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Copper-Catalyzed Heteroarylboration of 1,3-Dienes with 3-Bromopyridines: A *cine* Substitution

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Abstract

A method for the heteroarylboration of 1,3-dienes is presented. The process involves an unusual cine substitution of 3-bromopyridine derivatives to deliver highly functionalized heterocyclic products. Mechanistic studies are included that clarify the details of this unusual process.

Keywords

boron; copper; dienes; heterocycles; synthetic methods

Pyridine derivatives and related nitrogen heterocycles are common to many natural products and pharmaceutical agents.[1] Therefore, new methods for the synthesis and derivatization of nitrogen heterocycles are of significant interest.[2] A common strategy for the functionalization of nitrogen heterocycles is the activation of the nitrogen atom through either oxidation (N-oxide or hydrazone formation) or quaternization with reagents such as chloroformates or alkylhalides (Scheme 1).[3] In these reactions, either the unsaturated or saturated heterocycle is formed, depending on the reaction conditions and starting material. In one recent example, Ge and co-workers reported a copper-catalyzed hydroarylation of vinyl arenes with quinoline-*N*-oxides.[4] Herein, an alternative strategy for heterocycle functionalization is presented in which 3-bromopyridine derivatives undergo an unusual *cine* substitution without the need for activation of the nitrogen atom.[5] Furthermore, this reaction represents a new process for arylboration of 1,3-dienes.[6–11]

Our group recently reported a method for the palladium/copper-catalyzed regiodivergent arylboration of isoprene (Scheme 2A).[7f,12] A critical aspect of these studies was the use of 4-(*N*,*N*-dimethylamino)pyridine (DMAP), which allowed formation of a 2,1-arylboration adduct (**3**). In the context of these efforts, 2-chloro-5-bromopyridine (**4**) was evaluated with the expectation that **5** and/or **6** would be generated (Scheme 2B). Interestingly, the *cine*-substitution product **7** was observed as the major component with functionalization of 2-bromo-5-chloropyridine at C6, as opposed to the expected bond formation at C5. Further

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Conflict of interest

The authors declare no conflict of interest.

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control experiments led to the realization that the palladium catalyst was not required for the formation of **7**.

Based on the initial findings illustrated in Scheme 2B, the reaction conditions were optimized by performing the reaction at 60°C, which led to consistent results for a range of substrates. Variation from the standard reaction conditions with respect to the ligand revealed that the use of other N-heterocyclic carbenes led to inferior results. Copper complexes bearing bidentate phosphines, such as dppBzCuCl, were effective catalysts. However, the scope was determined to be narrower compared to reactions with I*t*BuCuBr.[13]

Under the optimized reaction conditions, a range of 3-bromopyridine derivatives were investigated (Scheme 3). While substitution at the 2-position with Me (product **10**), Cl (product **7**), or Br (product **9**) was tolerated, the use of derivatives without substitution at the 2-position, such as 3-bromopyridine and 3,5-dibromopyridine, led to a lower yield of the isolated product. Additional substitution around the pyridine ring was tolerated, as demonstrated by formation of the products **11** and **13**. It must be noted that 2-bromopyridine and 4-bromopyridine failed to undergo reaction, thus highlighting the necessity for the 3-bromopyridine motif.

With respect to the diene component, the reactions worked with a variety of substitution patterns. Derivatives of isoprene such as a siloxy diene (product **16**) and myrcene (product **18**) performed well (Scheme 3). Use of butadiene allowed synthesis of **14**, while 1-phenylbutadiene (product **15**) required the use of IPrCuCl as a catalyst. A 1,2-disubstituted 1,3-diene was also investigated and functioned well in the reaction to provide **17**. This example also serves to demonstrate tolerance to tertiary amines. Other types of activated alkenes, such as styrenes or vinyl silanes known to undergo borylcupration,[6] do not participate in this reaction.

Investigation of a related heterocycle, 3-bromoquinoline (**19**), led not to the formation of the expected *cine*-substituted product, but rather to the dihydroquinoline **20**, after treatment with AcCl for isolation and characterization by X-ray crystallography (Scheme 4). Furthermore, **20** was generated in greater than 20:1 d.r. The quinoline product 21 could be prepared through quenching the reaction mixture with the oxidant DDQ.

Based on the results illustrated in Scheme 4, the addition/oxidation sequence was extended to isoquinoline substrates. While I*t*BuCuBr was an effective catalyst for these reactions (not shown), it was identified that the reactions could be rendered enantioselective when (*R*,*R*)-QuinoxP*CuCl was employed (Scheme 5). As such, isoprene or myrcene could be merged with various isoquinolines to provide **22**–**25** in good yield and enantioselectivity. While enantioselective addition reactions to isoquinolines are known, preactivation is necessary in all reported cases.[14] The method shown in Schemes 4 and 5 provides a simple and practical way to achieve functionalization without preactivation. Extension of the enantioselective variant to other heterocycles, such as 2-bromo-5-chloropyridine, resulted in moderate selectivity.[13]

Mechanistic experiments revealed that addition of I*t*BuCu-Bpin to isoprene generated a mixture of the allyl-Cu-complexes **26** and **27**, and that it appears to converge to **7** upon addition of **4** prior to aqueous quench of the reaction mixture (Scheme 6A).[7f] At this time, we propose that **26** and **27** are in equilibrium as both appear to be converted into product. While the mechanism of the interconversion is unclear at this time, an attempted crossover experiment suggests **26** and **27** do not interconvert by retro-borylcupration to free isoprene and I*t*BuCu-Bpin.[13] Finally, the isotopic-labeling studies shown in Scheme 6B,C confirm that the C6−H(D) is transferred to C5 by an intramolecular process as the crossover products [D_4]**10** and **10** were not observed.

Taken together, these findings point towards the catalytic cycle illustrated in Scheme 7.[15] After formation of **26** and **27**,[7f] allylic addition of **26** to **4** occurs at C6 to furnish **31**. This complex can undergo formal 1,5-elimination to generate the copper-carbene complex **32**. The elimination process may occur through isomerization of the 31 to a C5-bound copper-complex and subsequent 1,1-elimination. From **32**, 1,2-migration results in transfer of the C6−H(D) to C5, which upon rearomatization provides **7** and regenerates I*t*BuCuBr. In the case of **19**, formal 1,5-elimination is slow because of formation of a stabilized copper-anilide (**34**). Salt metathesis of this intermediate with KO*t*Bu then occurs to form **35** and I*t*BuCuO*t*Bu. Quenching of the reaction mixture and subsequent acylation leads to formation of **20**.

While *cine* substitution (or the related *tele*-substitution) is relatively rare compared to *ipso*-substitution, it has been observed in several cases and is thus important to put the mechanism proposed herein in context.[5] Common examples of *cine* substitution are reactions that involve aryne intermediates,[16] proceed by electrophilic aromatic substitution pathways,[17] or are classified as a von Richter reaction.[18] Addition-elimination sequences are more rare, but have been observed with halogenated heteroarenes with amine nucleophiles.[19] The mechanism suggested here can be classified as an addition-elimination process. However, it is unique in that the overall elimination sequence involves the generation of a carbene and 1,2-migration (**31** to **7**).

In summary, a method for the heteroarylboration of 1,3-dienes with 3-bromopyridine derivatives is presented.[20] Anunusual *cine*-substitution process has been uncovered and a mechanism proposed based on key experiments. In addition, these efforts have led to processes for the direct functionalization of quinolines and isoquinolines.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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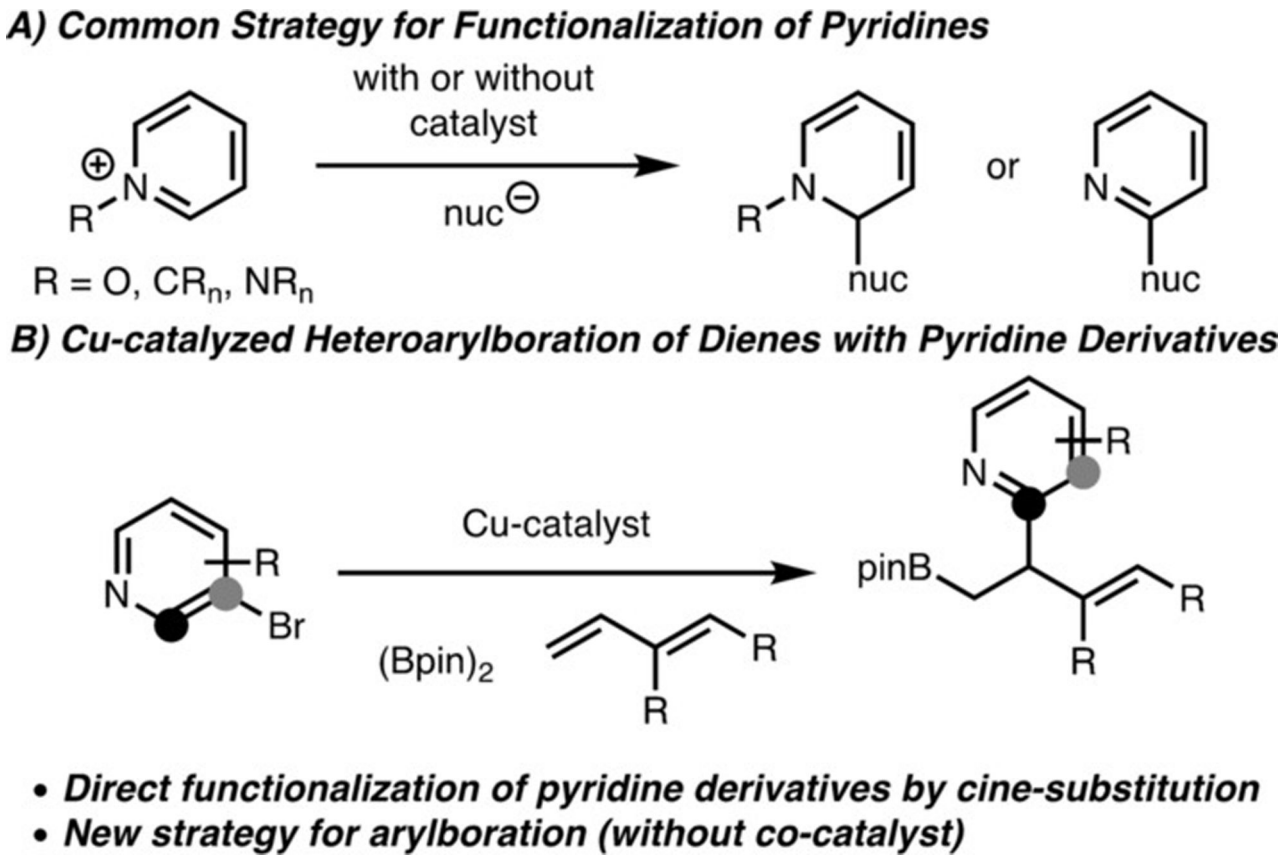
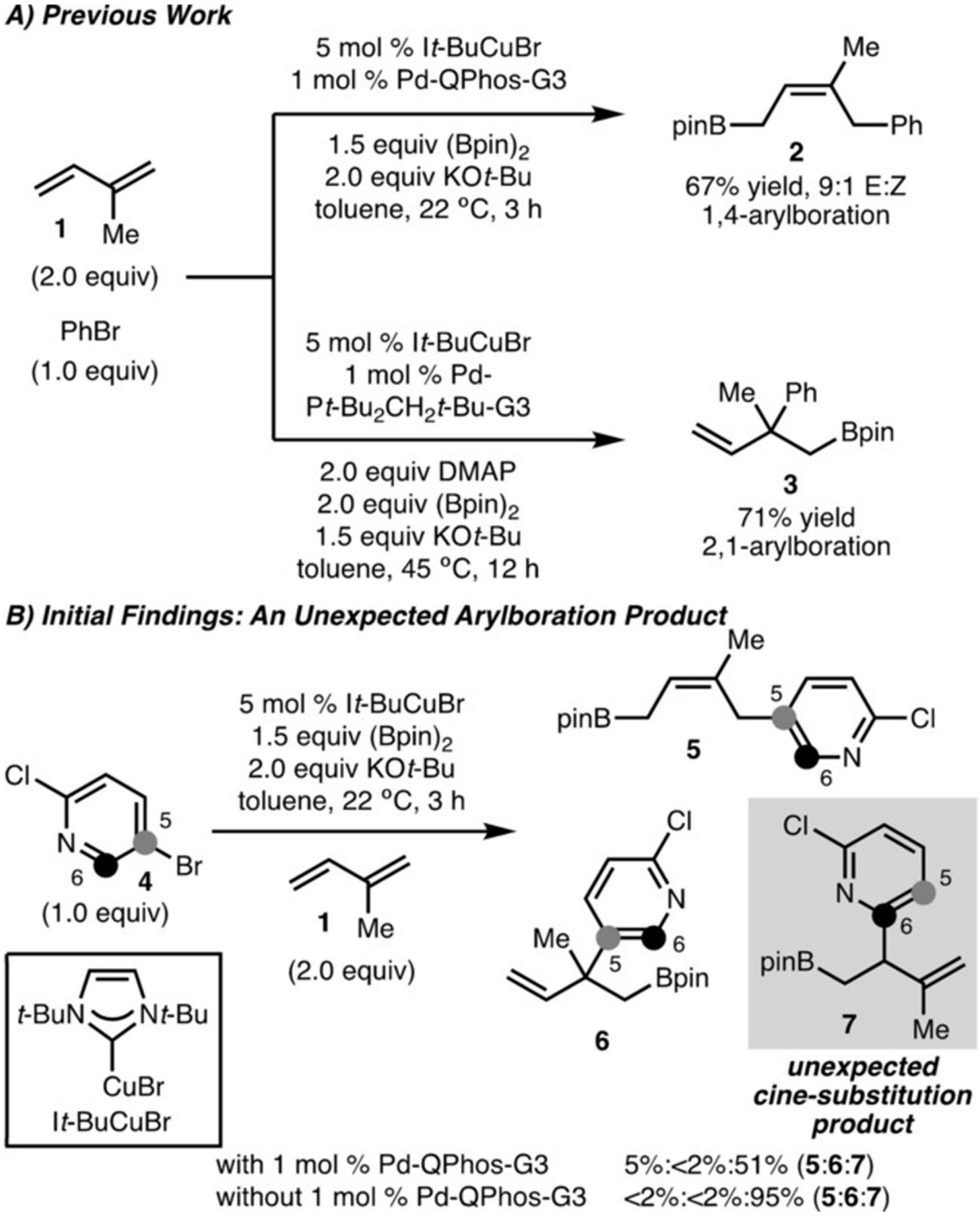
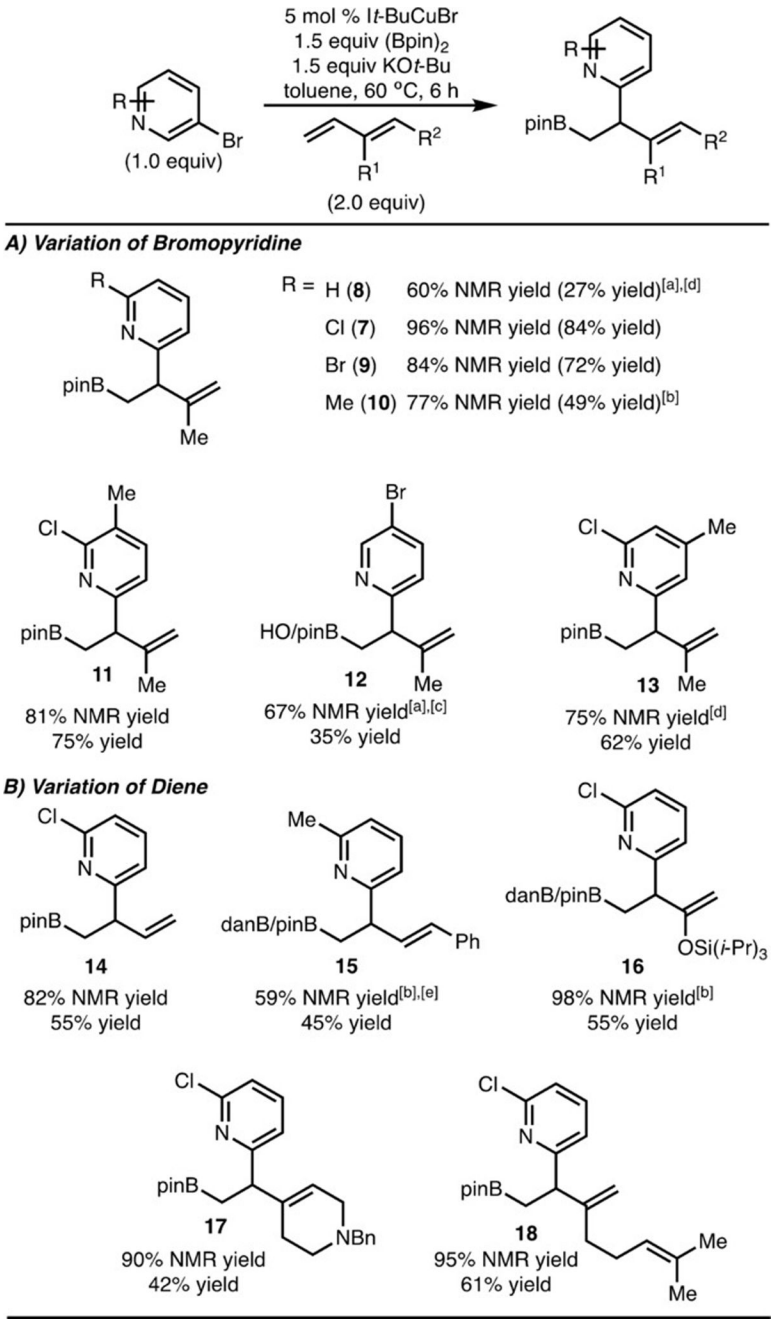


Scheme 1.
Functionalization of pyridines. pin = pinacol.



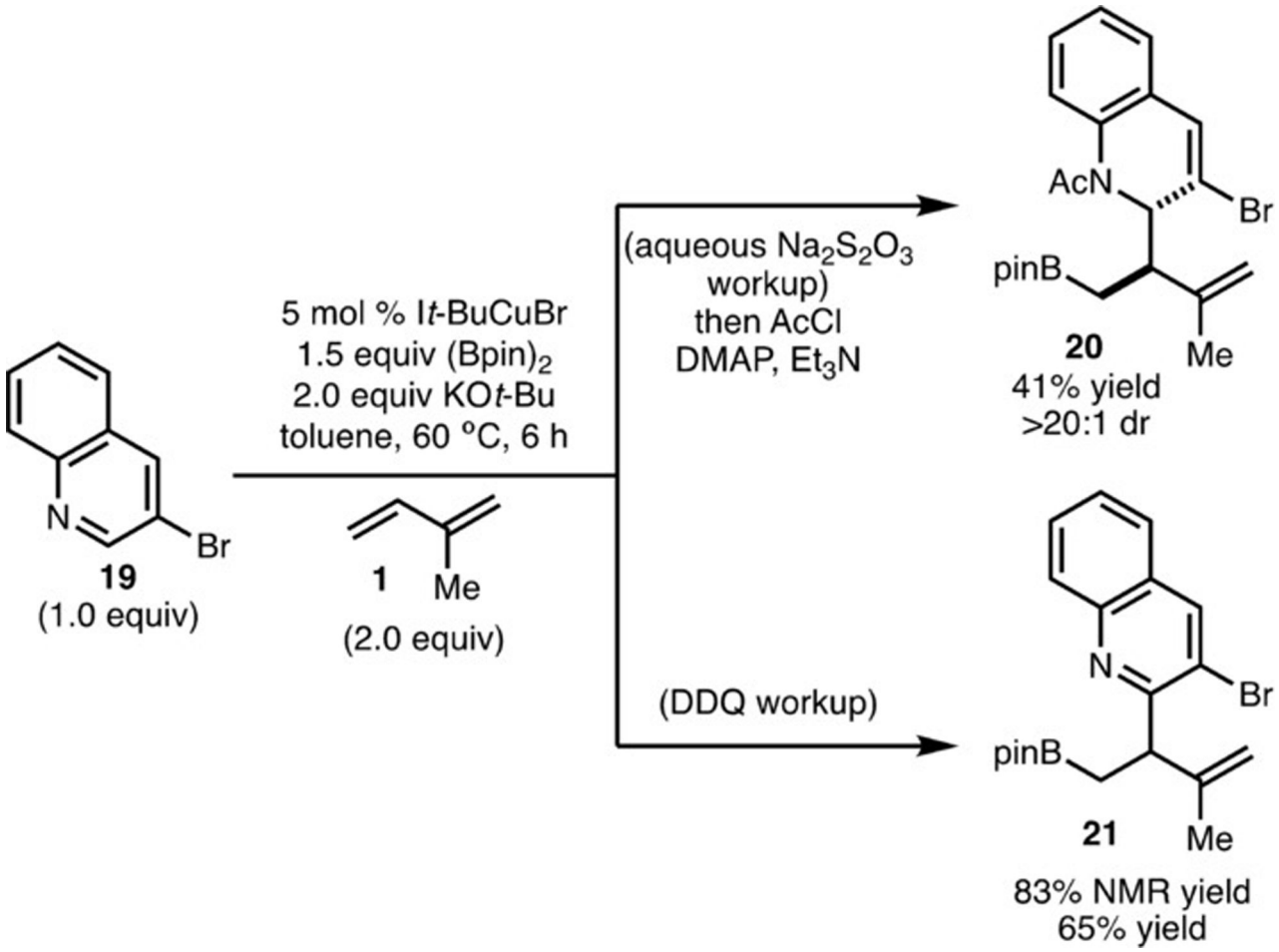
Scheme 2.
Initial findings.



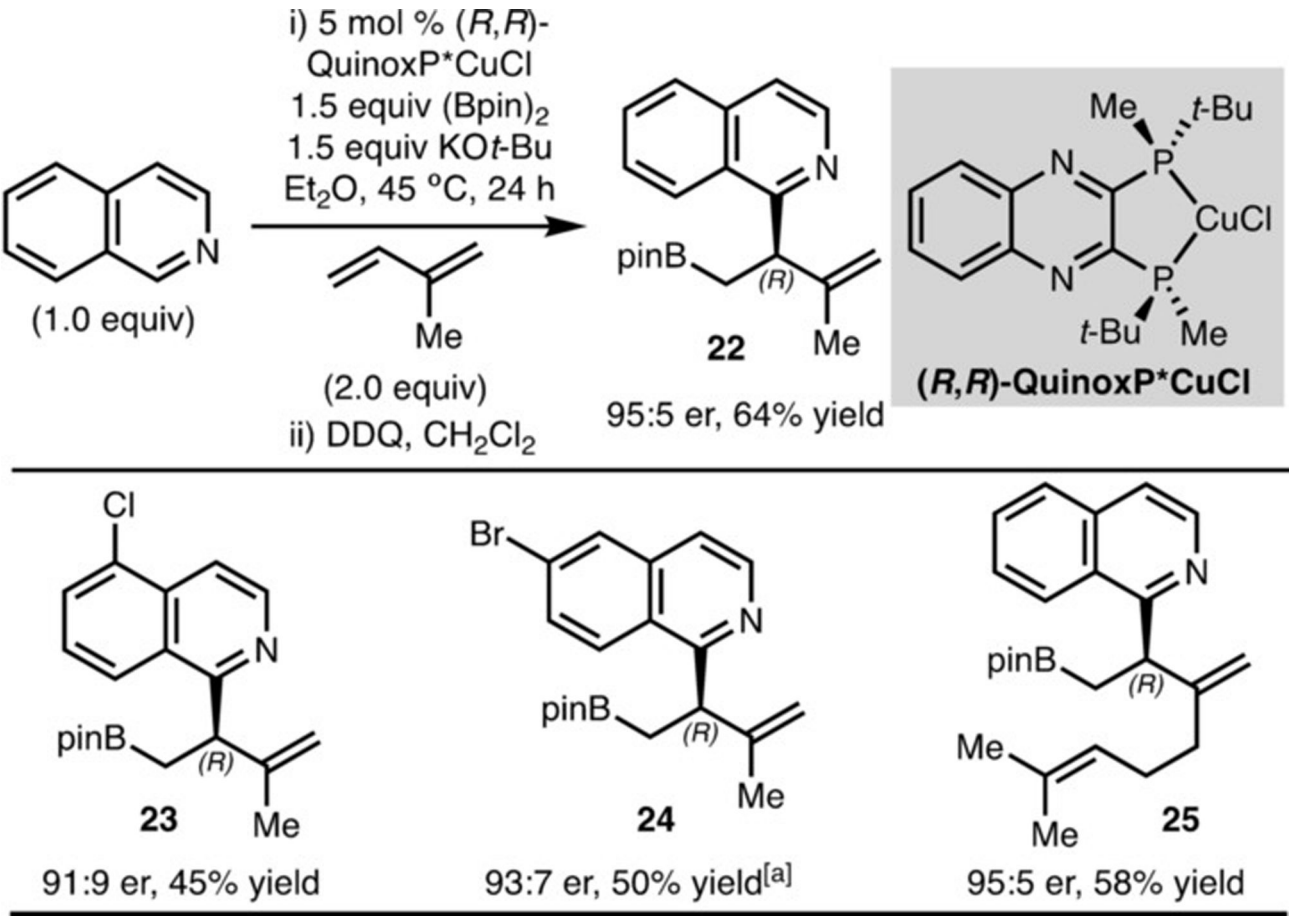
Scheme 3.

Substrate scope. NMR yield determined by analysis of the unpurified reaction mixture with an internal standard. Yield of the product after isolation by silica gel column chromatography (all examples are the average of two experiments run on 0.5 mmol scale). The discrepancy between NMR yield and yield of isolated product is due to a cumbersome isolation that results in partial decomposition of the product. [a] Isolated as the corresponding alcohol after oxidation; see the Supporting Information for details. [b] Isolated as the corresponding Bdan; see the Supporting Information for details. [c] Reaction run with 1.0 equiv isoprene and 2.0 equiv 3,5-dibromopyridine at 22°C for 15 h. [d]

Reaction run with 10 mol% I*t*BuCuBr for 15 h.[e] Reaction run with 5 mol% IPrCuCl instead of 5 mol% ItBuCuBr for 15 h.

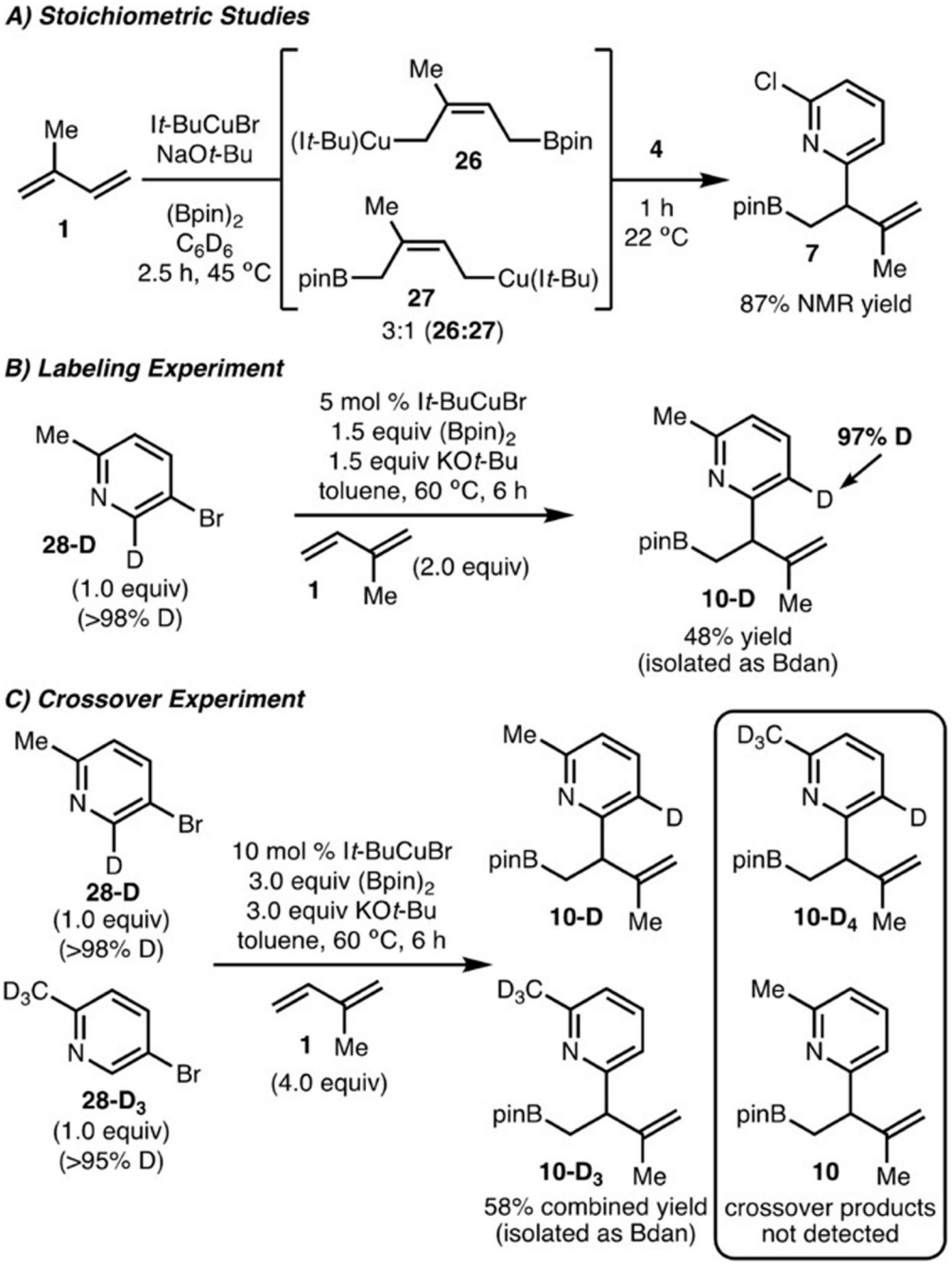


Scheme 4.
Direct functionalization of 3-bromoquinoline.

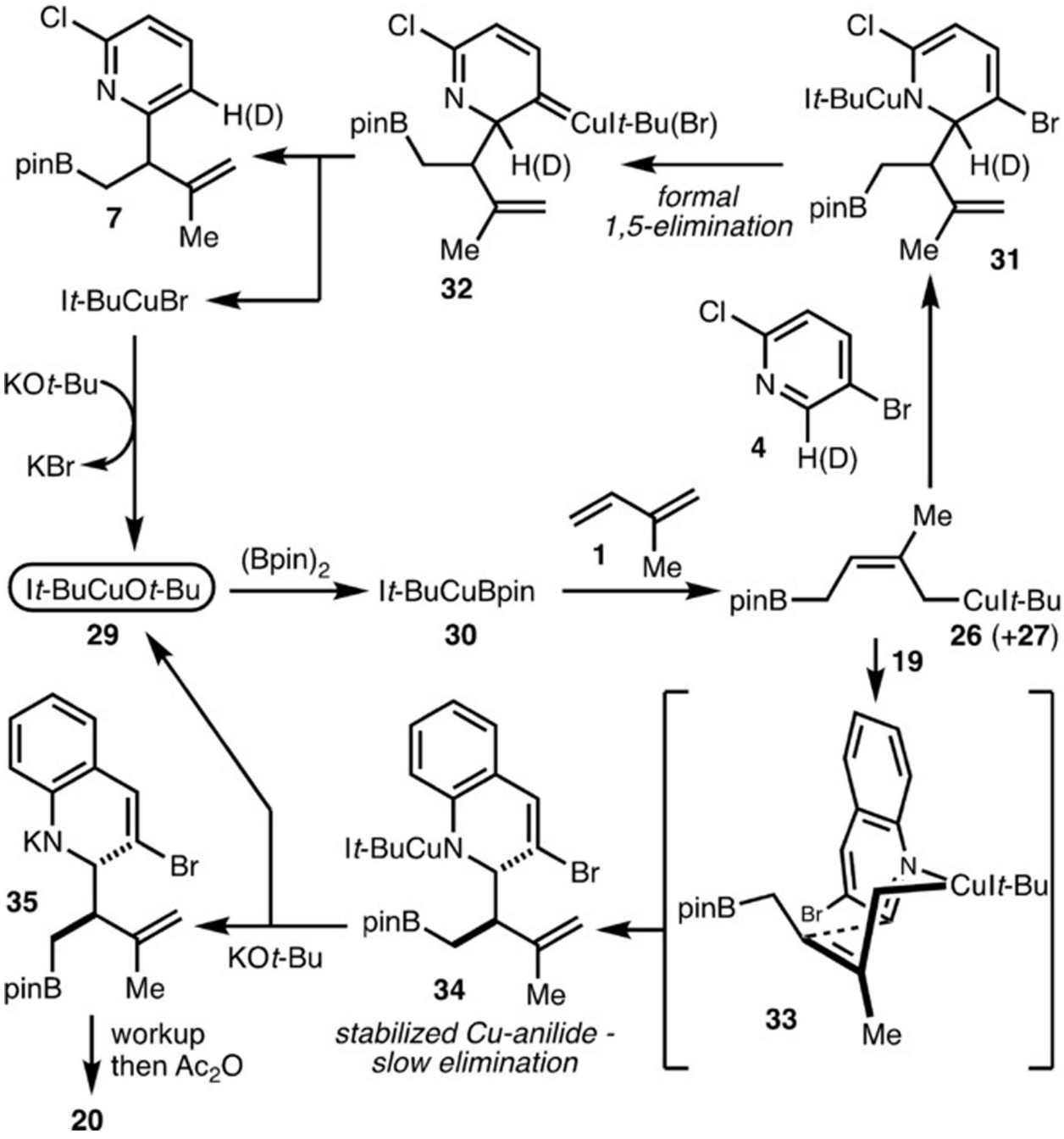


Scheme 5.

Enantioselective variant with isoquinolines. Yield of the product after isolation by silica gel column chromatography (all examples are the average of two experiments run on 0.3 mmol scale). Enantiomeric ratio (e.r.) determined by HPLC analysis with a chiral column. [a] Reaction run for 48 h.



Scheme 6.
Mechanistic investigations.



Scheme 7.
Proposed catalytic cycles.