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Synthesis of oxaboranes *via* nickel-catalyzed dearylative cyclocondensation†

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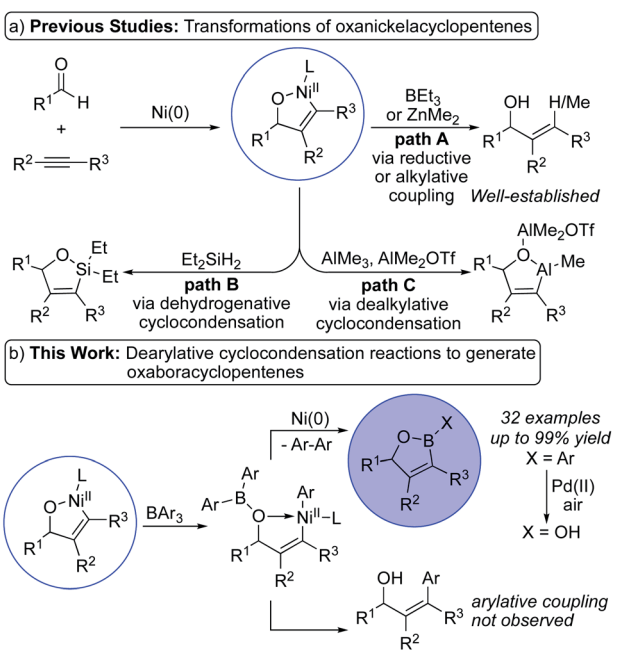
We report Ni-catalyzed dearylative cyclocondensation of aldehydes, alkynes, and triphenylborane. The reaction is initiated by oxidative cyclization of the aldehyde and alkyne coupling partners to generate an oxanickelacyclopentene which reacts with triphenylborane to form oxaboranes. This formal dearylative cyclocondensation reaction generates oxaboranes in moderate-to-high yields (47–99%) with high regioselectivities under mild reaction conditions. This approach represents a direct and modular synthesis of oxaboranes which are difficult to access using current methods. These oxaboranes are readily transformed into valuable building blocks for organic synthesis and an additional class of boron heterocycles. Selective homocoupling forms oxaboroles, oxidation generates aldol products, and reduction and arylation form substituted allylic alcohols.

Introduction

Nickel-catalyzed oxidative cyclization reactions of two π-components enable facile generation of nickelacycles with formation of a new C–C bond.[1–6] These reactions encompass a broad array of suitable π-components that provide access to a range of substituted nickelacycles. Among these π-components, nickel-catalyzed oxidative cyclizations of aldehydes and alkynes are established methods to generate an array of oxanickelacyclopentenes.[2] These oxanickelacyclopentenes are versatile intermediates that can be transformed into a variety of synthetically valuable building blocks. Early studies in this area focus on reductive and alkylative coupling reactions to form substituted allylic alcohols (Scheme 1a, path A).[2a,b] Subsequently, Montgomery and coworkers discovered that oxanickelacyclopentenes react with diethylsilane to form stable oxasilacyclopentenes *via* dehydrogenative cyclocondensation reactions (Scheme 1a, path B).[7] Ogoshi and coworkers reported related dealkylative cyclocondensation reactions of oxanickelacyclopentenes with trimethylaluminum to form oxaaluminacyclopentenes (Scheme 1a, path C).[8]

Oxaboranes[9] (X = Ar), oxaboroles[10] (X = OH), and related boron heterocycles[11] have garnered increased interest in recent years due to their biological activities,[12] optical properties,[13] and utility as synthetic building blocks. The ability to leverage the reactivity of oxaboracyclopentenes would enable rapid and tailorable syntheses of these boron heterocycles. However, dehydrogenative cyclocondensation reactions analogous to the synthesis of oxasilacyclopentenes would be challenging with dihydridoborane or trihydridoborane reagents due to competing hydroboration of the alkyne component.[14] Analogous reactions with a trialkylborane lead to reductive coupling instead of dealkylative cyclocondensation.[2b]

We envisioned dearylative cyclocondensation reactions of aldehydes, alkynes, and a triarylborane as direct, catalytic syntheses of oxaboracyclopentenes (Scheme 1b, top). The use of



Scheme 1 Reactivity of oxanickelacycles.

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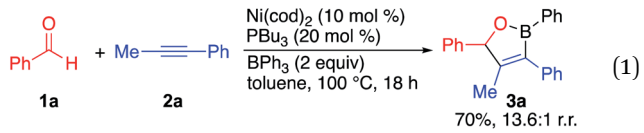
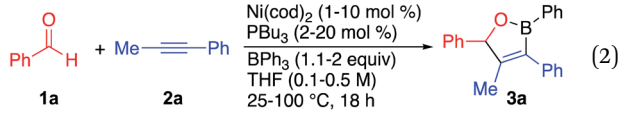
a triarylborane reagent eliminates the potential for reductive coupling to form allylic alcohols as shown in Scheme 1a. This approach also eliminates the need for complex starting materials,[10g] strongly basic reaction conditions,[10d] and multi-step synthetic procedures.[10e,f] The development of dearylative cyclocondensation reactions to form oxaboracyclopentenes would provide a straightforward and modular entry into these boron heterocycles that addresses the limitations of current synthetic methods. Key to the development of these dearylative cyclocondensation reactions is the identification of a nickel catalyst that mitigates the potential for arylative coupling to form substituted allylic alcohols (Scheme 1b, bottom).[3c] Herein, we report the first nickel-catalyzed couplings of aldehydes, alkynes, and triphenylborane to form oxaboracyclopentenes in high yields with excellent regio- and chemoselectivities.

Results and discussion

In our initial studies, we found that the reaction of benzaldehyde **1a**, 1-phenyl-1-propyne **2a**, and triphenylborane in the presence of a catalyst generated from $Ni(cod)_2$ and PBu_3 produced oxaborane **3a** in 70% yield and a 13.6 : 1 regioisomeric ratio (eqn (1)). Additionally, we observed the formation of equal amounts of biphenyl in the reaction with no observable arylative coupling product. This result is consistent with a reaction that proceeds *via* the dearylative cyclocondensation pathway shown in Scheme 1b.



(1)



(2)

We next chose to leverage design of experiment (DoE) to increase the yield of the reaction and lower the catalyst loading.[15] We first evaluated categorical factors (ligand and solvent) in the reaction (Table S1†) and found that a catalyst generated from $Ni(cod)_2$ and PBu_3 produced oxaborane product **3a** in quantitative yields when THF was used as the solvent. However, we recognized the potential to use DoE to further optimize the reaction by lowering the loadings of catalyst and the organoboron reagent (eqn (2)). We evaluated the level of significance of four continuous factors (catalyst loading, reaction concentration, temperature, and loading of the organoboron reagent, Scheme S1 and Table S2†) in 14 reactions using a linear model DoE. The results of this DoE showed that temperature and catalyst loading did not have a significant impact on the yield of the reaction, but the yield of the reaction is positively correlated with increased loadings of triphenylborane. We then performed a quadratic model DoE consisting of 15 reactions to further optimize our dearylative cyclocondensation reaction (Scheme S2 and Table S3†). This set of reactions showed that the loading of catalyst could be reduced if the loading of triphenylborane is increased (Fig. 1a). In addition, higher reaction temperatures generally lead to lower yields of the oxaborane product across a range of catalyst loadings (Fig. 1b). Based on the response surfaces in Fig. 1, we chose 5 mol% catalyst and 1.5 equivalents BPh_3 at 50 °C as reaction conditions to evaluate the scope of the dearylative cyclocondensation reaction.

We initially evaluated the scope of the dearylative cyclocondensation reaction with respect to the alkyne coupling partner (Scheme 2). The reaction of benzaldehyde with 1-aryl-1-hexyne derivatives **2b–2i** bearing electron-neutral, electron-donating, and electron-withdrawing *para*-substituents generated oxaborane products **3b–3i** in 73–98% yield with up to 11.4 : 1 regioisomeric ratios. A phenolic hydroxyl group was also tolerated in the reaction, with the reaction of alkyne **2i** producing oxaborane **3i** in 85% yield and 9.1 : 1 r.r. The reactions of alkynes containing *meta*-substituted aryl groups lead to oxaborane products **3j** and **3k** in 89% and 72% yield, respectively. The reaction of 1-(2-methylphenyl)-1-hexyne **2l** formed oxaborane **3l** in 80% yield and >20 : 1 regioselectivity as a 1.1 : 1 ratio of diastereomers when the reaction temperature was increased to 70 °C. The reaction of 2-(hex-1-yn-1-yl)naphthalene **2m** generated oxaborane **3m** in 99% yield and 11.1 : 1 r.r. A heteroaromatic ring was also tolerated in the reaction with benzofuran-derived alkyne **2n** leading to oxaborane **3n** in 90% yield. The reaction of enyne **2o** formed oxaborane **3o** in 40% isolated yield with 3.1 : 1 regioselectivity. The lower regioselectivity is presumably due to competing coordinating effects of the alkene.[16] The reaction of benzaldehyde with diphenylacetylene produced oxaborane product **3p** in 84% isolated yield. Aliphatic alkynes are also tolerated in the reaction, with reactions of 3-hexyne and 4-octyne leading to oxaboranes **3q** and **3r** in 80% and 94% yield, respectively. Limitations of the dearylative cyclocondensation reactions include: (1) aromatic aldehydes bearing strongly electron-withdrawing substituents, such as nitro groups; (2) alkynes containing bulky substituents, such as trimethylsilyl groups, and (3) terminal alkynes due to competing cyclotrimerization processes.[2b,d,3b,17]

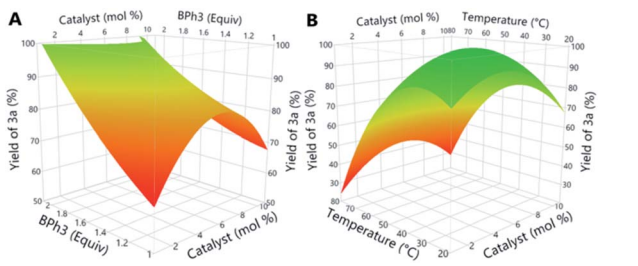


Fig. 1 Response surface analysis of quadratic design of experiment. (A) Yield of **3a** *versus* catalyst loading and equivalents of triphenylborane at 50 °C. (B) Yield of **3a** *versus* catalyst loading and temperature with 1.5 equivalents of triphenylborane.

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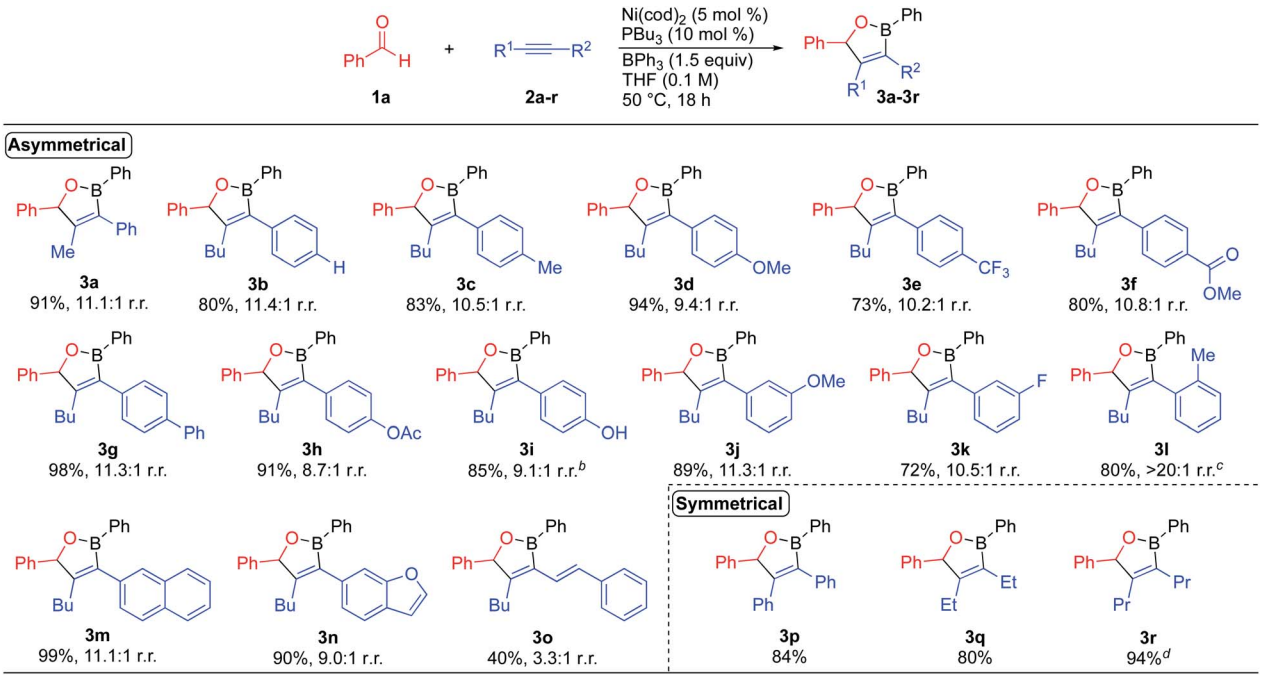
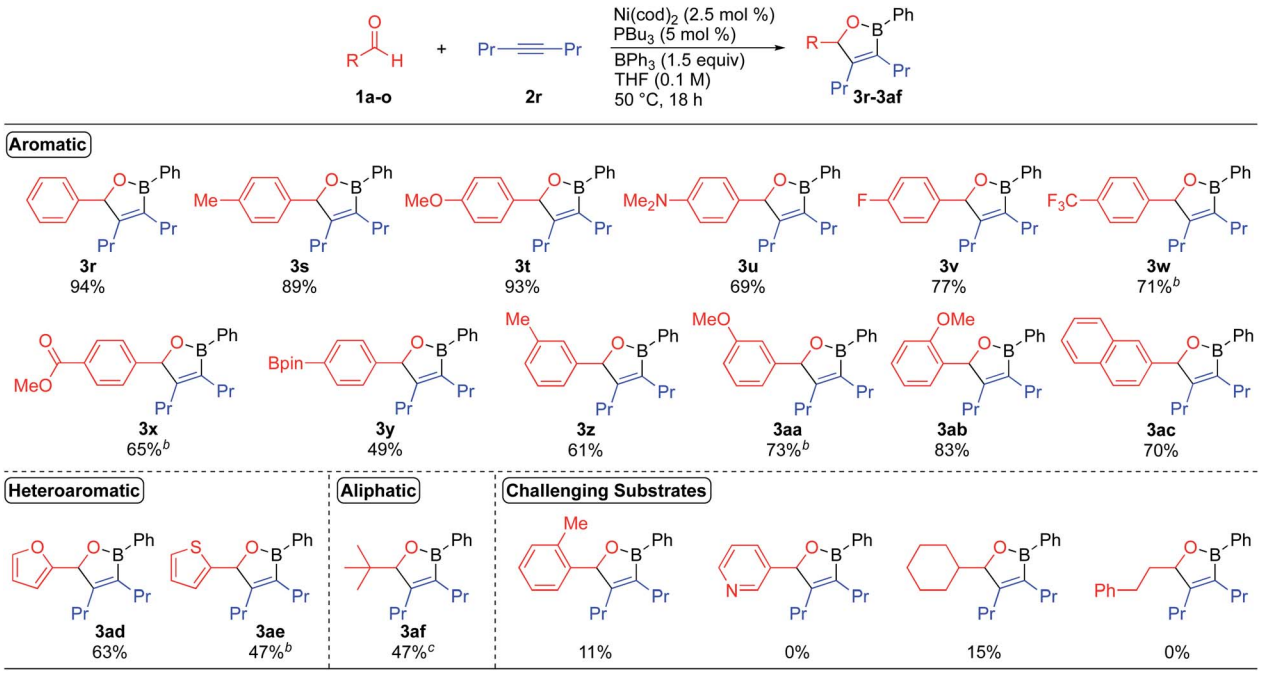


Scheme 2 Alkyne substrate scope for the nickel-catalyzed dearylative cyclocondensations. [a]Reaction conditions: **1a** (0.200 mmol), **2** (0.220 mmol), BPh_3 (0.300 mmol), $Ni(cod)_2$ (0.010 mmol), PBu_3 (0.020 mmol), THF (2.0 mL, 0.10 M), 50 °C, 18 h. [b]Reaction run with 10 mol% $Ni(cod)_2$, 20 mol% PBu_3, 1.5 equiv. alkyne, and 2 equiv. BPh_3. [c]Reaction run at 70 °C. [d]Reaction run with 2.5 mol% catalyst.

We next turned our attention to establishing the scope of aldehyde coupling partners (Scheme 3). While investigating the scope of aldehydes with 4-octyne as the alkyne coupling partner, we found that only 2.5 mol% of the catalyst was required to form oxaboranes derived from aromatic aldehydes containing electron-donating and electron-withdrawing substituents. These reactions lead to the formation of oxaboranes **3s–3ab** in good to excellent yields. In general, reactions of benzaldehyde



Scheme 3 Aldehyde substrate scope for the nickel-catalyzed dearylative cyclocondensations. [a]Reaction conditions: **1** (0.200 mmol), **2r** (0.220 mmol), BPh_3 (0.300 mmol), $Ni(cod)_2$ (0.005 mmol), PBu_3 (0.010 mmol), THF (2.0 mL, 0.10 M), 50 °C, 18 h. [b]Reaction run at 70 °C. [c]Reaction run with 10 mol% catalyst.

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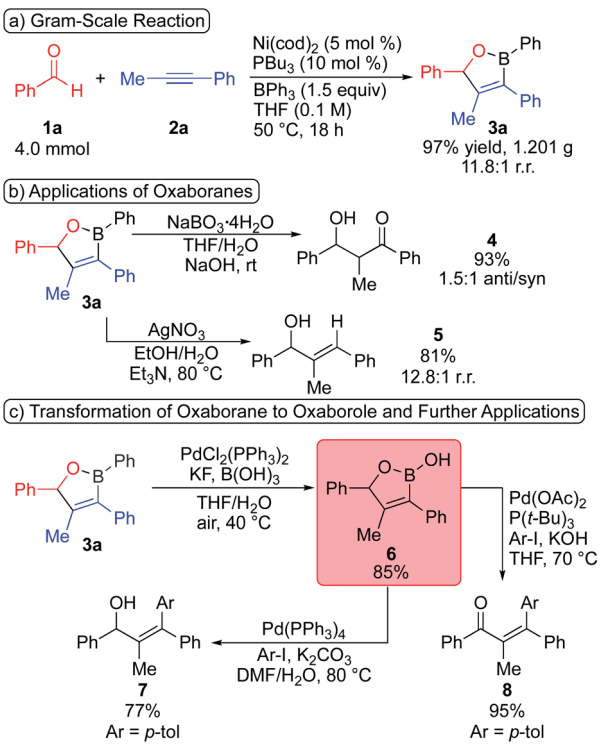
derivatives bearing electron-donating substituents occur at lower temperatures and form oxaboranes in higher yields, while reactions of benzaldehyde derivatives bearing electron-withdrawing substituents require higher temperatures to generate the corresponding oxaboranes, such as **3w**, **3x**, and **3aa**, in good yields. 2-Naphthaldehyde was also well tolerated, and this reaction formed oxaborane **3ac** in 70% yield. The dearylative cyclocondensation reaction also tolerates heteroaromatic aldehydes, such as furfural and 2-thiophenecarboxaldehyde, generating oxaboranes **3ad** and **3ae** in 63% and 47% yield, respectively. Pivaldehyde also proved to be a viable substrate, and this reaction generated oxaborane **3af** in 47% yield. However, aliphatic aldehydes containing alpha-hydrogens, such as cyclohexanecarboxaldehyde and 3-phenylpropanal, proved to be challenging substrates due to competing aldehyde oligomerization.[2a,18] Reactions of these aldehydes typically formed the corresponding oxaborane products in <15% yield.

The dearylative cyclocondensation reaction is currently limited to triphenylborane as the organoboron component. Reactions of other triarylboranes led to significantly lower yields of the corresponding oxaborane products. For example, the reaction of benzaldehyde, 1-phenyl-1-propyne, and tris(4-methoxyphenyl)borane formed the corresponding oxaborane in <20% yield.

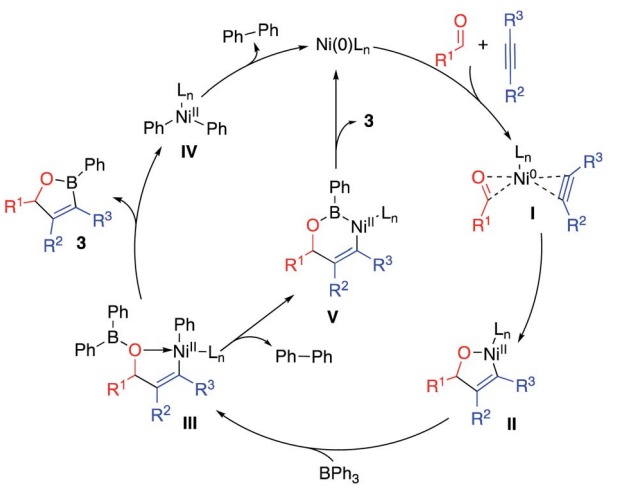
The utility of the dearylative cyclocondensation reaction to generate oxaboranes is shown in Scheme 4. The gram-scale reaction of benzaldehyde (4.0 mmol) and 1-phenyl-1-propyne (4.4 mmol) occurs to form oxaborane **3a** in 97% yield with an 11.8 : 1 regioisomeric ratio (Scheme 4a). We then conducted a series of transformations of oxaborane **3a** to demonstrate oxaboranes as versatile synthetic intermediates (Scheme 4b).[10e] Oxidation of oxaborane **3a** with sodium perborate produced β-hydroxy ketone **4** in 93% yield and 1.5 : 1 d.r.[19] The sequence of dearylative cyclocondensation and oxidation provides an alternative pathway to cross-aldol addition reactions. Protodeboronation of oxaborane **3a** leads to allylic alcohol **5** in 81% yield.[20]

We then attempted to transform our oxaborane product to an oxaborole. Dong and coworkers previously reported transformation of oxaborinanes to cyclic hydroxyl boronates *via* hydrolysis in the presence of H_2O/MeOH.[11d] However, oxaborane **3a** is unreactive under analogous hydrolysis conditions. We were pleased to observe that oxaborole **6** can be generated in 85% yield by selective homocoupling of oxaborane **3a** in the presence of $PdCl_2(PPh_3)_2$ (Scheme 4c).[21] The modularity of our oxaborane synthesis and ability to transform oxaboranes to oxaboroles provide access to the biologically active oxaborole motif with high levels of customizability. Additionally, these oxaboroles can also be utilized as versatile synthetic intermediates. Oxaborole **6** undergoes Suzuki–Miyaura coupling with 4-iodotoluene to form highly substituted allylic alcohol **7** in 77% yield when $Pd(PPh_3)_4$ is used as a precatalyst.[22] α,β-Unsaturated ketone **8** is formed in 95% yield through a sequence of Suzuki–Miyaura coupling and oxidation when the catalyst is generated from $Pd(OAc)_2$ and $P(t\text{-}Bu)_3$.[23]

Based on mechanisms proposed by Montgomery and Ogoshi for nickel-catalyzed dehydrogenative[7] and dealkylative[8,24] cyclocondensation reactions, we propose the following plausible catalytic cycles for this dearylative cyclocondensation reaction (Scheme 5). Coordination of the Ni(0) catalyst to the alkyne and aldehyde substrates forms intermediate **I**. Oxidative cyclization generates oxanickelacyclopentene intermediate **II**. Transmetalation with triphenylborane forms vinyl-Ni(II)-aryl intermediate **III**. We envision two potential pathways to generate oxaborane **3** from intermediate **III**. One potential pathway involves a second intramolecular transmetalation to form diaryl-Ni(II) intermediate **IV** with release of the oxaborane



Scheme 4 Synthetic transformations of oxaboranes.



Scheme 5 Proposed catalytic cycle.

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product **3**. Subsequent reductive elimination from **IV** generates biphenyl and reforms the Ni(0) catalyst. Alternatively, sigma-bond metathesis of the Ni–Ph and B–Ph bonds would lead to direct extrusion of biphenyl from intermediate **III** to form six-membered nickelacycle **V**. Reductive elimination of the vinyl and boryl ligands generates oxaborane product **3** and regenerates the Ni(0) catalyst.

Conclusions

In summary, we have developed a Ni-catalyzed dearylative cyclocondensation of aldehydes, alkynes, and triphenylborane. This reaction forms C–C and C–B bonds to generate a variety of oxaborane products in up to 99% yield under mild reaction conditions. These oxaborane products are readily transformed into oxaboroles, β-hydroxy ketones, a variety of substituted allylic alcohols, and highly substituted α,β-unsaturated ketones. Further studies to determine the mechanism and expand the scope of dearylative cyclocondensation reactions are ongoing in our laboratory.

Data availability

The data for this work, including optimization tables, experimental procedures, and characterization data for all compounds are provided in the ESI.†

Author contributions

M. T. K. and H. K. B. contributed equally to this work. M. T. K. and L. M. S. conceived the project. M. T. K. optimized the reaction conditions and performed design of experiment studies. M. T. K., H. K. B., and S. A. P. synthesized starting materials, evaluated the scope of the reaction, and completed synthetic applications. M. T. K., H. K. B., and L. M. S. wrote the manuscript with input from S. A. P.

Conflicts of interest

There are no conflicts to declare.

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