Copper(I)–Thiazol-2-ylidenes: Highly Reactive N-Heterocyclic Carbenes for Hydroboration of Terminal and Internal Alkynes. Ligand Development, Synthetic Utility and Mechanistic Studies.

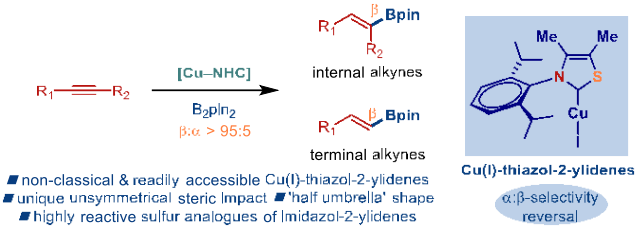
Jin Zhang,*,† Xue Li,† Tao Li,† Gaopeng Zhang,§ Kerou Wan,§ Yangmin Ma,† Ran Fang,*,† Roman Szostak,|| and Michal Szostak*,‡

†*College of Chemistry and Chemical Engineering, Key Laboratory of Chemical Additives for China National Light Industry, Shaanxi University of Science and Technology, Xi'an 710021, China*

§*Kaili Catalyst & New Materials CO., LTD, Xi'an 710299, China*

||*Department of Chemistry, Wroclaw University, F. Joliot-Curie 14, Wroclaw 50-383, Poland*

‡*Department of Chemistry, Rutgers University, 73 Warren Street, Newark, New Jersey 07102, United States*



ABSTRACT: In the last 15 years, copper-catalyzed borylative transformations utilizing boryl–copper have been established as a powerful activation mode in organic synthesis and catalysis, enabling direct transformations of various π-systems. Although many of these transformations use NHC ligands (NHC = N-heterocyclic carbene), these studies have been almost exclusively limited to the derivatives of imidazol-2-ylidenes. However, the molecular properties of N-aryl-imidazol-2-ylidenes, such as IPr (IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene), are limited by (1) the high degree of heteroatom stabilization, and (2) symmetrical substitution of the nitrogen atoms. Herein, we report a study on Cu(I)–thiazol-2-ylidenes, thiazole analogues of imidazol-2-ylidenes, which (1) feature distinct half-umbrella shape of the coordinating ligand, and (2) exhibit lower heteroatom stabilization of the ancillary ligand through reduced π donation from sulfur. We present the development of a family of stable Cu(I)–thiazol-2-ylidenes, where the combined sterics of thiazol-2-ylidenes lead to monomers [Cu(NHC)X] or bridged-halo dimers [Cu(NHC)(μ-X)]$_2$, their crystallographic characteristics, and application to the hydroboration of alkynes to afford trisubstituted vinylboronates by β-hydroboration of internal alkynes or terminal vinylboronates by β-hydroboration of terminal alkynes. Application to the late-stage modification and detailed mechanistic studies on the catalyst structure and activation are presented. Most crucially, Cu(I)–thiazol-2-ylidenes show much higher β-selectivity in hydroboration of alkynes than classical imidazol-2-ylidenes, affording vinylborons in excellent yields at ambient conditions. The unique 'half-umbrella' shape of thiazol-2-ylidenes reverses the α:β regioselectivity observed with imidazol-2-ylidenes in hydroboration of terminal alkynes. Kinetic studies demonstrate that Cu(I)–thiazol-2-ylidenes supersede imidazol-2-ylidenes. Considering the significant utility of borylative transformations of π-systems, we anticipate that Cu(I)–thiazol-2-ylidenes will advance the synthetic transformations of boryl–copper in organic synthesis and catalysis.

KEYWORDS: copper catalysis, thiazol-2-ylidene, *N*-heterocyclic carbenes, hydroboration, DFT studies

Introduction

Organoboron compounds are one of the most important motifs in organic synthesis. The versatile reactivity as organoborons as precursors to a plethora of molecules bearing diverse functional groups has spurred an array of methodologies for the synthesis of C–B bonds.[1-4] Among the methods developed, one of the most powerful are Cu-catalyzed functionalizations of π-systems (Figure 1A).[5]

These reactions enable to install a boronate and an electrophile in a programmed fashion across unsaturated systems and can be engaged in sequential and cooperative processes, resulting in a significant utility in the preparation of organoborons.[6] To date, this reactivity platform has been shown to be uniquely effective with a variety of π-systems and electrophiles, including alkynes, allenes, alkenes, heterocycles as well as polar derivatives, such as ketones, aldehydes, acid halides, imines and epoxides.[7] Mechanistically, these reactions involve generation of boryl–copper species, which adds across π-unsaturation to give organocopper that participates in subsequent transformations.[8]

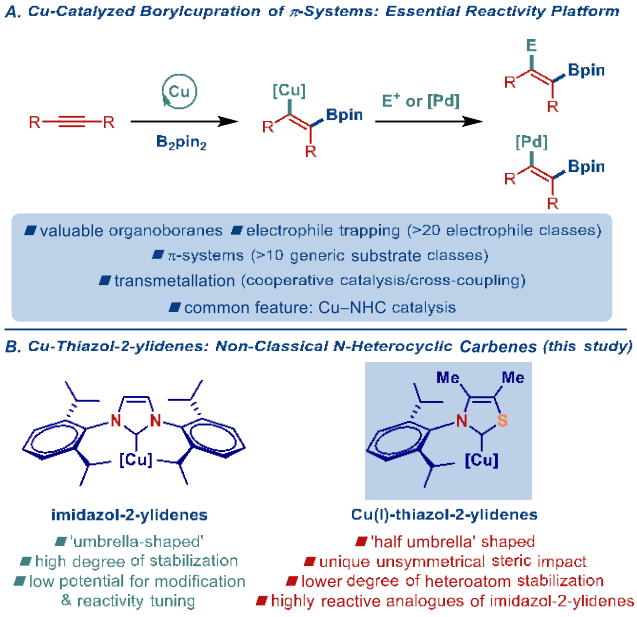


Figure 1. (A) Cu(I)-catalyzed borylcupration of π-systems. (B) Cu(I)-thiazol-2-ylidenes: non-classical, sterically- and electronically-unique Cu(I)–NHCs for borylcupration of π-systems (this study).

Since the seminal studies by Hoveyda,[9] Cu(I)–NHCs (NHC = N-heterocyclic carbenes) are a major direction in the development of new transformations of boryl–copper species. Studies by Sadighi,[10] Tsuji[11] and others[12] have shown the stabilization of NHC-ligated boryl–copper and its role as an active species in this particularly useful borylcuprative reactivity platform. While many of these transformations use NHC ligands, these studies have been almost exclusively limited to the derivatives of imidazol-2-ylidenes.[13] However, the properties of N-aryl-imidazolylidenes, such as IPr (IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene), are limited by (1) the symmetrical substitution of the nitrogen atoms, and (2) high degree of heteroatom stabilization.[14] To fully exploit the potential of NHC ligands in borylcupration of π-systems it is critical that new active NHC ligands are identified to expand the reactivity of imidazol-2-ylidenes.

Herein, we report the first study on Cu(I)–thiazol-2-ylidenes, thiazole analogues of imidazol-2-ylidenes (Figure 1B). These thiazole-based ligands (1) feature distinct half-umbrella shape of the coordinating ligand, which leads to a differential steric impact during the migratory insertion of the copper–boryl species to π-systems, and (2) exhibit lower degree of heteroatom stabilization of the ancillary ligand through reduced π-donation from sulfur, which results in higher kinetic reactivity of the catalyst system, while maintaining the beneficial effect of the NHC ligand.[15]

The following features of our study are noteworthy: (1) the development of a family of stable Cu(I)–thiazol-2-ylidenes, where the combined sterics of thiazol-2-ylidenes lead to monomers [Cu(NHC)X] or bridged-halo dimers $[Cu(NHC)(\mu\text{-}X)]_2$; (2) application to the valuable hydroboration of alkynes to afford trisubstituted vinylboronates by β-hydroboration of internal alkynes or terminal vinylboronates by β-hydroboration of terminal alkynes, including late-stage modification; (3) DFT studies on catalyst structure, activation and borylation selectivity. Most crucially, Cu(I)–thiazol-2-ylidenes show high activity in hydroboration of alkynes, affording vinylborons in excellent yields at ambient conditions. The unique 'half-umbrella' shape of thiazol-2-ylidenes reverses the α:β selectivity observed with imidazol-2-ylidenes in hydroboration of terminal alkynes. We fully expect that Cu(I)–thiazol-2-ylidenes will advance the synthetic transformations involving boryl–copper in organic synthesis and catalysis.

Results and Discussion

Design. As part of our program in catalysis, we sought to expand the chemical space of NHC ligands for organic transformations.[16] Cognizant of the properties of symmetrical and nitrogen-stabilized imidazol-2-ylidenes, we proposed that improvements in catalytic activity could be achieved by exploring unsymmetrical and less heteroatom stabilized thiazol-2-ylidenes. These thiazole analogues of classical imidazol-2-ylidenes are inherently reactive in organocatalysis,[17] where they stabilize enol Breslow intermediates, including ketyl radicals, through dispersive delocalization;[18] however, this class of ligands is vastly unexplored in transition-metal-catalysis.[16j, 19]

The molecular shape of thiazol-2-ylidenes presents a unique opportunity that can be defined as 'half-umbrella' shape (cf. 'umbrella' shape of classical imidazol-2-ylidenes, Figure 1B), while the lack of substitution at the sulfur atom renders thiazol-2-ylidenes geometrically similar to protic NHCs. Electronically, thiazol-2-ylidenes are more electrophilic than imidazol-2-ylidenes owing to the large radius of sulfur and reduced π donation from sulfur.

It is important to note that the 'half umbrella' shape refers to the lack of substituent on the sulfur atom, which creates an unsymmetrical environment and is in contrast to imidazol-2-ylidenes.[20] The presence of methyl groups on the thiazol-2-ylidene backbone hinders the rotation of the N-Ar wingtip, providing a defined catalytic pocket. This shape is also distinct from CAAC ligands featuring a quaternary carbon atom adjacent to the carbenic carbon.[13h] A recent study demonstrated [(CAAC)CuOTf] complexes to selectively promote dehydrogenative borylation of C(sp)–H bonds at room temperature. σ,π-Bis(copper) acetylide and copper hydride complexes were identified as catalytic species.[13h]

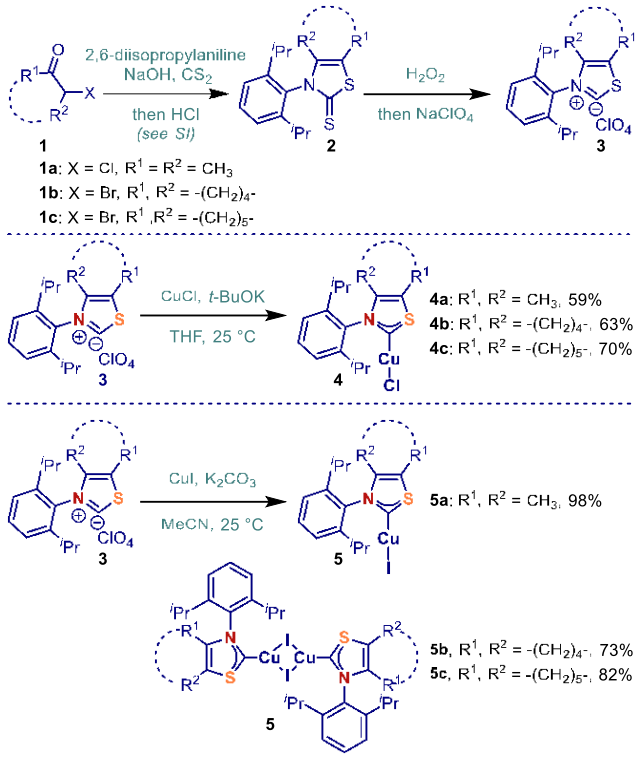
Our study commenced with probing the synthesis of Cu(I)–thiazol-2-ylidenes (Scheme 1). Prior to our study, Cu(I)–N-aryl-thiazol-2-ylidenes had not been reported, thus at the beginning it was not clear if the complexes would be stable to standard handling and isolation, factors that are critical for a successful use in catalysis.

Synthesis. After very extensive optimization, we identified conditions for the synthesis of Cu(I)–thiazol-2-ylidenes (Scheme 1, CuCl, 1.1 equiv; KO*t*Bu, 1.0 equiv, THF, 25 °C), which afforded the desired [Cu(NHC)Cl] complexes **4a–4c** in 59-70% yields. Note that the synthesis of **4a** has been

previously reported.[20] We also prepared the analogous iodo complexes **5a–5c** (CuI, 1.0 equiv; K_2CO_3, 2.0 equiv, CH_3CN, 25 °C) in 73-98% yields. Interestingly, these complexes exist as monomers [Cu(NHC)X] or bridged-halo dimers $[Cu(NHC)(\mu\text{-}X)]_2$ in the solid state depending on the steric properties of the thiazol-2-ylidene ligand (*vide infra*).

It should be noted that N-aryl thiazolium precursors are easily available on multigram scale (Scheme 1, **1–3**), providing facile entryway to study the properties of thiazol-2-ylidenes in transition-metal catalysis.[17,20] Furthermore, we also probed the synthesis of an IMes analogue of thiazol-2-ylidenes; however, this less sterically-hindered Cu(I) complex was found unstable.[16j] The synthesized complexes represent thiazole analogues of IPr in 3-aryl-4,5-dimethylthiazol-2-ylidene scaffold. The following abbreviations are used: **3a**: ^{Me}**TPr** (**^{Me}IPrS**) **3b**: ^{6}**TPr** (**^{6}IPrS**); **3c**: ^{7}**TPr** (**^{7}IPrS**).

Scheme 1. Synthesis of Cu(I)–Thiazol-2-ylidene Complexes[a]



[a]Conditions: CuCl (1.1 equiv), KO*t*Bu (1.0 equiv), THF, 25 °C, 16 h. **4a**: 59%; **4b**: 63%; **4c**: 70%; CuI (1.0 equiv), K_2CO_3 (2.0 equiv), CH_3CN, 25 C, 16 h; **5a**: 98%; **5b**: 73%; **5c**: 82%.

Crystallographic Characterization. All Cu(I)–thiazol-2-ylidene complexes **4a–4c** and **5a–5c** were found to be air- and moisture-stable. All complexes **4a–4c** and **5a–5c** were characterized by X-ray crystallography (Figure 2). Note that the crystal structure of **4a** has been previously reported.[20] The analysis is included for comparison purposes. Complexes **4a–4c** and **5a** are monomeric (**4a**: $C_{(NHC)}$–Cu–Cl, 177.0°; C–Cu, 1.871 Å; **4b**: $C_{(NHC)}$–Cu–Cl, 175.6°; C–Cu, 1.869 Å; **4c**: $C_{(NHC)}$–Cu–Cl, 177.2°; C–Cu, 1.868 Å; **5a**: $C_{(NHC)}$–Cu–I, 176.0°; C–Cu, 1.883 Å. Complexes **5b–5c** are symmetrical bridged halo dimers (**5b**: $C_{(NHC)}$–Cu–I, 107.1°, 141.9°; C–Cu, 1.911 Å; **5c**: $C_{(NHC)}$–Cu–I, 117.7°, 132.3°; C–Cu, 1.922 Å). The geometry of copper in $[Cu(NHC)(\mu\text{-}I)]_2$ (**5b–5c**) is trigonal planar, the bond lengths of $C_{(NHC)}$–C: 1.911-1.922 Å and Cu– I: 2.475-2.739 Å are significantly longer than in the mono-mer [Cu(NHC)X] (**5a**): $C_{(NHC)}$–C: 1.883 Å, Cu–I: 2.385 Å. These values can be compared with the imidazol-2-ylidene complex, [Cu(IPr)Cl]: $C_{(NHC)}$–Cu–Cl, 176.6°; C–Cu, 1.881 Å.

A clear distinctive feature of all Cu(I)–thiazol-2-ylidene complexes **4a–5c** is the geometry of the thiazole ring with 'half-umbrella' substitution and ring distortion (Figure 3), C–S–$C_{(carbene)}$: 93.8-94.6°; C–N–$C_{(carbene)}$: 116.3-117.9°; N–$C_{(carbene)}$–S: 106.7-107.3°; which can be compared with symmetrical C–N–$C_{(carbene)}$: 111.1° and smaller N–$C_{(carbene)}$–N: 104.3° in the imidazol-2-ylidene complex, [Cu(IPr)Cl]. The overall effect is a unique unsymmetrical and closer impact of the N-Ar wingtip on the catalytic pocket in thiazol-2-ylidenes. The linear monomeric [Cu(NHC)Cl] complexes **4a–4c** were analysed using the method by Cavallo[21] to evaluate catalytic pocket (Figure 4). The % buried volume (%V_{bur}) of

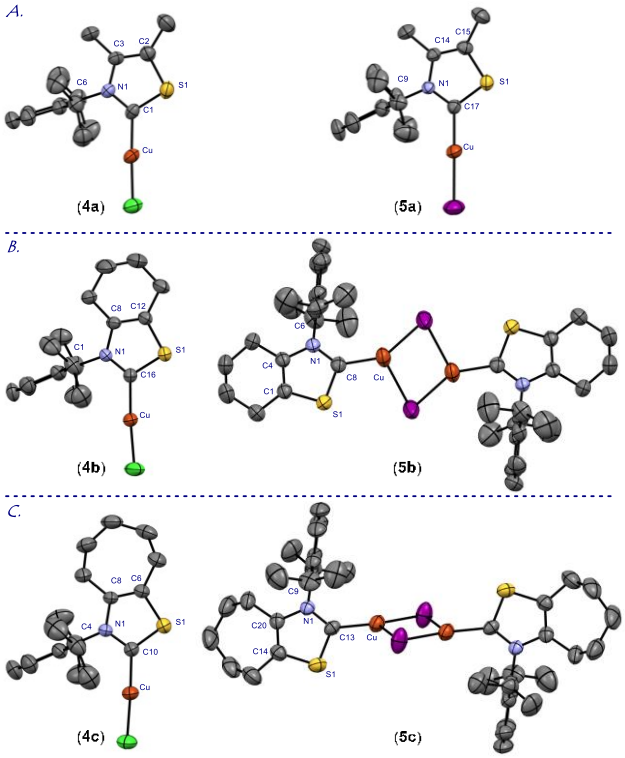


Figure 2. X-ray crystal structures of Cu(I) complexes (A) **4a–5a**; (B) **4b–5b**; (C) **4c–5c**. 50% ellipsoids. Hydrogen atoms have been omitted for clarity. CCDC 2117739 (**4a**); CCDC 2117744 (**4b**); CCDC 2117741 (**4c**); CCDC 2117740 (**5a**); CCDC 2117745 (**5b**); CCDC 2117743 (**5c**). Selected bond lengths [Å] and angles [°]: **4a**: Cu–C1, 1.871(2); Cu–Cl, 2.0947(7); C1–N1, 1.338(2); C1–S1, 1.700(2); C6–N1, 1.460(3); N1–C3, 1.402(3); S1–C2, 1.723(2); C1–Cu–Cl, 176.98(7); N1–C1–S1, 107.3(1); C6–N1–C1, 121.3(2); C3–N1–C1, 117.0(2); C2–S1–C1, 94.5(1). **4b**: Cu–C16, 1.869(4); Cu–Cl, 2.086(1); C16–N1, 1.338(5); C16–S1, 1.698(4); C1–N1, 1.452(5); N1–C8, 1.400(4); S1–C12, 1.724(4); C16–Cu–Cl, 175.6(1); N1–C16–S1, 107.3(1); C1–N1–C16, 120.2(3); C8–N1–C16, 116.3(3); C12–S1–C16, 93.8(2). **4c**: Cu–C10, 1.868(3); Cu–Cl, 2.086(1); C10–N1, 1.348(5); C10–S1, 1.695(3); C4–N1, 1.453(4); N1–C8, 1.402(4); S1–C6, 1.729(4); C10–Cu–Cl, 177.2(1); N1–C10–S1, 107.0(3); C4–N1–C10, 119.8(3); C8–N1–C10,

117.3(3); C6–S1–C10, 94.6(2). **5a**: Cu–C17, 1.883(3); Cu–I, 2.3854(6); C17–N1, 1.346(4); C17–S1, 1.703(4); C9–N1, 1.461(5); N1–C14, 1.397(4); S1–C15, 727(4); C17–Cu–I, 176.0(1); N1–C17–S1, 106.8(3); C9–N1–C17, 119.5(3); C14–N1–C17, 117.4(3); C15–S1–C17, 94.5(2). **5b**: Cu–C8, 1.911(6); Cu–I, 2.475(1); Cu–I, 2.7391(8); C8–N1, 1.348(7); C8–S1, 1.709(5); C6–N1, 1.456(6); N1–C4, 1.405(8); S1–C1, 1.728(6); C8–Cu–I, 107.1(2); C8–Cu–I, 141.9(2); I–Cu–I, 110.53(3); N1–C8–S1, 106.7(4); C6–N1–C8, 121.7(4); C4–N1–C8, 117.2(4); C1–S1–C8, 94.4(2). **5c**: Cu–C13, 1.922(4); Cu–I, 2.563(1); Cu–I, 2.6263(7); C13–N1, 1.344(4); C13–S1, 1.699(4); C9–N1, 1.460(5); N1–C20, 1.410(6); S1–C14, 1.728(4); C13–Cu–I, 117.7(1); C13–Cu–I, 132.3(1); I–Cu–I, 108.58(3); N1–C13–S1, 107.0(3); C9–N1–C13, 120.7(3); C20–N1–C13, 117.1(3); C14–S1–C13, 94.8(2).

(**4a–4c**) is 37.0%, 35.1%, 38.3%, respectively. These values can be compared with [Cu(**IPr**)Cl] of 47.6%. The buried volume analysis shows key differences in steric quadrant distribution between thiazol-2-ylidenes **4a–4c** and IPr. As such, the (%V_{bur}) of complexes **4a–4c** (**4a**: 50.2%, 52.0%, 22.6%, 23.1%; **4b**: 50.0%, 44.4%, 22.9%, 23.0%; **4c**: 56.0%, 51.3%, 23.4%, 22.6%) indicates sterically-differentiated 'half-umbrella' shape of the N-aryl thiazol-2-ylidene ligands, which can be compared with symmetrical and sterically much less differentiated 'umbrella' shape **IPr** (55.5%, 39.6%, 39.6%, 55.5%); note that crystal packing affects geometry distribution in the latter case (*vide infra*).

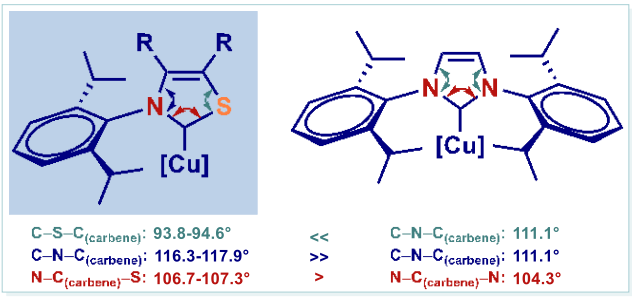


Figure 3. Key geometric features of Cu(I)–thiazol-2-ylidenes. Note dissymmetry and distortion of NHC in Cu(I)–thiazol-2-ylidenes.

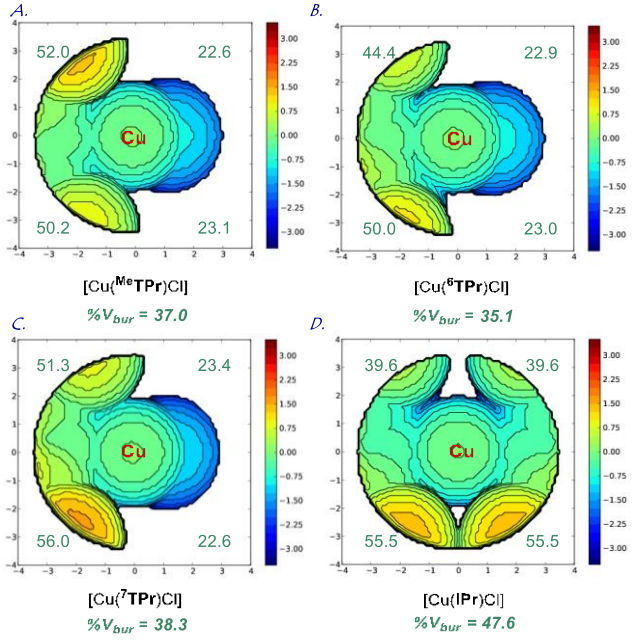


Figure 4. Topographical steric maps of Cu(I)–thiazol-2-ylidenes **4a–4c** and imidazol-2-ylidene [Cu(IPr)Cl] showing % V_{bur} per quadrant.

Steric Effect. To eliminate impact from steric packing, the percent buried volume (%V_{bur}) was calculated from the optimized structures of [Cu(NHC)Cl] complexes **4a–4c** and IPr at the B3LYP 6-311++g(d,p) level (Figure 5). These studies determined the %V_{bur} of NHC in [Cu(NHC)Cl] (**4a**) as 35.8% (SW, 49.2%; NW, 49.2%; NE, 22.4%; SE, 22.4%), in (**4b**) as 35.5% (SW, 49.1%; NW, 48.2%; NE, 22.4%; SE, 22.4%) and in (**4c**) as 35.7% (SW, 50.0%; NW, 48.2%; NE, 22.4%; SE, 22.4%). These values can be compared with the %V_{bur} of 42.6% (SW, 42.6%; NW, 42.6%; NE, 42.6%; SE, 42.6%) for standard imidazol-2-ylidene complex [Cu(IPr)Cl].

The optimized geometry clearly points at (1) tightening of the C–S–$C_{(carbene)}$ angle (**4a–4c**, avg. 93.9°), which can be compared with the analogous C–N–C(carbene) angle of 111.4° in [Cu(IPr)Cl]; and (2) opening of the C–N–$C_{(carbene)}$ and N–$C_{(carbene)}$–S angles in **4a–4c** (avg. 117.3° and 107.5°), which can be compared with the analogous angles of 111.4° and 104.0° in [Cu(IPr)Cl]. The outcome is a much tighter control of the catalytic pocket by the N-Ar wingtip in thiazol-2-ylidenes **4a–4c** than in classical imidazol-2-ylidenes (N-Ar(C_{ipso})–Cu: 3.289 Å vs. 3.378 Å in [Cu(IPr)Cl]; N-Ar($C_{i\text{-}Pr}$)–Cu: 3.982 Å vs. 4.205 Å in [Cu(IPr)Cl]).

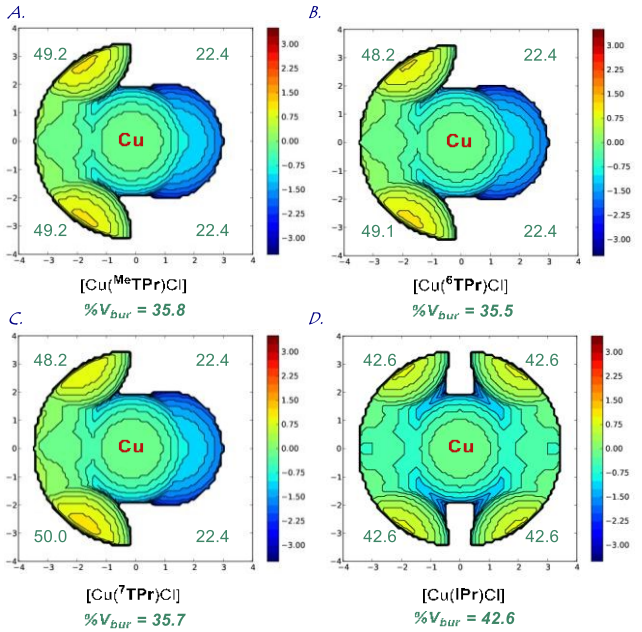
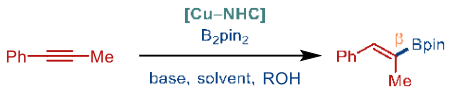


Figure 5. (A–D) Topographical steric maps of Cu(I)–thiazol-2-ylidenes **4a–4c** and imidazol-2-ylidene [Cu(IPr)Cl] showing % V_{bur} per quadrant at B3LYP 6-311++g(d,p) level. Note symmetry of [Cu(IPr)Cl].

Catalysis. With access to Cu(I)–thiazol-2-ylidenes **4–5**, we examined their reactivity in Cu(I)-catalyzed borylation (Table 1). Hydroboration of alkynes was selected as a model system because of the fundamental role of vinylborons in organic synthesis and the capacity of this method to serve as a versatile platform to develop subsequent reactions of boryl–copper with diverse π-systems and electrophiles. Initial experiments showed that the proposed hydroboration was possible and identified (**5a**) ([Cu(**MeTPr**)I] as the preferred catalyst (Table 1, entries 1-6). Interestingly,

Table 1. Optimization of Cu(I)–Thiazol-2-ylidene-Catalyzed β-Hydroboration of Alkynes[a]



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Entry	Catalyst (mol %)	Base	Solvent	ROH	Yield (%)
1	**4a** (10)	NaO*t*Bu	MTBE	MeOH	59
2	**4b** (10)	NaO*t*Bu	MTBE	MeOH	62
3	**4c** (10)	NaO*t*Bu	MTBE	MeOH	67
4	**5a** (10)	NaO*t*Bu	MTBE	MeOH	92
5	**5b** (10)	NaO*t*Bu	MTBE	MeOH	46
6	**5c** (10)	NaO*t*Bu	MTBE	MeOH	53
7	**5a** (5)	NaO*t*Bu	MTBE	MeOH	92
8	**5a** (2.5)	NaO*t*Bu	MTBE	MeOH	90
9	**5a** (1)	NaO*t*Bu	MTBE	MeOH	74
10	**5a** (2.5)	NaO*t*Bu	DCM	MeOH	87
11	**5a** (2.5)	NaO*t*Bu	^{i}PrOH	MeOH	69
12	**5a** (2.5)	NaO*t*Bu	dioxane	MeOH	84
13	**5a** (2.5)	NaO*t*Bu	anisole	MeOH	75
14	**5a** (2.5)	NaO*t*Bu	MeOH	MeOH	74
15	**5a** (2.5)	NaO*t*Bu	CPME	MeOH	97
16	**5a** (2.5)	NaO*t*Bu	THF	MeOH	79
17	**5a** (2.5)	NaO*t*Bu	toluene	MeOH	65
18	**5a** (2.5)	NaOH	CPME	MeOH	80
19	**5a** (2.5)	LiO*t*Bu	CPME	MeOH	85
20	**5a** (2.5)	NaOMe	CPME	MeOH	80
21	**5a** (2.5)	K_2CO_3	CPME	MeOH	77
22	**5a** (2.5)	KHMDS	CPME	MeOH	81
23	**5a** (2.5)	K_3PO_4	CPME	MeOH	70
24	**5a** (2.5)	NaO*t*Bu	CPME	EtOH	82
25	**5a** (2.5)	NaO*t*Bu	CPME	^{i}PrOH	68
26	**5a** (2.5)	NaO*t*Bu	CPME	^{t}BuOH	59

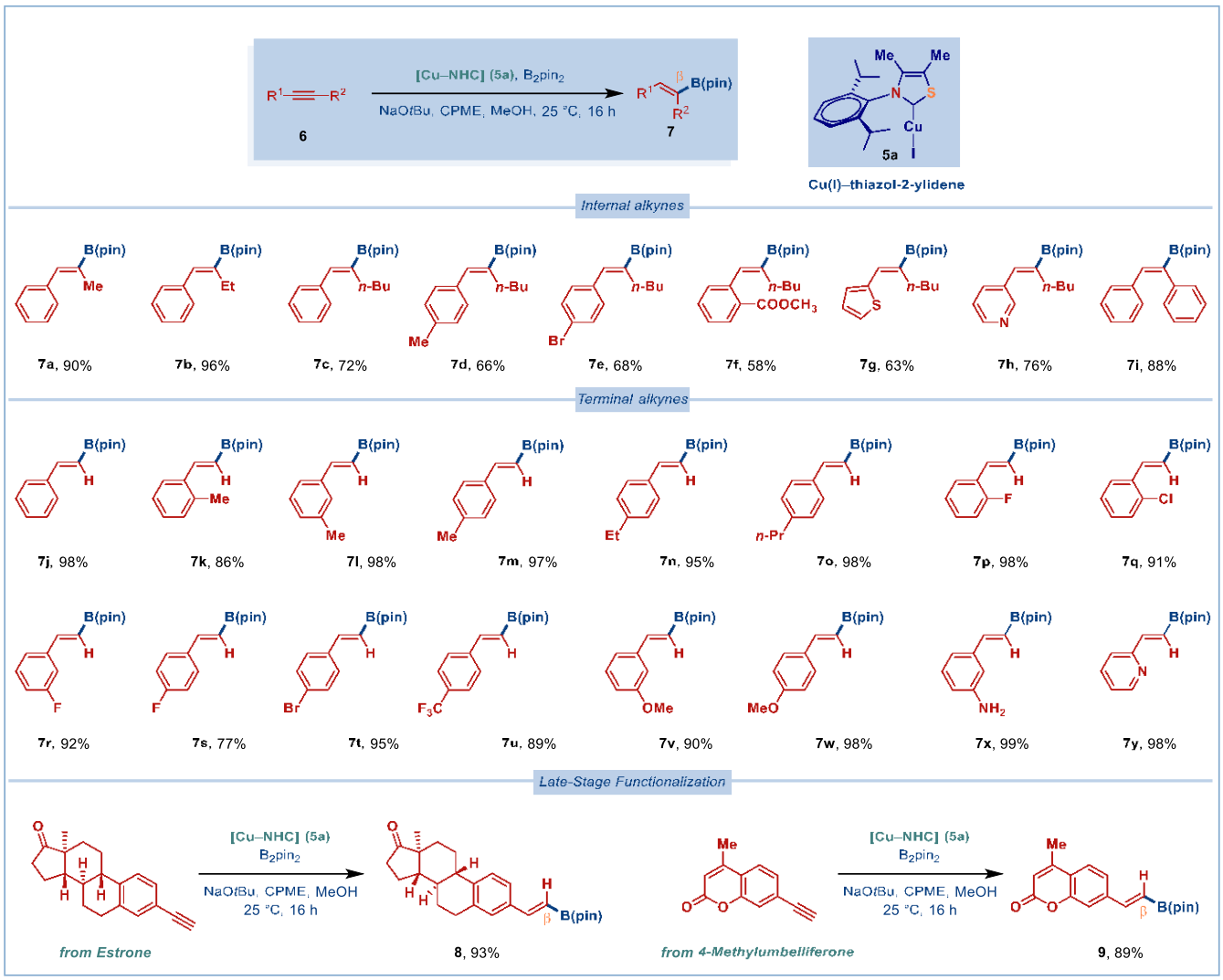
[a]Conditions: 1-Phenyl-1-propyne (1.0 equiv), B_2pin_2 (1.1 equiv), base (30 mol %), Cu(I)–NHC (1-10 mol%), ROH (2.0 equiv), solvent (0.5 M), 25 °C, 16 h. CPME: cyclopentyl methyl ether. See SI for details.

monomeric complexes **4a–4c**, **5a** showed in general higher reactivity than the dimeric complexes **5b–c**, suggesting that dimer dissociation might be a kinetically relevant step in this process. Further screening revealed that catalyst loading could be decreased to 2.5 mol% without a significant decrease in the reaction efficiency (Table 1, entries 7-9). An extensive evaluation of different solvents identified CPME (cyclopentyl methyl ether) as the preferred solvent for this reaction (Table, entries 10-17). Furthermore, we determined that a base selection had an important impact with NaO*t*Bu providing the optimum yield (Table 1, entries 18-23). Finally, we screened different proton sources and found that MeOH is the most suitable for capturing the organocopper under these conditions (Table 1, entries 24-25). It is worth noting that the product of this hydroboration is a trisubstituted vinylboronate formed by β-hydroboration with >95:5 regio and *Z*-selectivity, indicating high steric control over the borylcupration and electrophilic trapping steps by the thiazol-2-ylidene scaffold.

With the optimized conditions in hand, we next determined the scope of this Cu(I)-catalyzed hydroboration of alkynes using Cu(I)-thiazol-2-ylidene complex (**5a**) (Table 2). As shown, the scope of this hydroboration is broad and compatible with a wide range of internal and terminal alkynes. As such, various internal alkynes were found to be excellent substrates for this reaction, delivering β-hydroboration products as single *Z* isomers with >95:5 selectivity (**7a–7i**). Importantly, we found that this thiazol-2-ylidene catalyst system is compatible with halides (**7e**), electrophilic carbonyls (**7f**) and both electron-rich (**7g**) and electron-deficient (**7h**) heterocycles, providing handles for further functionalization and furnishing valuable trisubstituted boronates for medicinal chemistry research. Furthermore, this protocol could be applied to terminal alkynes to deliver β-vinylboronates (**7j–7y**). In all cases, the products were formed as single regioisomers (β:α >95:5). *Notably, this regioselectivity is reversed to the protocols using Cu(I)–imidazol-2-ylidene complexes, which deliver α-vinylborons,*[9b] *and clearly originates from a differential steric impact of the thiazol-2-ylidene scaffold (vide infra)*. We found that the scope of this hydroboration of terminal alkynes is very broad and accommodates a variety of phenylacetylenes was various steric hindrance (**7k**, **7p–7q**) and electronic nature of the substituents (**7l–7y**). Most notably, this catalyst system showed excellent tolerance towards functional groups, including halides (**7p–7t**), amino groups (**7x**) and coordinating heterocycles (**7y**), furnishing high yields and excellent regioselectivity across all substrates examined. At present stage, aliphatic terminal alkynes afford the borylation products in approximately 40% yield. These mild hydroboration conditions could also be applied in late-stage functionalization of complex substrates derived from steroids and coumarins (Table 2). Thus, the hydroboration of alkynes derived from estrone and 4-methylumbelliferone delivered the desired β-hydroboration products in excellent yields with >95:5 regioselectivity, highlighting the attractive potential of thiazol-2-ylidenes in medicinal chemistry.

To gain further insight into the reactivity of Cu(I)–thiazol-2-ylidenes, kinetic studies were conducted (Figure 6). As shown, the thiazol-2-ylidene based catalyst **5a** outperformed the standard IPr-based [Cu(IPr)I] in hydroboration of 1-phenyl-1-propyne. It is worthwhile to note that the side-by-side comparison is done between catalysts bearing the same halogen in both starting complexes. [Cu(IPr)I] gives approx. 10% faster conversions than [Cu(IPr)Cl] under the same conditions. Our ongoing studies are directed at determining the effect of throw-away ligands on thiazol-2-ylidene-metal complexes on their reactivity. Furthermore, the thiazol-2-ylidene based **5a** showed favorable reactivity in the hydroboration of phenylacetylene. Note that the latter process leads to different regioselectivity with thiazol-2-ylidene (β-product, >98:2) vs. imidazol-2-ylidenes (α:β product, IMes, 50:50; SIMes, 77:23, IPr, 40:60).[9a,b] In general, symmetrical imidazol-2-ylidene-copper give α or mixed selectivity of terminal alkynes depending on sterics of N-wingtip. The use of different metals affects the regioselectivity.[9b,7,13] Importantly, the kinetic studies are consistent with the high reactivity of Cu(I)–thiazol-2-ylidenes in the

Table 2. Scope of Cu(I)–Thiazol-2-ylidene-Catalyzed β-Hydroboration of Alkynes[a]



[a]Conditions: alkyne (1.0 equiv), B_2pin_2 (1.1 equiv), NaO*t*Bu (30 mol %), Cu(I)–NHC (**5a**) (2.5 mol %), MeOH (2.0 equiv), CPME (0.5 M), 25 °C, 16 h.

rate determining borylcupration step (*vide infra*).

Computational Studies. To gain insight into this intriguing class of Cu(I)-thiazol-2-ylidenes, density functional theory (DFT) computations based on two catalysts including [Cu(IPr)Cl] (series A) and Cu(I)-thiazol-2-ylidenes (series B) were conducted (Figure 7). The starting point for DFT calculations is LCu–Bpin. For [Cu(IPr)Cl] or Cu(I)-thiazol-2-ylidenes, alkyne **Re1** coordinates to Cu center, giving the coordination complexes **1a** and **1b** via **TS$_a$1** and **TS$_b$1**, respectively, depending on the two coordination modes. The free energies of activation for **TS$_a$1** and **TS$_b$1** are 18.8, 16.3 and 14.7, 13.2 kcal/mol series A and B, respectively. Subsequent to alkyne coordination, the alkyne group inserts to the Cu-B bond by crossing the transition states (**TS$_a$2** and **TS$_b$2**), affording the intermediates (**2a** and **2b**), respectively. Vibrational frequency calculations were carried out at the B3LYP/6-31G(d) level of theory to characterize all the stationary points as either minima (the number

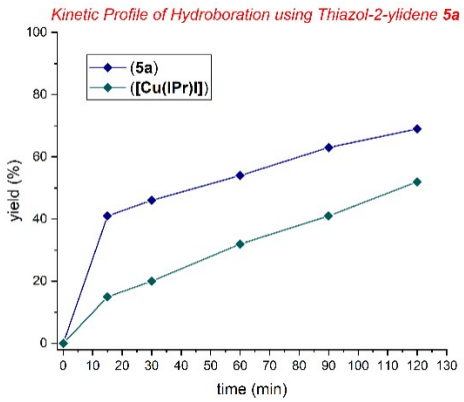


Figure 6. Kinetic profile using thiazol-2-ylidene **5a**. Conditions: 1-Phenyl-1-propyne (1.0 equiv), B_2pin_2 (1.1 equiv), NaO*t*Bu (30 mol%), Cu(I)–NHC (2.5 mol%), MeOH (2.0 equiv), CPME (0.5 M), 25 °C, 0-2 h.

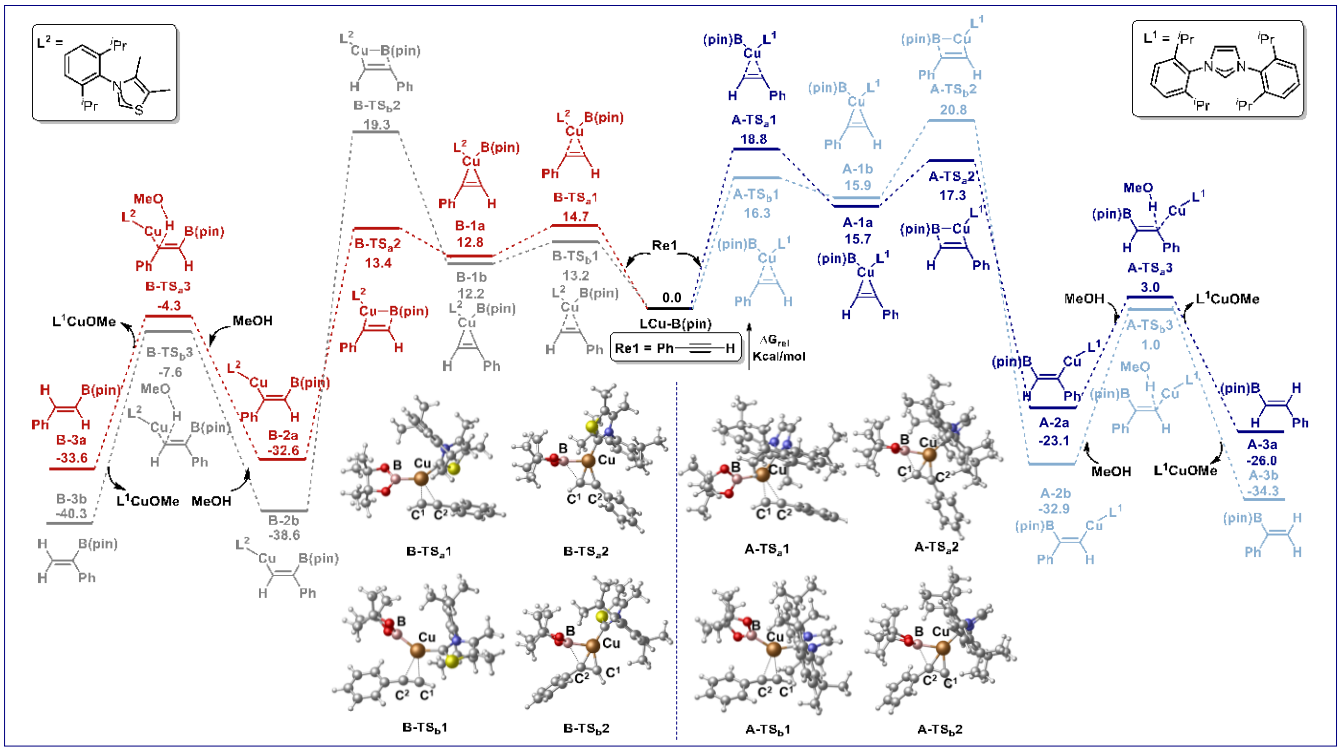


Figure 7. DFT-computed free energy profiles for Cu-NHC catalyzed hydroboration of alkynes. Selected bond lengths [Å]: **A-TS$_a$1**: Cu-C^1, 2.169; Cu-C^2, 2.667; Cu-B, 2.034. **A-TS$_a$2**: Cu-C^1, 1.917; Cu-C^2: 2.042; B-C^1, 2.157; Cu-B, 2.040. **A-TS$_b$1**: Cu-C^1, 2.332; Cu-C^2, 2.509; Cu-B, 2.022. **A-TS$_b$2**: Cu-C^1, 1.968; Cu-C^2, 1.964; B-C^2, 2.120; Cu-B, 2.064. **B-TS$_a$1**: Cu-C^1, 2.379; Cu-C^2, 2.529; Cu-B, 2.016. **B-TS$_a$2**: Cu-C^1: 1.915; Cu-C^2, 2.030; B-C^1, 2.234; Cu-B, 2.020. **B-TS$_b$1**: Cu-C^1, 2.116; Cu-C^2, 2.489; Cu-B, 2.029. **B-TS$_b$2**: Cu-C^1, 1.958; Cu-C^2, 1.962; B-C^2, 2.206 Å; Cu-B, 2.029 Å.

of imaginary frequencies (NIMAG=0) or transition states (NIMAG=1)). The calculation results show that all transition states have only one imaginary frequency. The number of imaginary frequencies are given in the supporting information. Relative to LCu-B(pin), the insertions overcome barriers of 17.3, 20.8 and 13.4, 19.3 kcal/mol for series A and B, respectively. These steps are exerognic by -23.1, -32.9 and -32.6, -38.6 kcal/mol series A and B, respectively. According to our calculation results, the free energies of activation for series B is lower than that of series A. Furthermore, the differences of free energies of activation between α and β selectivity are 2.0 and 4.5 kcal/mol for series A and B, respectively, which indicates that Cu(I)-thiazol-2-ylidenes should have significantly enhanced regioselectivity and activity than [Cu(IPr)Cl].

Conclusions

In summary, transformations involving boryl–copper rank among the most important processes in catalytic functionalization of π-systems. In this study, we have established Cu(I)–thiazol-2-ylidenes as a novel class of catalysts for borylcupration of alkynes. This process exploits unusual thiazol-2-ylidenes as unsymmetrical sulfur-based 'half-umbrella' shaped and less heteroatom stabilized NHC ligands. We have reported the synthesis of catalysts, their crystallographic characterization and high activity in hydroboration of internal and terminal alkynes. The hydroboration of internal alkynes using Cu(I)–thiazol-2-ylidenes affords valuable trisubstituted vinylboronates by β-hydroboration. Terminal alkynes afford β-vinylboronates with excellent regioselectivity, which is opposite to the regioselectivity observed with classical imidazol-2-ylidenes. This hydroboration occurs under mild conditions, in high yields and with excellent regioselectivity, including late-stage modification of complex substrates. Structural and DFT studies have been conducted to gain insight into the catalyst structure, activation and regioselectivity of borylcupration. The high reactivity of Cu(I)–thiazol-2-ylidenes makes it clear that this class of catalysts will be useful in advancing the borylcupration platform in organic synthesis and catalysis.

AUTHOR INFORMATION

Corresponding Author

zhangjin@sust.edu.cn

fangr@lzu.edu.cn

michal.szostak@rutgers.edu

Notes

The authors declare no competing financial interest.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, computational details, .cif files, coordinates and energies. This material is available free of charge via the Internet at http://pubs.acs.org.

ACKNOWLEDGMENT

J.Z. thanks National Natural Science Foundation of China (No. 22179075) and Scientific Research Project of Shaanxi Province Education Department (No. 22JC018). R.F. thanks National Natural Science Foundation of China (No. 21672090). M.S. thanks Rutgers University and the NSF (CAREER CHE-1650766) for support. We thank the Wroclaw Center for Networking and Supercomputing (grant number WCSS159).

REFERENCES

(1) Hall, D. G. Structure, Properties, and Preparation of Boronic Acid Derivatives. Overview of Their Reactions and Applications. In Boronic Acids; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, FRG, 2006; pp 1–99.

(2) Neeve, E. C.; Geier, S. J.; Mkhalid, I. A. I.; Westcott, S. A.; Marder, T. B. Diboron(4) Compounds: From Structural Curiosity to Synthetic Workhorse. *Chem. Rev.* **2016**, *116*, 9091-9161.

(3) Sandford, C.; Aggarwal, V. K. Stereospecific functionalizations and transformations of secondary and tertiary boronic esters. *Chem. Commun.* **2017**, *53*, 5481-5494.

(4) For additional studies, see: Whyte, A.; Torelli, A.; Mirabi, B.; Zhang, A.; Lautens, M., Copper-Catalyzed Borylative Difunctionalization of π-Systems. *ACS Catal.* **2020,** *10*, 11578-11622, and references cited therein.

(5) (a) Thapa, S.; Basnet, P.; Giri, R., Copper-Catalyzed Dicarbofunctionalization of Unactivated Olefins by Tandem Cyclization/Cross-Coupling. *J. Am. Chem. Soc.* **2017,** *139*, 5700-5703. (b) Whyte, A.; Burton, K. I.; Zhang, J.; Lautens, M., Enantioselective Intramolecular Copper-Catalyzed Borylacylation. *Angew. Chem., Int. Ed.* **2018,** *57*, 13927-13930. (c) Wickham, L. M.; Giri, R., Transition Metal (Ni, Cu, Pd)-Catalyzed Alkene Dicarbofunctionalization Reactions. *Acc. Chem. Res.* **2021,** *54*, 3415-3437. (d) Ozawa, Y.; Endo, K.; Ito, H., Regio- and Stereoselective Synthesis of Multi-Alkylated Allylic Boronates through Three-Component Coupling Reactions between Allenes, Alkyl Halides, and a Diboron Reagent. *J. Am. Chem. Soc.* **2021,** *143*, 13865-13877. (e) Akiyama, S.; Oyama, N.; Endo, T.; Kubota, K.; Ito, H., A Copper(I)-Catalyzed Radical-Relay Reaction Enabling the Intermolecular 1,2-Alkylborylation of Unactivated Olefins. *J. Am. Chem. Soc.* **2021,** *143*, 5260-5268.

(6) (a) Semba, K.; Fujihara, T.; Terao, J.; Tsuji, Y., Copper-catalyzed borylative transformations of non-polar carbon-carbon unsaturated compounds employing borylcopper as an active catalyst species. *Tetrahedron* **2015,** *71*, 2183-2197. (b) Zhong, C.; Kunii, S.; Kosaka, Y.; Sawamura, M.; Ito, H., Enantioselective Synthesis of trans-Aryl- and -Heteroaryl-Substituted Cyclopropylboronates by Copper(I)-Catalyzed Reactions of Allylic Phosphates with a Diboron Derivative. *J. Am. Chem. Soc.* **2010,** *132*, 11440-11442. (c) Whyte, A.; Burton, K. I.; Zhang, J.; Lautens, M., Enantioselective Intramolecular Copper-Catalyzed Borylacylation. *Angew. Chem., Int. Ed.* **2018,** *57*, 13927-13930.

(7) For additional studies, see: Yoshida, H. Borylation of Alkynes under Base/Coinage Metal Catalysis: Some Recent Developments. *ACS Catal.* **2016**, *6*, 1799-1811, and references cited therein.

(8) Lee, J.; Radomkit, S.; Torker, S.; del Pozo, J.; Hoveyda, A. H., Mechanism-based enhancement of scope and enantioselectivity for reactions involving a copper-substituted stereogenic carbon center. *Nat. Chem.* **2018,** *10*, 99-108.

(9) (a) Lee, Y.; Hoveyda, A. H., Efficient boron-copper additions to aryl-substituted alkenes promoted by NHC-based catalysts. Enantioselective Cu-catalyzed hydroboration reactions. *J. Am. Chem. Soc.* **2009,** *131*, 3160-3161. (b) Jang, H.; Zhugralin, A. R.; Lee, Y.; Hoveyda, A. H., Highly selective methods for synthesis of internal (α-)vinylboronates through efficient NHC-Cu-catalyzed hydroboration of terminal alkynes. Utility in chemical synthesis and mechanistic basis for selectivity. *J. Am. Chem. Soc.* **2011,** *133*, 7859-7871.

(10) (a) Laitar, D. S.; Tsui, E. Y.; Sadighi, J. P., Catalytic Diboration of Aldehydes via Insertion into the Copper-Boron Bond. *J. Am. Chem. Soc.* **2006,** *128*, 11036-11037. (b) Laitar, D. S.; Tsui, E. Y.; Sadighi, J. P., Copper(I) β-Boroalkyls from Alkene Insertion: Isolation and Rearrangement. *Organometallics* **2006,** *25*, 2405-2408.

(11) (a) Semba, K.; Shinomiya, M.; Fujihara, T.; Terao, J.; Tsuji, Y., Highly Selective Copper-Catalyzed Hydroboration of Allenes and 1,3-Dienes. *Chem. - Eur. J.* **2013,** *19*, 7125-7132. (b) Semba, K.; Fujihara, T.; Terao, J.; Tsuji, Y., Copper-catalyzed borylation of α-alkoxy allenes with bis(pinacolato)diboron: efficient synthesis of 2-boryl 1,3-butadienes. *Angew. Chem., Int. Ed.* **2013,** *52*, 12400-12403.

(12) (a) Borner, C.; Anders, L.; Brandhorst, K.; Kleeberg, C., Elusive Phosphine Copper(I) Boryl Complexes: Synthesis, Structures, and Reactivity. *Organometallics* **2017,** *36*, 4687-4690. (b) Ando, S.; Matsunaga, H.; Ishizuka, T., A Bicyclic N-Heterocyclic Carbene as a Bulky but Accessible Ligand: Application to the Copper-Catalyzed Borylations of Aryl Halides. *J. Org. Chem.* **2015,** *80*, 9671-9681. (c) Cheng, L.-J.; Mankad, N. P., Copper-Catalyzed Carbonylative Coupling of Alkyl Halides. *Acc. Chem. Res.* **2021,** *54*, 2261-2274. (d) Danopoulos, A. A.; Simler, T.; Braunstein, P., N-Heterocyclic Carbene Complexes of Copper, Nickel, and Cobalt. *Chem. Rev.* **2019,** *119*, 3730-3961.

(13) (a) Lazreg, F.; Nahra, F.; Cazin, C. S. J., Copper-NHC complexes in catalysis. *Coord. Chem. Rev.* **2015,** *293-294*, 48-79. (b) Trose, M.; Nahra, F.; Poater, A.; Cordes, D. B.; Slawin, A. M. Z.; Cavallo, L.; Cazin, C. S. J., Investigating the Structure and Reactivity of Azolyl-Based Copper(I)-NHC Complexes: The Role of the Anionic Ligand. *ACS Catal.* **2017,** *7*, 8176-8183. (c) Trose, M.; Lazreg, F.; Chang, T.; Nahra, F.; Cordes, D. B.; Slawin, A. M. Z.; Cazin, C. S. J., Neutral Dinuclear Copper(I)-NHC Complexes: Synthesis and Application in the Hydrosilylation of Ketones. *ACS Catal.* **2017,** *7*, 238-242. (d) Bidal, Y. D.; Lazreg, F.; Cazin, C. S. J., Copper-Catalyzed Regioselective Formation of Tri- and Tetrasubstituted Vinylboronates in Air. *ACS Catal.* **2014,** *4*, 1564-1569. (e) Itoh, T.; Shimizu, Y.; Kanai, M., Ligand-Enabled, Copper-Catalyzed Regio- and Stereoselective Synthesis of Trialkyl substituted Alkenylboronates from Unactivated Internal Alkynes. *J. Am. Chem. Soc.* **2016,** *138*, 7528-7531. (f) Han, J. T.; Yun, J., Copper-catalyzed synthesis of tetrasubstituted enynylboronates via chemo-, regio-, and stereoselective borylalkynylation. *Org. Lett.* **2018,** *20*, 2104-2107. (g) Li, K.; Yu, S.-H.; Zhuo, K.-F.; Lu, X.; Xiao, B.; Gong, T.-J.; Fu, Y., Synthesis of Conjugated Boron-Enynes via cis-Alkynylboration of Terminal Alkynes. *Adv. Synth. Catal.* **2019,** *361*, 3937-3942. (h) Romero, E. A.; Jazzar, R.; Bertrand, G. Copper-catalyzed dehydrogenative borylation of terminal alkynes with pinacolborane. *Chem. Sci.* **2017**, *8*, 165-168.

(14) (a) Bellotti, P.; Koy, M.; Hopkinson, M. N.; Glorius, F. Recent advances in the chemistry and applications of N-heterocyclic carbenes. *Nat. Rev. Chem.* **2021**, *5*, 711-725. (b) Mankad, N. P.; Gray, T. G.; Laitar, D. S.; Sadighi, J. P., Synthesis, Structure, and CO2 Reactivity of a Two-Coordinate (Carbene)copper(I) Methyl Complex. *Organometallics* **2004,** *23*, 1191-1193. (c) *N-Heterocyclic Carbenes in Transition Metal Catalysis*, Cazin, C. S. J., Ed.; Springer: New York, 2011, 1-22. (d) *N-Heterocyclic Carbenes: From Laboratory Curiosities to Efficient Synthetic Tools*, Diez-Gonzalez, S., Ed.; RSC: Cambridge, 2016, 46-98.

(15) (a) Arduengo, III, A. J.; Goerlich, J. R.; Marshall, W. J. A Stable Thiazol-2-ylidene and Its Dimer. *Liebigs Ann.* **1997**, 365-374. (b)Gusev, D. G. Donor Properties of a Series of Two-Electron Ligands. *Organometallics* **2009**, *28*, 763-770.

(16) For selected studies from our laboratory, see: (a) Shi, S.; Nolan, S. P.; Szostak, M. Well-Defined Palladium(II)-NHC (NHC = N-Heterocyclic Carbene) Precatalysts for Cross-Coupling Reactions of Amides and Esters by Selective Acyl CO–X (X = N, O) Cleavage. *Acc. Chem. Res.* **2018**, *51*, 2589-2599. (b) Zhao, Q.; Meng, G.; Li, G.; Flach, C.; Mendelsohn, R.; Lalancette, R.; Szostak, R; Szostak, M. IPr# - highly hindered, broadly applicable N-heterocyclic carbenes. *Chem. Sci.* **2021**, *12*, 10583–10589.

(c) Zhou, T.; Ma, S.; Nahra, F.; Obled, A. M. C.; Poater, A.; Cavallo, L.; Cazin, C. S. J.; Nolan, S. P.; Szostak, M. [Pd(NHC)(μ-Cl)Cl]$_2$: Versatile and Highly Reactive Complexes for Cross-Coupling Reactions that Avoid Formation of Inactive Pd(I) Off-Cycle Products. *iScience* **2020**, *23*, 101377. (d) Xia, Q.; Shi, S.; Gao, P.; Lalancette, R.; Szostak, R.; Szostak, M. [(NHC)PdCl$_2$(Aniline)] Complexes: Easily Synthesized, Highly Active Pd(II)–NHC Precatalysts for Cross-Coupling Reactions. *J. Org. Chem.* **2021**, *86*, 15648–15657. (e) Lei, P.; Wang, Y.; Zhang, C.; Hu, Y.; Feng, J.; Ma, Z.; Liu, X.; Szostak, R.; Szostak, M., Sonogashira Cross-Coupling of Aryl Ammonium Salts by Selective C-N Activation Catalyzed by Air- and Moisture-Stable, Highly Active [Pd(NHC)(3-CF$_3$-An)Cl$_2$] (An = Aniline) Precatalysts. *Org. Lett.* **2022,** *24*, 6310-6315. (f) Rahman, M. M.; Zhang, J.; Zhao, Q.; Feliciano, J.; Bisz, E.; Dziuk, B.; Lalancette, R.; Szostak, R.; Szostak, M., Pd-PEPPSI N-Heterocyclic Carbene Complexes from Caffeine: Application in Suzuki, Heck, and Sonogashira Reactions. *Organometallics* **2022,** *41*, 2281-2290. (g) Zhang, J.; Li, T.; Li, X.; Zhang, G.; Fang, S.; Yan, W.; Li, X.; Yang, X.; Ma, Y.; Szostak, M., An air-stable, well-defined palladium-BIAN-NHC chloro dimer: a fast-activating, highly efficient catalyst for cross-coupling. *Chem. Commun.* **2022,** *58*, 7404-7407. (h) Zhang, J.; Rahman, M. M.; Zhao, Q.; Feliciano, J.; Bisz, E.; Dziuk, B.; Lalancette, R.; Szostak, R.; Szostak, M., N-Heterocyclic Carbene Complexes of Nickel(II) from Caffeine and Theophylline: Sustainable Alternative to Imidazol-2-ylidenes. *Organometallics* **2022,** *41*, 1806-1815. (i) Zhang, J.; Wang, Y.; Zhang, Y.; Liu, T.; Fang, S.; Wang, R.; Ma, Y.; Fang, R.; Szostak, R.; Szostak, M., Application of Indazolin-3-ylidenes in Catalysis: Steric Tuning of Nonclassical Formally Normal N-Heterocyclic Carbenes with Dual Electronic Character for Catalysis. *Organometallics* **2022,** *41*, 1115-1124.

(17) (a) Biju, A. T.; Wurz, N. E.; Glorius, F. N-Heterocyclic Carbene-Catalyzed Cascade Reaction Involving the Hydroacylation of Unactivated Alkynes. *J. Am. Chem. Soc.* **2010**, *132*, 5970-5971. (b) Biju, A. T.; Glorius, F. Intermolecular N-Heterocyclic Carbene Catalyzed Hydroacylation of Arynes. *Angew. Chem. Int. Ed.* **2010**, *49*, 9761-9764. (c) Piel, I.; Pawelczyk, M. D.; Hirano, K.; Froehlich, R.; Glorius, F., A Family of Thiazolium Salt Derived N-Heterocyclic Carbenes (NHCs) for Organo-catalysis: Synthesis, Investigation and Application in Cross-Benzoin Condensation. *Eur. J. Org. Chem.* **2011,** *2011*, 5475-5484. (d) Das, T. K.; Biju, A. T., A Method for the Analysis of Free Carbenes Present after NHC-Organocatalyzed Transformations. *Eur. J. Org. Chem.* **2017,** *2017*, 4500-4506. (e) Ishii, T.; Ota, K.; Nagao, K.; Ohmiya, H., N-Heterocyclic Carbene-Catalyzed Radical Relay Enabling Vicinal Alkylacylation of Alkenes. *J. Am. Chem. Soc.* **2019,** *141*, 14073-14077. (f) Matsuki, Y.; Ohnishi, N.; Kakeno, Y.; Takemoto, S.; Ishii, T.; Nagao, K.; Ohmiya, H., Aryl radical-mediated N-heterocyclic carbene catalysis. *Nat. Commun.* **2021,** *12*, 3848.

(18) (a) Holloczki, O.; Kelemen, Z.; Nyulaszi, L., On the Organocatalytic Activity of N-Heterocyclic Carbenes: Role of Sulfur in Thiamine. *J. Org. Chem.* **2012,** *77*, 6014-6022. (b) Nandi, A.; Alassad, Z.; Milo, A.; Kozuch, S., Quantum Tunneling on Carbene Organocatalysis: Breslow Intermediate Formation via Water-Bridges. *ACS Catal.* **2021,** *11*, 14836-14841.

(19) Limited examples of N-alkyl (benzo)thiazol-2-ylidenes have been reported: (a) Huynh, H. V.; Meier, N.; Pape, T; Hahn, F. E. Benzothiazolin-2-ylidene Complexes of Iridium(I) Organometallics **2006**, *25*, 3012-3018. (b) Ding, N.; Hor, T. S. A. Ruthenium(ii) N,S-heterocyclic carbene complexes and transfer hydrogenation of ketones. *Dalton Trans.* **2010**, *39*, 10179-10185. (c) Ding, N.; Zhang, W.; Hor, T. S. A. One-step entry to olefin-tethered N,S-heterocyclic carbene complexes of ruthenium with mixed ligands. *Dalton Trans.* **2012**, *41*, 5988-5994.

(20) Zhang, J.; Li, T.; Li, X.; Lv, A.; Wang, Z.; Wang, R.; Ma, Y.; Fang, R.; Szostak, R.; Szostak, M. Thiazol-2-ylidenes: Versatile N-Heterocyclic Carbene Ligands with Enhanced Electrophilicity for Transition-Metal-Catalysis. *Comm. Chem.* **2022**, *5*, 60.

(21) Falivene, L.; Cao, Z.; Petta, A.; Serra, L.; Poater, A.; Oliva, R.; Scarano, V.; Cavallo, L. Towards the Online Computer-Aided Design of Catalytic Pockets. *Nat. Chem.* **2019**, *11*, 872-879.