Cell Reports
Physical Science

CellPress
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Review

Flourishing reactivities of isocyanates and isothiocyanates using group 13 elements

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SUMMARY

Due to the upswing in interest in the development of efficient hydroelementation reactions to construct C–heteroatom bonds either stoichiometrically or catalytically, the activation of isocyanates and isothiocyanates has received recent attention. The activation and derivatization of isocyanates and isothiocyanates using earth-abundant and inexpensive group 13 main-group compounds have lately been observed more frequently. In this review, we aim to highlight the activation of the C=N vs. C=O and C=S bonds, the scope of cycloaddition reactions of iso(thio)cyanates with group 13 compounds, and recent findings using frustrated Lewis pairs (FLPs). In addition, the hydroboration and hydroamination reactions of these substrates are also discussed to formulate synthetically important urea/amide or thioamide derivatives.

INTRODUCTION

The distinct features of transition metals have led to their diverse reactivity in homogeneous and heterogeneous catalysis by possessing valence d-orbitals. This makes them able to readily activate metal-bound ligands through synergic bonding and back-bonding effects.[1] Due to the increasing emphasis on the reduction of sustainability and toxicity of some transition metal catalysts, a need has arisen for greener and complementary alternatives for catalysis by avoiding the high energetically accessible oxidative additions and reductive eliminations seen in traditional catalytic cycles.[2] Despite the inaccessibility of the valence d-orbitals for bonding, the main-group elements have started presenting their potential toward versatile reactivity more commonly associated with transition metals. Among them, the group 13 elements have been investigated for the discovery of new chemistry as efficient organometallic compounds for stoichiometric reagents as well as single-site catalysts for a large range of organic transformations featured both in academia and industry.[3] Along with the widespread use of group 13 compounds for stoichiometric organic transformations,[4–6] mainly functionalization of unsaturated compounds, they are also widely applied in frustrated Lewis pair (FLP) chemistry, including small-molecule activation, and C–H insertion reactions.[7–12]

In recent years, the construction of amide and thioamide bonds,[13] one of the fundamental building blocks in organic chemistry, has received tremendous attention in parallel synthesis and combinatorial chemistry due to their widespread presence in natural products, peptides, and biologically active compounds along with several applications in the agrochemical, pharmaceutical, and polymer industries.[14,15] Despite amides and thioamides being quite sensitive to various conditions and known to be notoriously toxic, their importance has steadily increased over the past decades because they are unavoidable precursors for urea and

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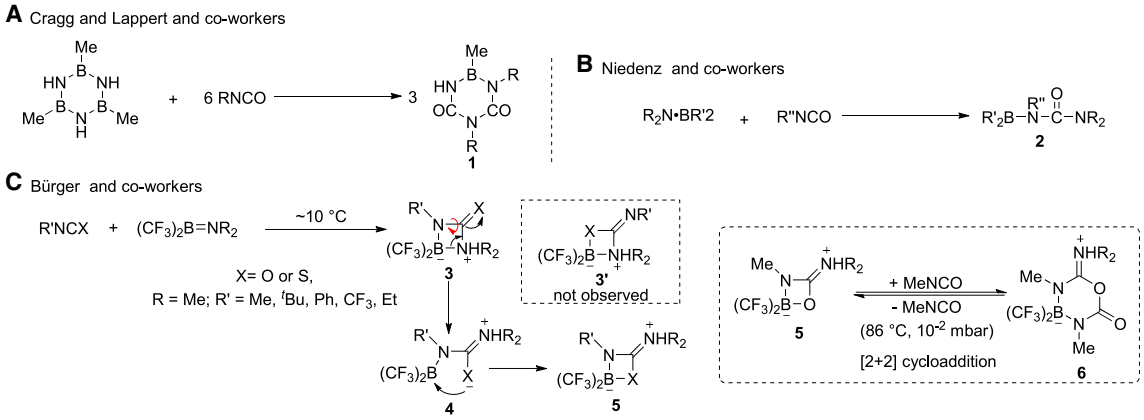
https://doi.org/10.1016/j.xcrp.2023.101745

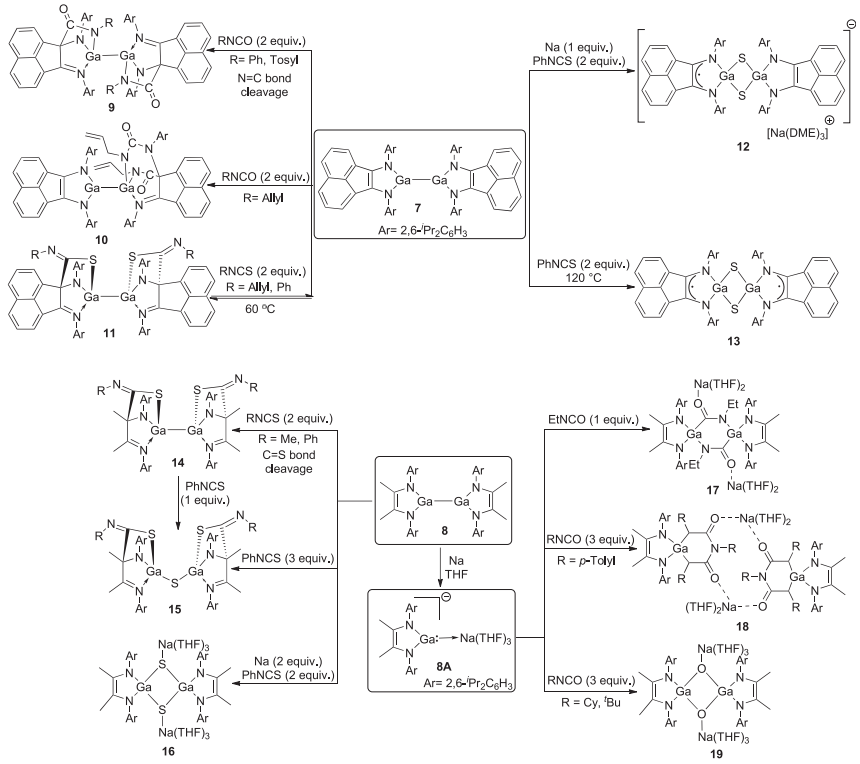


Scheme 1. The synthesis of N-boronated ureas and thioureas versus [2+2] cycloaddition

carbamate linkages found in polyurethanes, drugs, pesticides, etc. In efforts to design more atom-economical, greener, milder, and more selective reactions in the synthetic methods, the previously rarely used group 13 compounds have recently been shown to provide suitable reaction strategies and have revealed new synthetic approaches in synthesis and catalysis. This has opened the door to hitherto unknown reactivities of the isocyanates (R−N=C=O) and isothiocyanates (R−N=C=S) by reducing the difficulties of the synthesis, producing less toxic oxoamides and thioamides. This mini review will highlight the use of several group 13 compounds (boron, aluminum, and gallium) by exploring the remarkable stoichiometric reactions of isocyanates and isothiocyanates involving C=O(S) vs. C=N adduct formation along with the growth of the versatile catalytic transformations using isocyanates and isothiocyanates. Construction of several heterocyclic compounds has been reported using hydroamination of iso(thio)cyanates introducing other main-group compounds as well.[16–18]

REACTIVITY OF ISOCYANATES AND ISOTHIOCYANATES WITH GROUP 13 COMPOUNDS

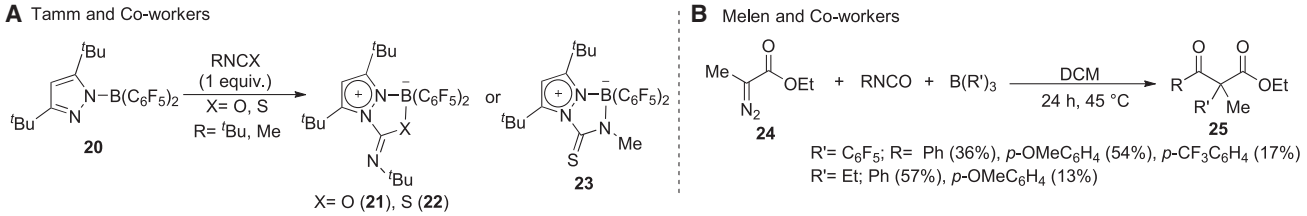
The activation of simple single σ-bonds by main-group elements has made prominent progress in recent years, showing many examples of small-molecule activation and other organic transformation reactions. Even though the cleavage of multiple bonds is less explored, the complete cleavage of an isonitrile bond (^{t}BuNC) promoted by the presence of a diborane has been reported by Asakawa et al.[19] in 2014. The preparation of boron derivatives of isocyanate and isothiocyanate compounds from the corresponding boron halides and the salt of cyanic or thiocyanic acids has been reported as far back as early 1960.[20] The formation of thermally stable polymers from organoboric acid and bifunctional isocyanates can also be postulated through the elimination of carbon dioxide, but there is no report to confirm the results. The reaction of phenyl isocyanate (PhNCO) with boric acid ($B(OH)_3$) in the presence of triethylamine generated trisphenylaminoborane ($(PhNH)_3B$), whereas with borazines, a new cyclic compound (**1**) was formed through the cleavage of the B–N ring of the borazine, generating a B/N/C heterocyclic product with exo-oxygen atoms (Scheme 1A).[21] The treatment of isocyanates with aminoboranes was reported for the formation of *N*-boronated ureas (**2**) by Beyer et al.[20] in 1964 (Scheme 1B), where [2 + 2] cycloaddition was commonly observed earlier under similar conditions. Later, Ansorge et al.[22] demonstrated the exclusive [2+2] cycloaddition of organic isocyanates and isothiocyanates with bis(trifluoromethyl)-boron derivatives



Scheme 2. Reactions of digallanes and gallylene with isocyanates and isothiocyanates

to yield four-membered rings (Scheme 1C). The strong electron-withdrawing effect of the two CF_3 groups at boron stabilizes the four-coordinate over the three-coordinate boron and thus favors ring system **3**, which contains a tetracoordinate boron atom. Here, **3** is formed over the isomer **3'**. In the rearrangement **3**→**5**, a strong C=X double bond and a weak B–N single bond are replaced by a B–X (X = O, S) single bond and a C–NR_2 bond with partial double bond character. The product of a [2+2] cycloaddition reaction was only observed with excess MeNCO, and a six-membered ring (**6**) was isolated from the rearranged cycloadduct **5** of MeNCO (Scheme 1C).

Another group explored the [2+4] and [1+2] cycloaddition reactions of isocyanates and isothiocyanates with digallanes (LGa–GaL, L = 1,2-[(2,6-^{i}Pr$_2$C$_6$H$_3$)NC]$_2$C$_{12}$H$_6$) **7** and **8** and gallylene (L_1Ga:, L_1= (2,6-^{i}Pr$_2$C$_6$H$_3$)N[C(CH$_3$)]$_2$) (**8A**) (Scheme 2).[23,24] Treatment of digallanes **7** and **8** with 2 equiv of RNCO (R = Ph or *p*-tosyl) and RNCS (R = allyl and Ph) at room temperature led to the formation of the [2+4] cycloaddition products (**9**, **11**, and **14**), whereas for allyl isocyanates, the first equivalent added across the dpp-bian ligand (1,2-[(2,6-^{i}Pr$_2$C$_6$H$_3$)NC]$_2$C$_{12}$H$_6$) fragment of **7** and then the second equivalent inserted into the Ga–N(Ar) bond through cleavage of the C=N bond over the comparatively strong C=O bond, generating **10**. The treatment of digallanes **7** and **8** with PhNCS in the presence of Na metal accelerated the unique reductive cleavage of the C=S bond and resulted in simple bis-sulfide-bridged digallium species with Ga_2S_2 core (**12** and **16**), while the same core formation (**13**) was also observed for the reaction between **7** and PhNCS at 120°C. The simple α-diimine ligand-supported digallane **8** reacted in a different manner with isocyanate substrates, where the monomeric gallylene counterpart **8A** reacts with EtNCO to form *N*-hetero-1,4-digallacyclohexane (**17**) with a six-membered $Ga_2C_2N_2$ ring



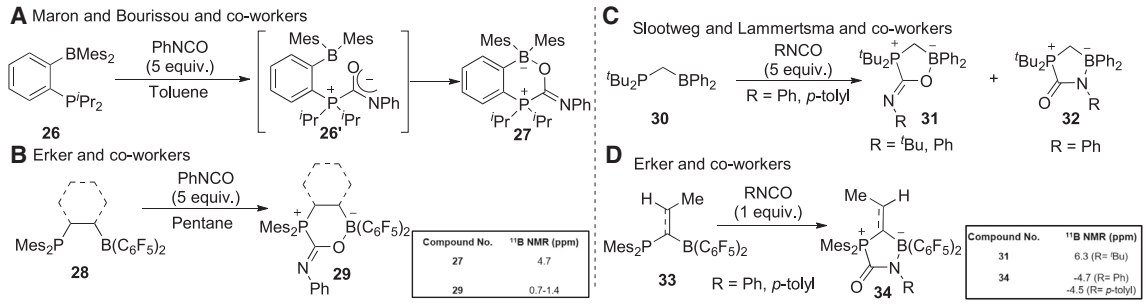
Scheme 3. Boron-ligand cooperative addition reactions of pyrazolylborane with iso(thio)cyanates and the three-component reaction of isocyanates with boranes and α-diazoesters

and to form **18** with *p*-tolyl isocyanate through the cleavage of the N=C bond and loss of 1 equiv of carbon monoxide. Use of the gallylene led to the reductive cleavage of the C=O double bond with bulkier substituents on the isocyanates, such as CyNCO and ^{t}BuNCO, and yielded μ-oxo-bridged digallium compound **19** (Scheme 2).

Theuergarten et al.[25] reported the reaction between the equimolar mixture of bifunctional pyrazolylborane **20** with both isocyanates and isothiocyanates. The boron ligand cooperativity of the pyrazolylborane derivative **20** directed the reactivity to the C=O bond for isocyanates, giving **21**, driven by the strength of the B–O bond. The isothiocyanates, on the other hand, were less selective, reacting with either the C=N or C=S bonds, giving **22** or **23**, depending on the sterics of the substituents on the isothiocyanate (Scheme 3A).[25] The construction of C=O adduct **21** was determined by the ^{13}C NMR spectrum analysis, which displayed a resonance at δ = 139.8 ppm, corresponding to the sp^2 hybridized carbon of the NCO moiety, whereas the presence of a resonance at δ = 146.2 and 171.3 ppm validated the formation of the C=S and C=N products (**22** and **23**) for *tert*-butyl isothiocyanate and methyl isothiocyanate, respectively.

A three-component reaction of electrophilic isocyanates with ethyl α-diazoesters was reported by Kaehler et al.,[26] using functionalized boranes BR'$_3$ (R' = C_6F_5, Et) to prepare a range of β-keto esters and α-aryl substituted β-keto esters under mild conditions (Scheme 3B). The reaction of ethyl α-diazomethylacetate (**24**) with benzonitrile in the presence of 1 equiv of the strong Lewis acid B(C_6F_5)$_3$ formed an imine derivative that subsequently produced an α-aryl-substituted β-keto ester **25** upon acidic workup. In the presence of B(C_6F_5)$_3$, electron-rich aryl isocyanate with a *p*-OMe substituent provided the highest yield of the product **25** in 54% yield, whereas the *p*-CF_3-substituted isocyanate offered only 17% yield. A much lower yield (13%) was obtained when BEt_3 was used under similar reaction conditions with the p-OMe-substituted compound.

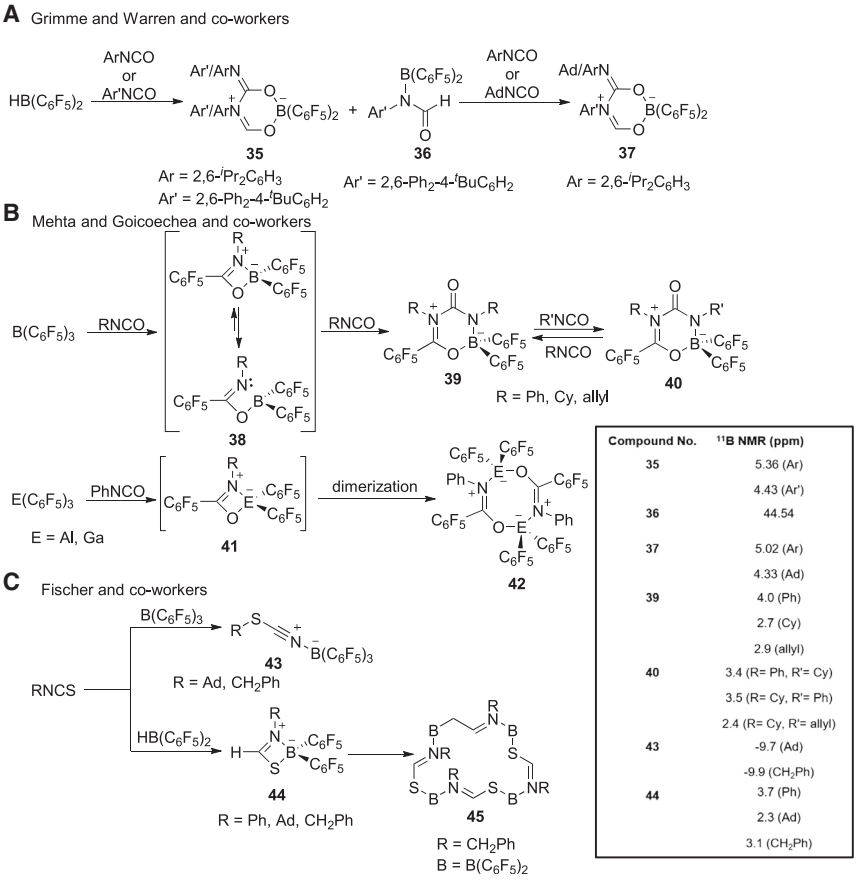
FLPs consisting of a bulky Lewis acid (e.g., BR_3) and a bulky Lewis base (e.g., PR'$_3$) are well explored for small-molecule activation and catalysis. One substrate class that has been investigated for activation studies by FLPs is isocyanates and their heavier sulfur analogs isothiocyanates. Moebs-Sanchez et al.[27] reported the reaction of PhNCO with ambiphilic phosphino-borane ($^{i}Pr_2P$(*o*-C_6H_4)$BMes_2$, **26**), a P/B-based FLP. The addition of the FLP to the C=O bond of the isocyanate led to the formation of product **27** selectively and was further confirmed spectroscopically and structurally (Scheme 4A).[27–29] Erker introduced similar B/P FLPs for the reaction with isocyanates; namely, the ethylene- and cyclohexylene-bridged intramolecular frustrated P/B Lewis pairs (**28**).[28,29] These FLPs activate PhNCO to obtain the similar isocyanate adduct products (**29**) in both cases (Scheme 4B). The ^{11}B NMR spectra showed shifts



Scheme 4. Activation of C=O versus C=N bonds of isocyanates by P/B-based FLPs

at δ = 0.7 and δ = 1.4 ppm, proving the formation of borate-type adducts, which was further confirmed by the ^{13}C NMR spectroscopic resonance at δ = 149.1 and 150.3 ppm for the sp^2 hybridized carbon atom on the imine functional group. In 2012, Bertini et al.[30] introduced an electron-poor geminal P/B-based FLP (**30**) and reported its reaction with ^{t}BuNCO, showing again the formation of the FLP adduct from the addition of the FLP to the C=O bond of the isocyanate leading to **31** (R = ^{t}Bu), and no C=N adduct formation was observed due to the steric repulsion between the ^{t}Bu and Ph groups on N and P atoms, respectively (Scheme 4C). The formation of **31** was confirmed by extensive NMR spectroscopy studies (^{13}C, ^{11}B, ^{31}P) along with single-crystal X-ray analysis with P–C and B–O bond lengths of 1.8341(11) Å and 1.5514(15) Å, respectively. On the other hand, the treatment of PhNCO with the same FLP generates the adducts from the addition of the FLP to either the C=O and C=N bonds of the isocyanate, generating **31** and **32**, respectively, at a 1:1 ratio (Scheme 4C). The compounds were both identified by ^{31}P NMR spectroscopy, showing resonance at δ = 47.2 and δ = 58.5 ppm, respectively.[30] As can be seen from the above reactions, adduct formation of FLPs with the isocyanates typically occurs through addition to the C=O bond, presumably due to the preference of forming a stronger and less hindered B–O bond. However, Stute et al.[31] and Rosorius et al.[32] have managed to demonstrate the selective reactivity of isocyanates with FLPs through reaction with the C=N bond. Here the authors used electronically modified intramolecular geminal frustrated P/B Lewis pair systems (**33**), including the electron-withdrawing C_6F_5 substituents at both the phosphorus and boron centers.[31,32] The addition of phenyl or *p*-tolyl isocyanate with **33** generated solely the C=N adduct (**34**) with 80% yield (Scheme 4D) due to the formation of a stabilized carbocation-like borane adduct as the reactive intermediate. The identity of the product was confirmed by the observation of a ^{13}C NMR spectroscopic resonance at δ = 158.9 ppm and a peak in the infrared (IR) spectrum at 1,700 cm^{-1} corresponding to the carbonyl functional group.[31] Another geminal frustrated P/B pair having the double bond at the backbone of **33** also reacted in a similar fashion and led to the formation of the thermodynamically stable adduct from addition of the FLP to the C=N bond of the isocyanate through the formation of a stable cationic borane–N(R)CO intermediate over the more commonly reported C=O adduct with both PhNCO and *p*-tolyl isocyanate.[32]

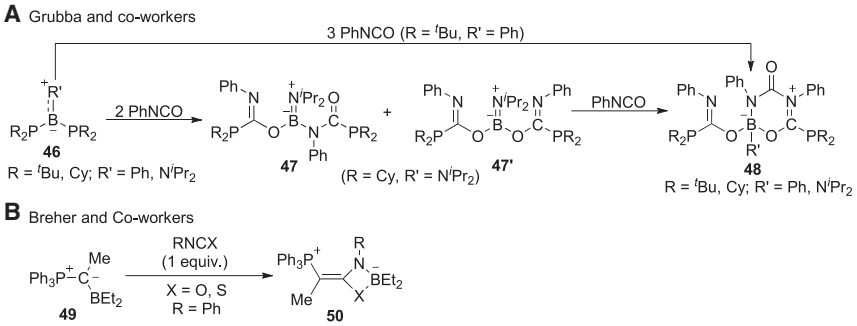
In 2016, McQuilken et al.[33] used Piers' borane ($HB(C_6F_5)_2$) in the reactions with ArNCO (Ar = 2,6-^{i}Pr$_2$C$_6$H$_3$), which led to the six-membered heterocycle **35** (Scheme 5A). A singlet at δ = 7.18 ppm in the ^{1}H NMR spectrum determined the presence of a formamidate proton, while three signals at δ = −136.4, −156.0, and −164.4 ppm in the ^{19}F NMR spectrum confirmed the *ortho*-, *para*-, and *meta*-F atoms, respectively, on the C_6F_5 groups. The addition of bulky



Compound No.	^{11}B NMR (ppm)
35	5.36 (Ar)
	4.43 (Ar')
36	44.54
37	5.02 (Ar)
	4.33 (Ad)
39	4.0 (Ph)
	2.7 (Cy)
	2.9 (allyl)
40	3.4 (R= Ph, R'= Cy)
	3.5 (R= Cy, R'= Ph)
	2.4 (R= Cy, R'= allyl)
43	-9.7 (Ad)
	-9.9 (CH_2Ph)
44	3.7 (Ph)
	2.3 (Ad)
	3.1 (CH_2Ph)

Scheme 5. Reaction of isocyanates and isothiocyanates with $B(C_6F_5)_3$ and $HB(C_6F_5)_2$

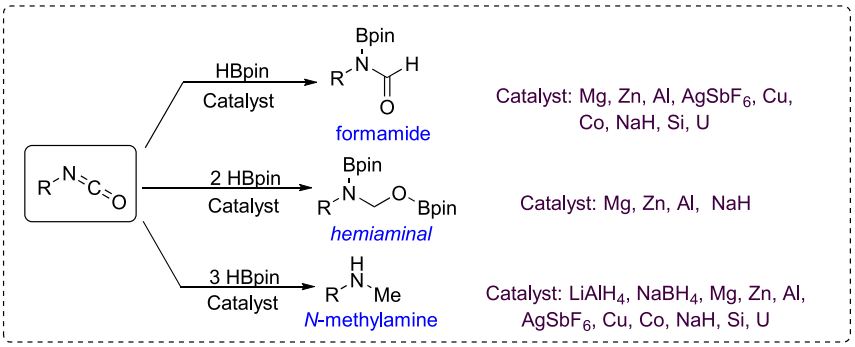
isocyanates (Ar'NCO; Ar' = 2,6-Ph_2-4-^{t}Bu-C_6H_2) with $HB(C_6F_5)_2$ produced an analog of **35** in a mixture with compound **36**. In both of these cases, hydroboration of the C=O bond in the isocyanate occurred (see below). Compound **36** reacted with excess ArNCO (Ar = 2,6-^{i}Pr$_2$C$_6$H$_3$) or 1-adamantyl isocyanate (AdNCO) in fluorobenzene and converted rapidly into compound **37**. ^{1}H NMR spectroscopic shifts at δ = 7.42 and δ = 6.80 ppm proved the formation of the product structure **37** through identifying the formamidate proton. The equivalent $B(C_6F_5)_2$ groups were further validated with ^{19}F NMR spectroscopy analysis.[33] Mehta and Goicoechea[34] demonstrated the formation of a slightly different six-membered heterocycle (**39**) from the reaction of excess isocyanates (RNCO, R = Ph, Cy, allyl) with the strong Lewis acid $B(C_6F_5)_3$. Instead of a hydroboration step of the C=O bond, a carboboration reaction occurred, in which one of the B–C_6F_5 bonds adds across the C=O bond to give the proposed intermediate (**38**). This then reacts with another equivalent of isocyanate through an FLP-type mechanism to form the final six-membered ring. Here, the FLP adds across the C=N bond of the second isocyanate rather than the more common addition to the C=O bond seen above (Scheme 5B).[34] Addition of an excess of a different isocyanate (CyNCO) was found to produce a new six-membered heterocycle **40** by exchange of the trapped isocyanate of **39** for the new one. Those two species exist in equilibrium, and therefore, by addition of a large excess of CyNCO, an almost pure sample of **40** can be obtained, which then can be turned back into **39** by the reverse reaction. When heavier analogs of $E(C_6F_5)_3$ (E = Al, Ga) were used, an



Scheme 6. Reaction of isocyanates and isothiocyanates with diphosphinoboranes and phosphorus ylides

eight-membered heterocyclic ring **42** was generated. It was proposed that an initial 1,2-carboelementation reaction of PhNCO with $E(C_6F_5)_3$ leads to the formation of **41**, which then undergoes a head-to-tail dimerization to afford the eight-membered ring products (Scheme 5B).[34] In 2020, Fischer and Schmidtmann[35] reported other reactivities of $B(C_6F_5)_3$ and $HB(C_6F_5)_2$ with isothiocyanates. The treatment of alkyl-substituted isothiocyanates with $B(C_6F_5)_3$ resulted in a rearrangement reaction of the isothiocyanate to thiocyanate–$B(C_6F_5)_3$ adduct **43**. For adamantyl- and benzyl-substituted isothiocyanates, the reaction proceeded via the coordination of the boron atom to the nitrogen atom of the isothiocyanate and a subsequent 1,3 shift of the alkyl group from nitrogen to sulfur to afford compound **43**. IR stretching frequencies of 2,231 cm^{-1} (R = Ad) and 2,247 cm^{-1} (R = Bn) confirm the formation of a C≡N triple bond within the compounds. No reaction was observed for the phenyl isothiocyanate even at higher temperatures. The reaction of all of the three isothiocyanates with $HB(C_6F_5)_2$, on the other hand, yielded 4-membered B/N/C/S heterocycles **44** through a 1,2-hydroboration similar to that described above by McQuilken et al.[33] (Scheme 5C). When compound **44** had a benzyl substituent, it formed a tetramer yielding a 16-membered B/N/C/S-heterocycle **45** in the solid-state, which was characterized by a single crystal X-ray analysis and ^1H DOSY (Diffusion Ordered Spectroscopy) NMR.[35] The two heterocycles were sensitive to air and moisture and readily decomposed to generate corresponding thioformamides, pentafluorophenylboron acid, and 1,2,3,4,5-pentafluorobenzene.

Recently, Szynkiewicz et al.[36] designed some unique structurally and electronically assorted diphosphinoboranes containing P–B–P bonding, which can be used for the activation of small molecules.[36] Due to the presence of two adjacent P–B bonds, the diphosphinoboranes can act as intramolecular FLPs with two basic sites and one acidic site present within the same molecule. They reported that the diphosphinoborane **46** (R = Ph) reacts with 3 equiv of PhNCO to produce compound **48** with high yields and without the formation of any side products (Scheme 6A). However, with less than 3 equiv of PhNCO, several products were formed. The group has also utilized the less Lewis acidic -N^iPr_2-substituted diphosphinoborane **46** (R = N^iPr_2), which reacted with 2 equiv of PhNCO in toluene at room temperature, giving **47**. The insertion of PhNCO into both the P–B bonds was further confirmed from recorded IR stretching frequencies and NMR chemical shifts. However, single-crystal X-ray analysis confirmed the alternative binding mode of PhNCO, where the first equivalent connected to the boron atom via the oxygen atom and the second equivalent linked to the boron center via its nitrogen atom to form **47** as the major product (Scheme 6A). The other constitutional isomer **47'**, containing a symmetrical



Scheme 7. Stepwise hydroboration of isocyanates using several efficient catalysts

skeleton, where the boron atom is connected to two oxygen atoms, was also formed. This, in the presence of an excess amount of PhNCO, afforded the 6-membered ring **48**. The crystal structure proved the insertion of the PhNCO molecules into the P–B bonds through the PhNC=O fragment, generating two B–O bonds. No rearrangements or further reactions leading to **48** from **47** were reported.

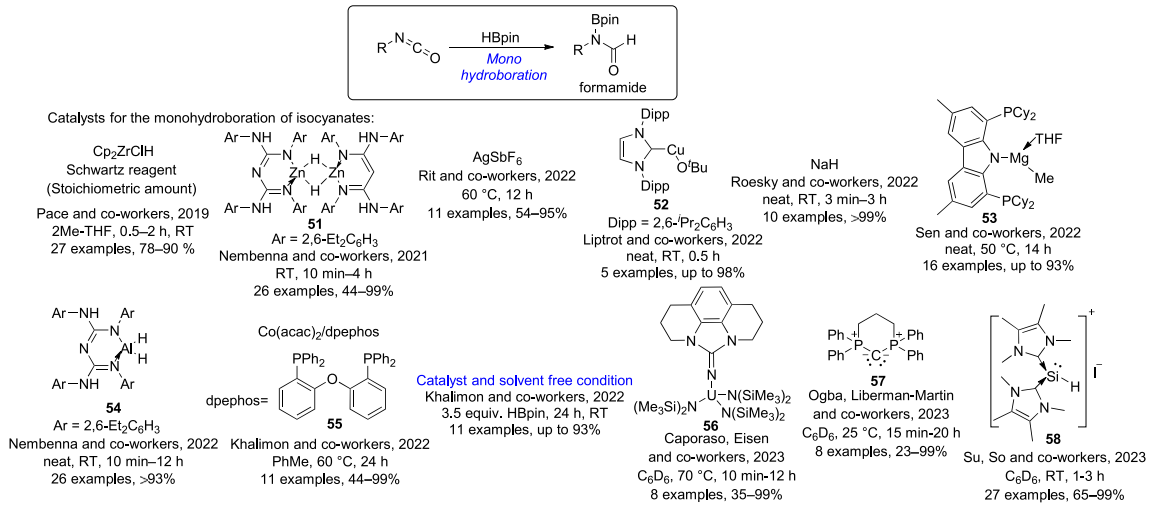
Radius and Breher[37] introduced α-borylated phosphorus ylide (α-BCP) (**49**), analogous to FLP systems, for the synthesis of heterocumulenes with isocyanates and isothiocyanates. An equimolar mixture of PhNCO or PhNCS with this ylide afforded **50** (Scheme 6B), having a ^{13}C NMR spectroscopic resonance at δ = 172.6 (OCN) and 177.34 (SCN) ppm. Further, both structures were confirmed using single-crystal X-ray diffraction.

HYDROBORATION OF ISOCYANATES

Hydroboration of unsaturated organic compounds is one of the most straightforward, atom-efficient, and extremely useful synthetic approaches for the preparation of organoboranes, which are widely used as synthetic intermediates in various processes.[38] The reduction of isocyanates using boron reagents leads to the formation of a mixture of three possible products, depending on the catalyst used and the number of equivalents of reducing agent used. The possible products are (1) formamides, (2) hemiaminals, and (3) *N*-methylamines (Scheme 7). Hence, design of a chemoselective method for the preparation of any of these has recently gained a lot of attention.[39]

MONOHYDROBORATION OF ISOCYANATES TO FORMAMIDES

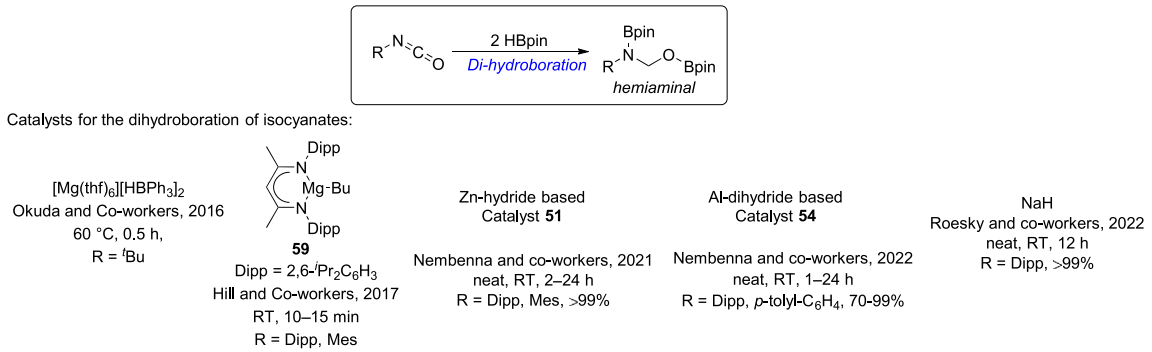
There is a great demand for the selective formation of formamides from isocyanates using mild and chemoselective reductive conditions because formamides are important raw materials for the manufacturing of valuable heterocycles, bioactive substances, pharmaceuticals, herbicides, and pesticides.[15,40] Pace et al.[41] applied an *in situ*-generated Schwartz reagent (Cp_2ZrClH) for this purpose in a transformation of isocyanates into formamides. The main disadvantage of this method, however, was the requirement for an excess of Schwartz reagent, which is not only expensive but also difficult to store due to its sensitivity to air, light, and moisture. Recently, chemoselective formamide synthesis from isocyanate using boranes has been studied extensively by Gudun et al.,[42] Kumar et al.,[39] Sahoo et al.,[43] Sarkar et al.,[43,44] Pandey et al.,[45] English et al.,[46] Ni et al.,[47] Makarov et al.,[48] Janda et al.,[49] and Teo et al.[50] (Scheme 8). In 2021, the first chemoselective reduction



Scheme 8. Catalysts for the monohydroboration of isocyanates to *N*-(boryl)formamide

of isocyanates using a novel conjugated bisguanidinate (CBG)-stabilized zinc hydride (**51**) was reported by Sahoo et al.[43] They synthesized a wide range of substrates featuring various functional groups with both mono- and di-isocyanates, obtaining up to 99% yields. The authors calculated a TON (turnover number) of 400 and a TOF (turnover frequency) of 400 h^{-1} for the monohydroboration of *p*-tolyl isocyanate because this substrate was highly active under the reaction conditions. Pandey et al.[45] demonstrated that a simple and well-known silver(I) salt can also be used for the selective hydroboration of isocyanates with electron-withdrawing as well as electron-donating substituents under ligand-free mild conditions. They focused on the formation of *N*-boryl formamides and methylamines, which was controlled by alternation of the catalyst loading, reaction time, and temperature. The selective formation of *N*-boryl formamides was observed with 54%–95% yields within 12 h using only 2 mol % of the catalyst.

English et al.,[46] on the other hand, studied the chemoselective reduction of 11 aryl and alkyl isocyanates using 2 mol % of a copper-based catalyst (**52**). They observed the selective boraformamide formation for the electron-rich substrates at room temperature, and no further reduction was detected even in the presence of excess pinacolborane. In the case of all of the electron-poor isocyanates, over-reduction occurred, leading to the formation of a mixture of products. Subsequently, Ni et al.[47] introduced hydroboration utilizing 0.1 mmol% of inexpensive and commercially available NaH under solvent-free and mild reaction conditions. The methodology was expanded to show a high functional group tolerance and selectivity, affording up to 99% yields for both aliphatic and aromatic isocyanates.[47] Later, Kumar et al.[39] reported a highly selective protocol using earth-abundant, non-toxic, and environmentally friendly main-group bis(phosphino)carbazolido-magnesium methyl complex **53**, while Sarkar et al.[44] introduced conjugated bisguanidinate (CBG) supported aluminum dihydride **54** as efficient catalysts. A large variety of aryl and alkyl isocyanates, including mono- and di-isocyanates, were investigated with 2 mol % catalytic loading of **53** and **54** under neat reaction conditions at 50°C–80°C, generating the desired *N*-boryl formamides. In both cases, the reducing agents showed excellent tolerance to other functional groups susceptible to reduction, such as alkyl, halide, nitro, nitrile, and alkene. After that, Gudun et al.[42] described chemoselective hydroboration of isocyanates,



Scheme 9. Catalysts for the dihydroboration of isocyanates to *N*-,*O*-bis(boryl)hemiaminals

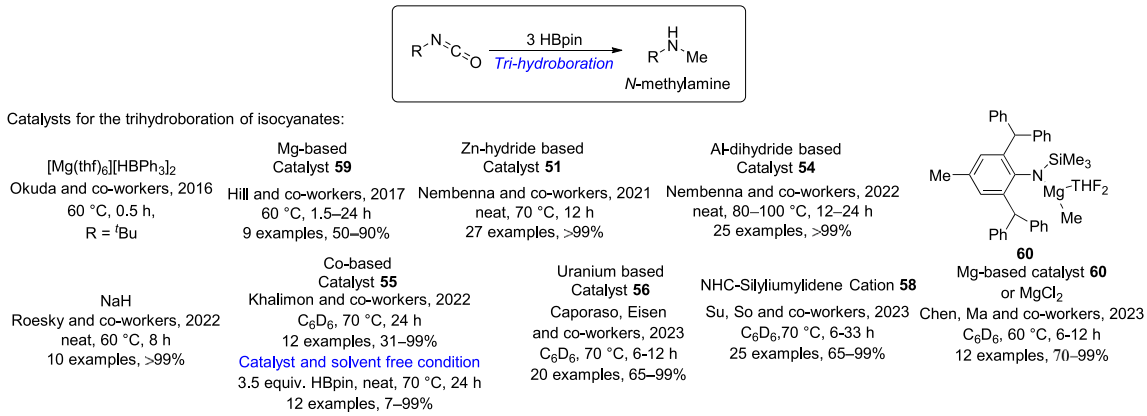
proceeding under catalyst-free and solvent-free conditions at room temperature with 3.5 equiv of HBpin.[42] Under the same reaction conditions at 50°C–70°C, *N*-methylamines can be formed in up to 99% yields. The catalyst-free monohydroboration with the use of solvent was observed only for a few isocyanates, such as phenyl, *p*-tolyl, *p*-methoxyphenyl, benzyl, and isopropyl derivatives; however, the reaction took longer compared with the previously reported Zn, Al, Mg, NaH, and $AgSbF_6$-catalyzed systems. However, to further expand the substrate scope, the authors introduced 2 mol % of a bench-stable $Co(acac)_2$/dpephos catalyst (**55**) with 1 equiv of HBpin in benzene-d_6 or toluene to afford *N*-borylformamides with good to excellent yields. Very recently, a five-membered *N*-heterocyclic iminato ligand-supported uranium complex (**56**)[48] and carbodiphosphorane (**57**)[49] and the first *NHC*-supported, low-oxidation-state containing silyliumylidene cation (**58**)[50] have been reported to hydroborate the isocyanates chemoselectively using similar reaction conditions with a wide range of substrates, affording good to excellent yields.

DIHYDROBORATION OF ISOCYANATES TO BIS(BORYL)HEMIAMINALS

The selective dihydroboration of isocyanates to generate corresponding *N*,*O*-bis(-boryl) hemiaminal products is extremely challenging because it often produces a mixture of mono-, di-, and over-reduced products for many substrates, with the exception of a few sterically hindered isocyanates in presence of highly selective catalysts. The first breakthrough was reported by Mukherjee et al.[51] in 2016, from the reaction of *tert*-butyl isocyanate with 2 equiv of HBpin at 60°C using a magnesium-based catalyst $[Mg(THF)_6][HBPh_3]_2$. Here, the product of dihydroboration was formed selectively within 30 min (Scheme 9).[51] Moreover, bisborylation was reported for the extremely bulky 2-isocyanato-1,3-diisopropylbenzene using Mg (**59**)-, Zn (**51**)-, and Al (**54**)-based catalysts, as well as the commercially available NaH, by Hill,[52] Nembenna,[43,44] and Roesky,[47] respectively, with high yields. The formation of a mixture of products was observed for most of the other substrates used (Scheme 9).[43,44,47,52] Additionally, **51** and **56** were able to cleanly produce the *N*,*O*-bis(boryl) hemiaminal for MesNCO, whereas **54** converted 4-bromophenyl isocyanate in a similar fashion.

DEOXYGENATIVE HYDROBORATION OF ISOCYANATES TO *N*-METHYLAMINES

N-methyl amines are important target molecules in the production of pharmaceuticals and other vital chemicals.[53] They can be readily generated in the reductive methylation of carbonyls; however, there are multiple side reactions occurring in



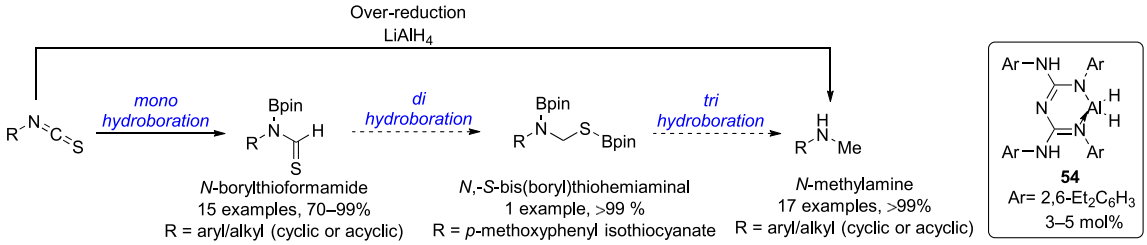
Scheme 10. Catalysts for the deoxygenative hydroboration of isocyanates to *N*-methylamines

this method, it can be applied only to a narrow substrate scope, and it produces a large amount of chemical waste. Hence, the development of a chemoselective protocol for the synthesis of this class of amines, avoiding all of the mentioned disadvantages, is an important issue to be addressed.

A complete reduction of isocyanates to *N*-methylamines was reported by stoichiometric reactions with $LiAlH_4$ or by catalytic use of $Li[Al(OMe)_3]_3$, $NaBH_4$, and other reducing agents, such as $Ph_2SiH_2/B(C_6F_5)_3$ or $NaBH_4/CF_3COOH$.[54–57] The Hill research group first reported the deoxygenative hydroboration of isocyanates by using Nacnac [HC{(Me)CN(Dipp)}$_2$ (Dipp = 2,6-diisopropylphenyl)] supported magnesium *n*-butyl derivative **59** as a catalyst with a 3-fold HBpin loading.[52] Several other catalysts, such as lithium triethylborohydride (super hydride),[58] sodium hydride,[47] zinc hydride (**51**),[43] aluminum dihydride (**54**),[44] $AgSbF_6$,[45] uranium complex (**56**),[48] NHC-silyliumylidene cation (**58**),[50] and magnesium methyl complex (**60**)[59] along with commercially available $MgCl_2$[59] were also applied for this purpose with good to excellent yields of the products using a wide range of substrates, including aryl and alkyl, cyclic, and acyclic substrates. These catalysts also demonstrated a high tolerance of other reducible functional groups, such as halide, nitro, nitrile, and alkene (Scheme 10). In 2022, Gudun et al.[42] described a catalyst-free deoxygenative hydroboration of isocyanates with 3 equiv of HBpin to generate *N*-methylamines. However, the reaction was not selective for the cyano moiety, with heteroaromatic (pyridine and thiophene) functionalities undergoing analogous transformations. Therefore, commercially available **55** was introduced as a pre-catalyst to enable the formation of this class of bioactive *N*-methylamine with high yields.[42]

HYDROBORATION OF ISOTHIOCYANATES

Thioamide can be generated by a simple replacement of amide oxygen with sulfur, which leads to their improved reactivity patterns and physico-chemical properties, such as stability and/or crystallinity.[60] Formation of thioformamides from thioamides is especially significant because they are versatile frameworks in organic synthesis to produce essential intermediates for the construction of biologically significant sulfur-containing heterocycles and amidines.[61] The synthetic pathways giving easy access to thioformamides are extremely limited in the literature, and thus this has recently gained considerable attention within the academic community. The synthesis of *N*-borylthioformamides has only been explored by a handful

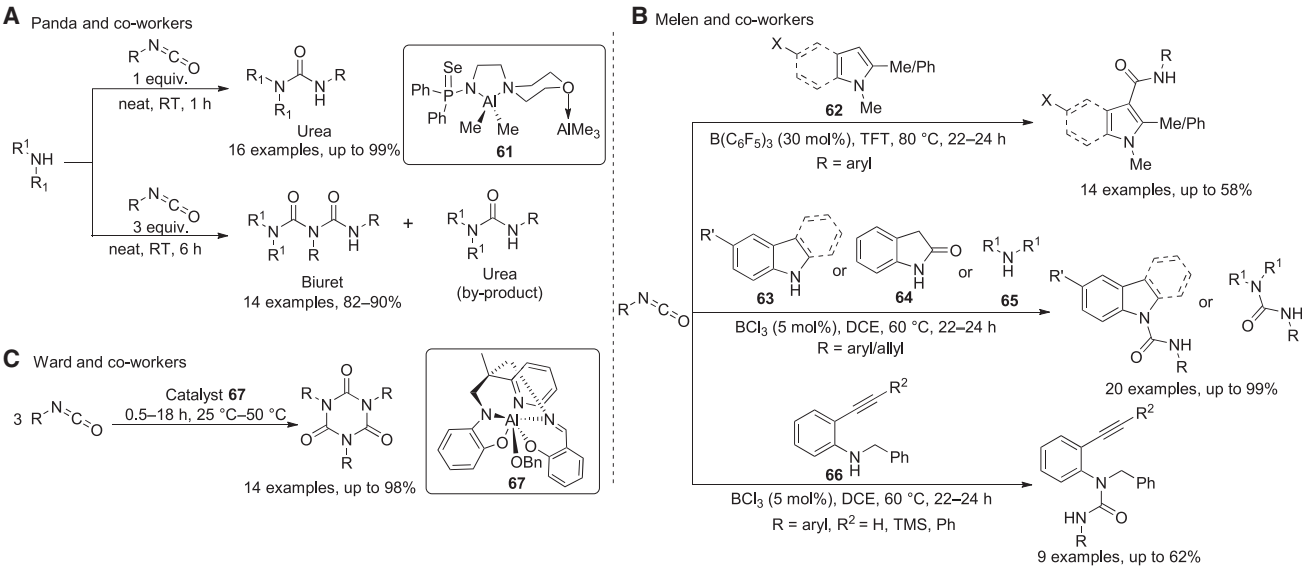


Scheme 11. Stepwise hydroboration of isothiocyanate using an aluminum catalyst

of groups; they reported a reduction of isothiocyanates with HBpin and Bu_3SnH,[62] SmI_2,[63] or Schwartz's reagent (Cp_2ZrClH; generated *in situ*)[64] with the formation of other byproducts. Sarkar et al.[44] first introduced the partial hydroboration of isothiocyanates to selectively obtain monohydroborated *N*-borylthioformamides by using 3 mol % of aluminum-based compound **54** in a neat reaction mixture. No product formation was observed in the absence of the catalyst.[44] A wide range of various substrates, such as aryl and alkyl isothiocyanates, including mono- and diisothiocyanates, together with several other reducible functional groups, such as alkyl, halide, nitro, nitrile, and alkene, were studied and successfully transformed into *N*-boryl thioformamides with good to excellent yields and high selectivity (Scheme 11). An exceptional tolerance was noted for allyl isothiocyanate, where the product was obtained without disturbing the allyl moiety in 80% yield. The only isothiocyanate that was successfully dihydroborated was *p*-methoxyphenyl isothiocyanate, with 3 mol % of **54** at 80°C with 2 equiv of HBpin (Scheme 11). In efforts to expand the scope of the reaction, a variety of substrates were examined; however, all attempts led to the formation of a mixture of products. The synthesis of *N*-methylamines from isothiocyanate derivatives was not much explored in the literature due to the formation of a sulfur-containing by-product, which further reacts with the catalyst through hydrosulfurization.[65,66] **54** (5 mol %) was examined for the over-reduction of the aryl isothiocyanates to generate *N*-methylamines with 99% product formation for many compounds substituted with electron-rich (methyl and methoxy) and electron-deficient (nitro, bromo, and fluoro) functional groups.[44]

HYDROAMINATION OF ISOCYANATES

Urea and its derivatives have a substantial role in biological systems, synthetic chemistry, supramolecular chemistry, materials chemistry, and medicinal chemistry as well as the agrochemical industry. The catalytic hydroamination reaction of alkynes, alkenes, and carbodiimides to form C–N bonds is an established method of urea synthesis, using group 2, titanium, zinc, actinide complexes, etc. Although a variety of other methods have also been developed, the hydroamination of isocyanates has gained much attention since the report from Mistry et al.[67] about the application of cyrene as an efficient and bioactive solvent for the preparation of urea derivatives with high yields. This year, Bano et al.[68] have demonstrated a novel and resourceful catalytic system involving earth-abundant, environmentally friendly, non-toxic binuclear aluminum complex **61** for selective synthesis of urea derivatives, occurring under mild conditions at room temperature (Scheme 12A). The equimolar mixture of secondary amines and either *p*-tolylisocyanate or *p*-chlorophenyl-isocyanates afforded the corresponding urea scaffolds within 1 h under neat conditions with 1 mol % of the catalyst. The protocol worked well with various dialkyl amines, diallyl amines, dibenzyl amines, and arylalkyl amines as well as pyrrolidine, piperidine, and morpholine with up to 99% yields. Further



Scheme 12. Hydroamination, hydroamidation, and trimerization reactions of isocyanates

functionalization of the urea to form derivatives with multiple urea moieties is quite challenging because the nucleophilicity of urea compared with secondary amines is significantly lower. For the synthesis of such compounds, only a few catalytic transformations have been reported so far using transition metal-based catalysts. In 2023, Bano et al.[68] tested the aluminum complex **61** as a catalyst to selectively prepare the biuret derivatives and successfully executed smooth conversion of diethylamine, diallylamine, *N*-methylaniline, and heterocyclic secondary amines such as pyrrolidine, piperidine, and morpholine. They used 3-fold *p*-tolylisocyanate or *p*-chlorophenyl isocyanate and observed the reaction to reach completion within 6 h under neat reaction conditions. The obtained yields were as high as 90% with the urea derivatives as minor products (Scheme 12A). The addition of an excess of isocyanate yielded a mixture of urea, biuret, and triuret without significant selectivity.

The design of catalytic pathways to form new C–C and C–N bonds for the synthesis of amide/urea derivatives under mild conditions has remained a significant challenge that needs resolving because they are very important frameworks in medicinal chemistry. The functionalization of the indoles via the introduction of an amide moiety at the C3 position using isocyanate derivatives is an important synthetic pathway being currently widely explored. For unprotected indoles, a variety of transition metals, including Pd, Cu, Ru, and Rh, have been extensively used with isocyanates to generate urea derivatives in functionalization of the N1 position. In 2022, Dasgupta et al.[69] reported the use of Lewis acidic $B(C_6F_5)_3$ as an efficient catalyst for chemo- and regioselective functionalization of both protected and unprotected indoles with isocyanates (Scheme 12B). The reaction with the *N*-protected analogs (**62**) with aryl isocyanates gave the corresponding C3-substituted products in moderate yields (up to 58%) using 30 mol % $B(C_6F_5)_3$ in trifluorotoluene (TFT) at 80°C. The reaction scope was expanded with pyrroles (**63**), affording the C3 amidation products in moderate yields (up to 52%). For unprotected indoles (**63**), the amidation reaction occurred at the nitrogen center to form an *N*-carboxamidated urea scaffold with up to 98% yields. In this case, BCl_3 was used as a more effective catalyst over $B(C_6F_5)_3$. The attempt to prepare urea

derivatives using carbazole and *1H*-benzo[*d*]imidazole with PhNCO was also successful with 97% product formation. The reaction was well tolerated by non-aromatic aliphatic secondary amines (**65**) such as dipropylamine and diethylamine with phenyl/cyclohexyl isocyanate to obtain corresponding urea derivatives (in up to 99% yields). Using a similar reaction protocol, the authors were able to prepare the core structure of a VEGFR-2 inhibitor,[70] an anti-vascular endothelial growth factor therapeutic compound, with 82% yield in gram scale without a need for use of previously reported excess NaH or copper iodide as catalyst. They further performed the reaction between 2-alkynyl anilines (**66**) with isocyanates using BCl_3 as the catalyst and were able to produce an *N*-carboxamidation product instead of the expected cyclised-C3-derivatized product.

TRIMERIZATION OF ISOCYANATES

Trimerization of isocyanates[71] is one of the rapidly growing areas because this inexpensive and atom-efficient route can produce isocyanurates, which are useful in an innumerable range of applications, like selective anion binding,[72] medicines,[73] microporous materials, and coating materials.[74] The catalytic trimerization using amines,[75] phosphines,[76,77] carbenes,[78] and other main-group[79–81] and transition metals[82] have been reported in the literature with the formation of other oligomers (a mixture of products) and with high catalyst loading and high temperature, whereas the trimerization of isothiocyanates has only been reported under high-pressure reaction conditions.[83] In 2019, the clean trimerization of isocyanates was reported by Bahili et al.[84] under mild reaction conditions using a hemi-labile pyridyl donor-supported aluminum alkoxide complex (**67**) with up to 98% yield (Scheme 12C). The active catalyst **67** quantitively converted alkyl, aryl, and allyl isocyanates as well as di-isocyanates into their corresponding *N*,*N*',*N*''-triphenyl isocyanurates within 18 h.[84]

CONCLUSIONS AND OUTLOOK

In this review, we outlined the diverse applications and advances of the group 13 elements in both their stoichiometric and catalytic reactivity with isocyanates and isothiocyanates. The activation of isocyanates and isothiocyanates is challenging from a selectivity point of view due to the competition between reaction with the C=N and C=O or C=S bonds. However, with the increasing importance of sustainability and non-toxicity of industrially used chemicals, group 13 compounds have turned out to be extremely effective in the activation of both isocyanates and isothiocyanates. In stoichiometric reactions, this has been demonstrated in their activation by FLPs. Recently, stepwise hydroboration of both isocyanates and isothiocyanates to produce chemo- and regioselective hydroborated products has gained much attention due to the high utility of organoboranes as synthetic intermediates in several processes. Moreover, tremendous progress has been made in the development of new methods of formation of carbon–carbon and carbon–nitrogen bonds using group 13 catalysts. The perpetual exploration toward the activation and catalytic transformations of isocyanates and isothiocyanates with group 13 compounds are continuing to date, making the scientific community realize that the chemistry of those compounds may be closer to transition-metal complexes than we would think.

ACKNOWLEDGMENTS

We are grateful to the EPSRC for funding and the award of an EPSRC Early Career Fellowship (EP/R026912/1). S.P., E.R., and R.L.M. would like to acknowledge the

Leverhulme Trust for a research grant (RPG-2020-016). A.G. would like to thank Cardiff University for funding.

AUTHOR CONTRIBUTIONS

S.P. and A.G. wrote and prepared the draft manuscript. E.R. and R.L.M. provided the funding, supervision, and writing – review & editing. All authors proofread the manuscript and commented on the draft.

DECLARATION OF INTERESTS

R.L.M. is a member of the *Cell Reports Physical Science* external advisory board.

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