Copper-Catalyzed Borylative Couplings with C–N Electrophiles

Fabien J. T. Talbot†, Quentin Dherbassy†, Srimanta Manna, Chunling Shi, Shibo Zhang, Gareth P. Howell, Gregory J. P. Perry, and David J. Procter*

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Copper-catalyzed borylative multicomponent reactions (MCRs) involving olefins and C–N electrophiles are a powerful tool to rapidly build up molecular complexity. The products from these reactions contain multiple functionalities, such as amino, cyano and boronate groups, that are ubiquitous in medicinal and process chemistry programs. Copper-catalyzed MCRs are particularly attractive because they use a relatively abundant and non-toxic catalyst to selectively deliver high-value products from simple feedstocks such as olefins. In this Minireview, we explore this rapidly emerging field and survey the borylative union of allenes, dienes, styrenes and other olefins, with imines, nitriles and related C–N electrophiles.

1. Introduction

Building molecules that contain nitrogen is of great importance: amines constitute 80% of the bioactive targets used in drug discovery,[3] and the number of nitrile-containing drugs has been steadily increasing in recent decades.[4] In addition, the versatile reactivity of nitrogen-containing functional groups makes them highly useful building blocks in synthesis. Likewise, boron-containing compounds are involved in 11% of C–C bond forming reactions in process chemistry.[3] Thus, the union of nitrogen and boron-containing functional groups in defined molecular scaffolds is highly sought after. Indeed, to venture into underexplored regions of chemical space, novel disconnects of targets containing these important functionalities are needed.[4] Multicomponent reactions (MCRs) figure amongst the most promising strategies for addressing this challenge as they transform readily available feedstocks into complex structures in a single step.[26] In addition, due to their favorable atom and waste economics,[5] MCRs are ideal for the synthesis of bioactive targets.[6]

The need to replace precious metals with more abundant and less toxic elements, such as copper, is a pervading theme in contemporary synthesis.[7] Since the first reports by Hosomi and Miyaura at the turn of the century,[13] the copper-catalyzed borylation of C–C multiple bonds, along with the powerful extension of this methodology in MCRs, has been extensively studied.[9] The aim of this Minireview is to highlight recent advances in copper-catalyzed borylative MCRs involving C–N electrophiles and olefins for the synthesis of highly functionalized amines, nitriles and other nitrogen-containing products (Scheme 1).

2. Mechanistic Aspects in Copper-Catalyzed Borylative Couplings

Organocopper reagents can be generated in situ through borocupration of olefins, and then intercepted by C–N electrophiles (Scheme 2A). A copper salt is first transformed into a copper(I) alkoxide complex int-1 by treatment with base.[18] Transmetalation then occurs between int-1 and a diboron reagent I, typically via α-bond metathesis (step A).[11] NHCs and phosphines are popular ligands in these processes, in fact, the first isolated copper-boryl complexes int-2 featured NHCs as stabilizing ligands.[12] 1,2-Borocupration of an activated olefin 2 (internal, non-conjugated olefins are unreactive)[13] with int-2 produces the borylated organocopper complex int-3 (step B and Scheme 2B).[14] The regioselectivity and stereoselectivity of the borocupration is not easy to predict as both kinetic and thermodynamic factors must be taken into account.[13] Furthermore, isomerization[15] and rearrangement[14] can lead to epimerization[16] of the organocopper. Finally, reaction with a suitable electrophile 3/4 delivers the product 5/6 (step C/D). The catalyst is regenerated using an equivalent of base and diboron, or by protonation of the product with an alcohol (step D). This simplified mechanism encompasses many of the transformations in this Minireview. As steps B and C determine the regio- and stereoselectivity of these reactions, they will be highlighted in the text when mechanistic evidence is available.

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and moisture sensitivity, safety risks and pre-functionalized starting materials. Copper species are well known to modulate the reactivity of organometallic reagents[19] and can induce stereocontrol in additions to ketimines[20] and aldimesines.[20]

The use of copper catalysts to generate organocopper species in situ in MCRs is an attractive solution to the problems

3. Copper-Catalyzed Borylative Couplings with Imines

Classical syntheses of amines often involve the addition of organometallic reagents to imines.[17] However, these reactions suffer from the inherent limitations associated with pre-formed organometallic reagents: cryogenic temperatures, air

Fabien Talbot received his BSc from the University of Angers (France) with one year spent at the University of Strathclyde (UK). He then undertook an MSc at the University of Strasbourg (France) and did his research project at the University of Manchester (UK) working on nickel catalysis in Prof. David Procter’s research group. In 2017, he stayed in the Procter group for a PhD funded by AstraZeneca and the EPSRC. He is also the recipient of an SCI Scholarship. His research aims to develop new copper-catalyzed processes.

Quentin Dherbassy received his MChem from the University of Strasbourg (France) in 2014 and his PhD in 2017, working in the group of Prof. Françoise Colobert (CNRS, Strasbourg, France). His doctoral studies focused on the control of axial chirality by sulfoxide-directed C–H activation. After a short post-doctoral post in the Colobert group, he joined the Procter Group as a PDRA in 2018, and is studying borylative copper-catalyzed asymmetric multicomponent reactions.

Srimanta Manna received his MSc from IIT Bombay (India) in 2012, and his PhD from the Max Planck Institute of Molecular Physiology, Dortmund (Germany), in 2017. His doctoral studies were carried out in the Antonchick group and focused on hypervalent iodine mediated C–H amination and copper-catalyzed oxidative cyclopropanation. In 2017, he joined the Procter group and was awarded a Marie Curie Fellowship in 2018. Currently, he is focusing on the development of copper-catalyzed asymmetric multicomponent coupling reactions.

Chunling Shi received her MChem from Jiangsu Normal University (P. R. China) in 2005. In 2009, she obtained her PhD from Southeast University (P. R. China). Her doctoral studies were carried out in the group of Prof. Min Ji on the organocatacatlytic synthesis of heterocyclic compounds. In 2009, she moved to a Lectureship at Xuzhou University of Technology and was promoted to Associate Prof. in 2013. In 2020, she joined the Procter Group as a visiting scholar.

Shibo Zhang received his undergraduate degree from Wuhan Institute of Technology (P. R. China) having carried out research in the area of green chemistry under the supervision of Prof. Zhibing Dong. In 2020, he joined the University of Manchester for his MPhil in the Procter group where he is working on borylative copper-catalyzed asymmetric multicomponent reactions.

Gareth P. Howell obtained an MChem in 2007 from the University of York including a one-year internship within Process Chemistry at GlaxoSmithKline. Focussing on asymmetric synthesis and catalysis, he obtained a PhD from the University of Nottingham with Professor James C. Anderson in 2004 before moving to Groningen (NL) to work with Professor Ben L. Feringa as a postdoctoral fellow sponsored by The Leverhulme Trust. He has worked within Process Chemistry at AstraZeneca in the UK since 2006 and is currently an Associate Principal Scientist, leading drug development projects.

Gregory J. P. Perry obtained his PhD from the University of Manchester (UK) in 2016. His doctoral studies with Prof. Igor Larrosa focused on decarbonylative transformations. In 2017, he moved to Nagoya University (Japan) to work in the group of Prof. Kenichiro Itami, applying C–H activation in chemical biology. Since 2018, Greg has been working as a Lecturer in Organic Chemistry within the group of Prof. David Procter at the University of Manchester (UK).

David J. Procter obtained his PhD from the University of Leeds (UK) in 1995 working with Prof. Christopher Rayner on organosulfur and organoselenium chemistry. He then spent two years as a PDRA with Prof. Robert Holton at Florida State University (USA) working on the synthesis of Taxol. In 1997, he took up a Lectureship at the University of Glasgow (UK). In 2004, he moved to the University of Manchester (UK) for a Readership and was promoted to Professor in 2008.
associated with stoichiometric organometallic reagents in amine synthesis.

### 3.1. Allenes

In an effort to circumvent the need for pre-formed allylmetal reagents in additions to imines,[21] Procter and co-workers[22] reported the first multicomponent copper-catalyzed borylative coupling of imines and allenes in 2016. Homoallylic amines 9 were formed from the addition of allylcopper complexes (e.g. int-6), formed in situ by borocupration of 1-monosubstituted or 1,1-disubstituted allenes 8, to aldimines 7 (Scheme 3A). A range of substituents on the imine were well tolerated, including electron-rich and electron-deficient (hetero)aromatic groups (to give 9a–e, Scheme 3B). Interestingly, X-ray and 11B NMR analysis of the products revealed a donor-acceptor interaction between the amine and the Bpin moiety (as illustrated in 9e). A density functional theory (DFT) study was performed to rationalize the observed anti-diastereoselectivity. After considering various possibilities, a lowest energy pathway featuring a 6-membered, Zimmerman–Traxler-type transition-state TS1 from (Z)-allylcopper species int-6 and aldimine 7 was proposed.

Procter and co-workers[23] also reported an enantioselective variant of the reaction. By using the enantiopure NHC precursor L1 with CuI (5 mol%), excellent levels of stereinduction and good to excellent yields were obtained (Scheme 3C). Importantly, scalability was achieved using a low catalytic loading (1 mol %) on a 2 gram scale, affording 10a in almost quantitative yield, and with excellent diastereo- and enantioselectivity.

These reports triggered the development of similar MCRs involving imine derivatives. For example, the Procter group[24a] used the approach to prepare quaternary α-amino acid derivatives 11 from ketiminoesters (Scheme 3D), for which an enantioselective variant has been reported by Chen et al.[24b] In addition, Zhang and co-workers[25] realized the enantioselective coupling of arylallenes with cyclic imines to access functionalized dibenzo-1,4-oxapines 12 (Scheme 3D).

In 2017, Hoveyda and co-workers[26] developed an enantioselective, copper-catalyzed borylative coupling of allenes and N–H ketimines (Scheme 4A). The instability of ketimine electrophiles was cleverly managed by using the HCl salt of N–H ketimines 13, which were prepared through addition of an organolithium reagent to the corresponding nitrile and subsequent acidification. Using an enantiopure NHC ligand L2 with CuCl (5–10 mol %), the ketimine salts were combined with 1-substituted allenes 8 and B2pin2 to give the desired products in good to excellent yields and excellent diastereo- and enantioselectivities (Scheme 4B). In agreement with the studies of Procter and co-workers (Scheme 3B), DFT calculations supported a mechanism involving a six-membered transition state TS2 (Scheme 4C). They postulated that a combination of N–Na coordination and steric repulsion between the ligand and the Bpin moiety accounts for the high enantioselectivity of the transformation.
3.2. Vinylarenes

In 2018, Kanai, Shimizu and co-workers[27] disclosed the first enantioselective copper-catalyzed borylative coupling of aldimines 15 and vinylarenes 16 using mesitylcopper (MesCu) as a pre-catalyst (Scheme 5A).[28] Notably, they were able to selectively access either anti- or syn-diastereomeric products by varying the chiral ligand (L3a or L4). A wide range of products was obtained in high yields and high enantiomeric ratios (Scheme 5 B). Provided that a large excess (10 equiv) of vinylarene was used, aliphatic imines were also suitable candidates in spite of their potential to tautomerase to enamines.

Prior to the report by the Kanai lab, Lam and co-workers[29] had disclosed a related borylative coupling of aryl-substituted, N-Boc aldimines 19 with vinylazaarenes 20 (Scheme 5C). A combination of CuF(PPh3)3·MeOH and dppf L5 afforded, after in situ oxidation, 1,3-amino alcohols 21 with moderate to high diastereoselectivity (Scheme 5D).

Following these reports, three groups simultaneously reported a related intramolecular coupling (Scheme 6).[30] N-(2-Vinylphenyl) aldimines 22 were reacted with B2pin2 in the presence of a copper catalyst to give 2,3-disubstituted indolines 23. Both Xiong and co-workers[30b] and Yun and co-workers[30c] reported an enantioselective coupling using (5S)-Ph-BPE L3b (Scheme 6 A). A range of (hetero)aryl substituents on the imines and aryl-substituents on the alkene were well tolerated (Scheme 6 B). Shen, Xu and co-workers[30a] reported a diastereoselective variant using dppf L5 (Scheme 6 C). Interestingly, the products arising from the reaction of 2-bromo-aryl imines were further transformed into the corresponding tetrahydroindenoidoles 25 through a palladium-catalyzed Suzuki–Miyaura coupling.

3.3. Dienes

In 2016, Cao, Liao, and co-workers[31] reported the copper-catalyzed diastereo- and enantioselective borylative coupling of imines 26 and dienes 27. Following in situ oxidation, 1,3-amino alcohols 28 were obtained (Scheme 7 A). Very high diastereoselectivities and excellent enantioselectivities were obtained with the bulky phosphine ligand (R)-DM-BINAP L6. This three-component coupling reaction was effective with dienes ranging from the highly abundant 1,3-butadiene (to give 28f) and isoprene (to give 28a, 28b, 28d).
Unfortunately, the reactions with internal, cyclic, and 2,3-substituted dienes were unsuccessful. The authors were able to isolate the (Z)-allyl copper species int-8b, which they suggested was formed from initial 1,2-borocupration of 1,3-butadiene, followed by migration of copper to the least hindered position (Scheme 7C). This (Z) geometry is often thermodynamically favored in allylmetals.\[32,33\]

In 2018, Yun and co-workers\[34\] reported an intramolecular copper-catalyzed borylative coupling of 1-dienylarenes 29 with tethered imines to give 7-membered benzolo[b]azepines 30 (Scheme 8A). Aryl and alkyl aldimines, and aryl, alkyl ketimines, were suitable substrates and gave products with high diastereocontrol (Scheme 8B).

In 2020, Procter and co-workers\[36\] used a copper-catalyzed borylative coupling of enynes 36 and aldimines 26 to prepare homopropargylic-1,3-aminoalcohols\[37\] 37, containing up to three contiguous stereocenters, with high enantiocontrol (Scheme 10A). Interestingly, (S,S)-Ph-BPE L3b (c.f. Schemes 5 and 6) was again used to impart enantioselectivity. A wide range of aromatic imines and electron-rich aromatic enynes were well tolerated (Scheme 10B). Based on a related DFT study involving carbonyl partners,\[15\] the authors suggested a mechanism involving rearrangement of the propargyl int-10a to the allenyl copper int-10b (Scheme 10C) followed by coupling via 6-membered TS3 to give 37.

In 2018 Brown and co-workers\[35\] serendipitously discovered the borylative cine-substitution of 3-bromopyridines 31 with dienes 32 (Scheme 9A). Labelling and crossover experiments suggested a concerted deuterium migration from the 6-to the 5-position in intermediate int-9 (Scheme 9B). Quinolines and isoquinolines did not undergo cine-substitution, but direct addition after borocupration of 2-alkyl-1,3-dienes 32. For example, direct addition occurred at the 1-position of isoquinolines and afforded 1-hydroisoquinolines, which were prone to re-aromatization upon treatment with DDQ. This transformation was rendered enantioselective using L7CuCl (Scheme 9C,D).

3.4. Enynes

In 2020, Procter and co-workers\[36\] used a copper-catalyzed borylative coupling of enynes 36 and aldimines 26 to prepare homopropargylic-1,3-aminoalcohols\[37\] 37, containing up to three contiguous stereocenters, with high enantiocontrol (Scheme 10A). Interestingly, (S,S)-Ph-BPE L3b (c.f. Schemes 5 and 6) was again used to impart enantioselectivity. A wide range of aromatic imines and electron-rich aromatic enynes were well tolerated (Scheme 10B). Based on a related DFT study involving carbonyl partners,\[15\] the authors suggested a mechanism involving rearrangement of the propargyl int-10a to the allenyl copper int-10b (Scheme 10C) followed by coupling via 6-membered TS3 to give 37.
3.5. Direct Borylation of Imines

The hydroboration of imines affords important α-amino-boronic acids that are bio-isosteres of α-amino acids.[38]

In 2013, Tian, Lin and co-workers[39] used N-benzoyl arylaldimines 38 to obtain α-amido boronic esters 39 in good yields and moderate enantioselectivities (Scheme 11A,B). In 2015, Liao and co-workers[40] reported an improved copper-catalyzed enantioselective hydroboration of N-Boc aldimines 38 using a chiral sulfoxide-phosphine ligand L9 (Scheme 11A,C). Interestingly, the absolute configuration of the resulting α-amido boronic esters 39 could be controlled by the copper counter ion (Scheme 11 C).

The direct borylation of imines has been used in related multicomponent reactions. In 2019, Song and co-workers[41] reported the copper-catalyzed boroacylation of aldimines 40 (Scheme 12A). The two-step protocol involves formation of the iminium salt int-11 then copper-catalyzed borylation to yield the desired N-acylated α-amino boronic esters 42. The process was efficient across a wide range of aryl imines bearing alkyl and aryl N-substituents, and various aromatic and heteroaromatic acyl chlorides (Scheme 12B). The direct conversion of aldehydes and amines through an in situ condensation/boroacylation sequence (to give 42e and 42f) was also possible.

Shortly after, Zhang, Luo, Hou and co-workers[42] reported a highly efficient copper-catalyzed borylative functionalization of aldimines involving CO₂ fixation (Scheme 12A). Following borocupration of the aldimines, intramolecular N/B Lewis pair formation was proposed to efficiently activate CO₂ (TS4; supported by DFT calculations), yielding versatile borocarbamate salts 43. The methodology was applied to an extensive scope of aryl imines using only 1 mol% of a readily available NHC-ligated copper catalyst (Scheme 12C). Finally, carbamate-containing α-amino boronic esters 44 and 45 were generated upon treatment with a methylating agent or an acyl chloride.

4. Copper-Catalyzed Borylative Couplings with Nitriles

The cyanation of olefins delivers versatile nitrile-containing products.[2] Electrophilic cyanating agents, such as N-cyano-N-phenyl-p-methylenesulfonamide (NCTS 46a), have emerged as a safer and more practical alternative to traditional cyanating reagents, such as hydrogen cyanide and cyanide salts.[43] They can be used to intercept nucleophilic organocopper species, and have recently featured as electrophilic partners in copper-catalyzed borylative MCRs.

4.1. Allenes

In 2016, Montgomery and co-workers[44] reported the copper-catalyzed borylative trifunctionalization of terminal allenes 8 with the cyanating reagent NCTS 46a (Scheme 13 A). The process demonstrated high diastereoselectivity, good functional group compatibility, and high yields (Scheme 13B). As discussed previously (Scheme 2), initial borocupration forms an allyl copper intermediate int-12 (Scheme 13C). Subsequent cyanation with NCTS affords intermediate 48. A second borocupration, followed by protodemetalation, delivers the trifunctionalized product 47 via int-13.
4.2. Vinylarenes

In 2014, Yang and Buchwald\textsuperscript{[45]} reported a copper-catalyzed, regioselective borylative cyanation of 2-vinylnaphthalene derivatives\textsuperscript{49} using NCTS\textsuperscript{46a} (Scheme 14A). The reaction displayed a clear selectivity for ortho-cyanation over benzylic cyanation (observed in less than 5%), and an exclusive preference for the most hindered ortho position (C1 vs. C3). Substitution at the C6 position of the 2-vinylnaphthalene derivatives was well tolerated (Scheme 14B). Interestingly, deuterium labelling and crossover experiments showed an intramolecular transfer of the C1 deuterium of labelled 1-D-49a to the benzylic position of 50d.

Shortly after, Montgomery and co-workers\textsuperscript{[46]} reported the copper-catalyzed borylative cyanation of vinylarene derivatives\textsuperscript{49} with NCTS\textsuperscript{46a} (Scheme 14A). The same ortho-selectivity was observed using the copper-NHC pre-catalyst IMesCuCl. For 2-vinylnaphthalene, cyanation at C1 was observed (51a). However, in the case of substituted styrenes, the nitrile group was directed to the least sterically hindered ortho-carbon (Scheme 14C).

The origin of regioselectivity was studied by Yang and Liu\textsuperscript{[47]} using DFT (Scheme 15). They proposed that benzylic cyanation is disfavored as a high energy 4-membered transition state TS6 is required, whereas the ortho-cyanation features a more favorable six-membered TS (TS5a and TS5b). The selectivity for C1 over C3 cyanation in 2-vinylnaphthalene derivatives comes from a lower disruption of the aromaticity of the naphthalene system in TS5a than in TS5b. Facile 1,2-elimination of the copper tosylamide from int-14 then leads to a deaeromatized intermediate. Next, as previously demonstrated by Yang and Buchwald in a deuterium labeling experiment, rearomatization occurs by an intramolecular 1,3-migration of the CI hydrogen via a six-membered transition state TS7, followed immediately by benzylic protonation TS8.

Yang\textsuperscript{[48]} recognised the potential of the deaeromatized intermediates to undergo rearomatization-driven sigmatropic rearrangement and disclosed a catalytic borylation/ortho-cyanation/Cope rearrangement sequence (Scheme 16A). After the initial borocupration and ortho-cyanation (vide supra), pre-installed allyl chains at the C1 position of 2-vinylnaphthalene derivatives\textsuperscript{52} migrate to the benzylic position in a [3,3]-sigmatropic Cope rearrangement to re-establish aromaticity without the need for an alkoxide-assisted [1,3]-H...
shift (see int-15, Scheme 16A). Neither benzylic cyanation or functionalization at the allyl moiety were observed.

In 2018, Xiao, Fu and co-workers\textsuperscript{[49]} reported a complementary copper-catalyzed benzylic cyanation of vinylarenes 49 (Scheme 17A). The unprecedented regioselectivity was achieved by using dimethylalononitrile (DMMN) 54, instead of NCTS derivatives 46, as the electrophilic cyanating agent. Benzylic nitriles were obtained in good yields from a wide range of vinylarenes, encompassing 2-vinylnaphtalene and styrene derivatives (Scheme 17B). Notably, the presence of an allyl chain at the C1 position of 2-vinylnaphtalene did not lead to the Cope rearrangement seen by Yang.

4.3. Dienes

In 2018, Procter and co-workers\textsuperscript{[50]} reported the ligand-controlled, regiodivergent borocyanation of 1,3-dienes 27 (Scheme 18A). The bidentate phospine ligand XantPhos L13 and 4-methoxy substituted NCTS derivative 46b gave excellent regiocontrol and very good yields of the 4,3-borocyanated product 56 (Scheme 18B). Whereas, switching to the monodentate phospine ligand PCy\textsubscript{3} L14 and para-CF\textsubscript{3} NCTS derivative 46c enabled 1,2-borocyanation to give products 57 with good selectivity and excellent yields (Scheme 18B).

Shortly after, both Huang and co-workers\textsuperscript{[51]} and Li and co-workers\textsuperscript{[52]} investigated the origin of the regiodivergency through DFT calculations (Scheme 18C). They suggested that, due to the steric bulk of ligand L13, borocupration occurs across the less hindered C4–C3 double bond to give the allyl copper species int-16a followed by rearrangement to int-16b. Subsequent cyanation gives the 4,3-borocyanated product 56. Conversely, borocupration occurs across C1–C2 with the less bulky ligand PCy\textsubscript{3} L14 due to the greater contribution of C1 to the LUMO, ultimately leading to the 1,2-borocyanated isomer 57.

Soon after, Meng and co-workers\textsuperscript{[53]} disclosed the copper-catalyzed cyanation of substituted 1,3-diene derivatives 58 (Scheme 19A). Excellent regioselectivity and E-stereoselectivity was achieved using CuCl and ligand L13 across a wide range of substrates (Scheme 19B). 4,3-Borocyanation dominated with 1-substituted, 1,2-disubstituted, and 1,3-disubstituted dienes yielding products 59 exclusively (see 59a–g). On the other hand, 1,1-disubstituted dienes afforded products such as 59h, arising from 4,1-borocyanation.

In the same year, Procter and co-workers\textsuperscript{[54]} disclosed an enantioselective 1,2-borocyanation of 1,3-dienes 60 that delivered enantiomerically enriched allylic nitriles 61 (Scheme 20A). Substrates bearing heterocycles and substituted arenes were compatible, and gave the anticipated products with excellent regio- and enantiocontrol (Scheme 20B).

4.4. Addition Across Nitriles

In 2019, Hoveyda and co-workers\textsuperscript{[55]} presented a borylative coupling of allenes and nitriles to access primary alkylamines (Scheme 21A). The process consists of two copper-catalyzed cycles: first, borocupration of 8 gives an allyl copper species that adds to nitriles 62, giving ketimine intermediates...
In a second cycle, these intermediates are reduced to the desired amine by a copper hydride species. Alkylallenes were coupled to a range of aromatic and aliphatic nitriles using L16 to afford syn-63 in good yields, with very good diastereo- and enantiocontrol (Scheme 21A). Intramolecular N/B coordination was shown to be essential to activate the ketimine towards CuH reduction and to achieve excellent stereocontrol (TS9, Scheme 21C). Through a three-step process, anti-63 products were obtained utilizing ligand L17 (Scheme 21B). As spontaneous reduction does not occur with this system, Al(OTf)3 was added to promote decoordination of the N/B pair and allow LiBH4 reduction (TS10, Scheme 21C).

Competition experiments (Scheme 21D) showed that formation of the copper-hydride int-20, hydrocupration of the allene 8 and addition of the resulting organocopper species (e.g. int-19b) to the nitrile were all faster than the equivalent borylative process. To avoid this undesired process, Hoveyda and co-workers used an excess of the polymeric silane, polymethylhydroisloxiane (PMHS), and a finely tuned mixture of alcohols to engage the copper hydride catalyst in an unproductive cycle (Scheme 21D).

Prior to this work, Liu and co-workers had reported a related intramolecular borylative cyclization of o-(cyano)phenyl propargyl ethers 64 (Scheme 22A). Allenes were first generated in situ by DBU isomerization (int-21). Borocupration by a copper/dppf complex followed by addition to nitriles formed ketimine intermediates that spontaneously isomerized to gain aromaticity and form naphthylamines 65 (Scheme 22B).

In 2020, Mazet and co-workers reported the synthesis of chiral β-borylated secondary amides from the coupling of styrenes with isocyanates (Scheme 23A). Good yields were obtained using an achiral NHC ligand (Scheme 23B). Other olefins were also evaluated as coupling partners: strained bicyclic alkenes, 1,3-dienes, and alkynes afforded good yields, however, other coupling partners were also found to be successful.

Scheme 20. Procter’s Cu-catalyzed regio- and enantioselective borylation of dienes. CuTc = copper(I) thiophene-2-carboxylate.

Scheme 21. Hoveyda’s Cu-catalyzed borylative couplings of nitriles and allenes. PMHS = polymethylhydroisloxiane.

Scheme 22. Liu’s Cu-catalyzed borylative cyclization of o-cyanophenyl propargyl ethers.

Scheme 23. Mazet’s Cu-catalyzed borylative couplings of isocyanates and olefins.
substituted and heteroaromatic styrene derivatives were not effective. In addition, an enantioselective functionalization of styrenes was developed with the chiral phosphine ligand L18 (Scheme 23, A,C).

6. Summary and Outlook

The past decade has seen significant progress made in the development of a suite of copper-catalyzed processes for the borofunctionalization of olefins using C–N electrophiles. Numerous olefins, ranging from complex polyenes to simple styrene feedstocks, have been validated as coupling partners. Similarly, various C–N inputs have been utilized. Early transformations using achiral catalysts have rapidly evolved into highly enantioselective processes and the approach now allows efficient, catalytic access to important synthetic building blocks.

A number of challenges face this nascent area of research. For example, copper-catalyzed MCRs are still limited to activated alkenes and extension of this methodology to unactivated, “simple” alkenes remains a goal for the future. Furthermore, a full understanding of the factors affecting regio- and stereoselectivity is needed and will aid our ability to predict reaction outcomes and to systematically develop new regio- and stereoselective borofunctionalizations.

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Conflict of interest

The authors declare no conflict of interest.

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