noted again in 2007 by Clayden et al., who showed that the use of the enantiomerically pure starting material **39** led to the rearranged urea **40** with complete retention of configuration.[56] After urea cleavage, the otherwise inaccessible enantiomerically pure tertiary substituted amines[57] **41** can be obtained. The reaction is remarkably general—it proceeds by nucleophilic aromatic substitution by the benzyllithium onto Ar^2, but Ar^2 can be electron poor or electron rich; even 3,4-dimethoxy-substituted rings undergo successful migration. The stereospecificity of the reaction is presumably a consequence of the configurational stability of the intermediate dipole-stabilized organolithium **42**.[58] In the case of a naphthyl ring migrating, oxidative conditions return the dearomatized spirocycle **44**—evidence that rearrangement proceeds through the dearomatized intermediate **43** (Scheme 12). X-ray crystallography confirmed the absolute configuration of **43** and proved that the rearrangement proceeded with retention of stereochemistry, rather than inversion.

The rearrangement of lithiated *N*-allyl and *N*-vinyl ureas (**46**) is also successful (Scheme 13).[59] The enantioenriched rearrangement products **45** can be obtained by replacing LDA with a chiral lithium amide, which gives stereoselectively, an allyllithium onto which the Ar^2 ring migrates. Using alkyllithium bases instead of LDA results in stereospecific carbolithiation of the vinyl urea **46** instead of deprotonation.[60] The addition to the alkene (see **48** and **49**) is stereospecific and regioselective with the normally nucleophilic β-carbon atom of the *N*-carbamoyl enamine acting as the electrophilic center. Carbolithiation is followed by stereospecific rearrangement of the resulting benzyllithium in a sequence involving two nucleophilic attacks of an organolithium on an electron-rich π system (see **50** and **51**). It is proposed that the reaction proceeds by umpolung carbolithiation of **48** (Scheme 13) to give the substituted benzyllithium **49**, which is configurationally stable on the time scale of the reaction. In general, however, the benzyllithium **49** undergoes N→C aryl migration with retention by attack of the organolithium center on the *N*-aryl ring Ar^2 (**50**), thus transferring Ar^2 to the position α to N and yielding the lithiourea **51** and hence **47** upon protonation.

Many of these new rearrangements make use of the vinyl urea functional group—a class of acylated enamines[61] that has rarely been exploited until now. The vinyl ureas may be made from their parent imines, or by rearrangement of the isomeric allylic ureas.[59a] Both *N*-vinyl and *N*-aryl ureas display usual electrophilic character towards organolithium reagents, a property which can be ascribed to the combination of the electron-rich lithium-coordinating C=O group and the unique properties of the electron-deficient urea nitrogen atom bonded to the reactive π system.

5. Conclusion

The structural features of amides have been exploited by biology for billions of years; carbamates have been invaluable protecting groups for the last 100 years. But only in the few years since the beginning of this century have the diverse and versatile structural properties of ureas come to the fore. The chemistry described in this Minireview highlights some of the features which have, after nearly two centuries, brought ureas back to the center of synthetic developments. This most classical of functional groups has at last emerged from the dark ages and is undergoing an exciting rebirth.

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