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Nickel-Catalyzed Three-Component Olefin Reductive Dicarbofunctionalization to Access Highly Functionalized Alkylborates

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Abstract

We report a three-component olefin reductive dicarbofunctionalization for constructing densely functionalized alkylborates, specifically, nickel-catalyzed reductive dialkylation and alkylarylation of vinyl boronates with a variety of alkyl bromides and aryl iodides. This reaction exhibits good coupling efficiency and excellent functional group compatibility, providing convenient access to the late-stage modification of complex natural products and drug molecules. Combined with versatile alkylborate transformations, this reaction could also find applications in the modular and convergent synthesis of complex, densely functionalized compounds.

Keywords

nickel catalyst, olefin dicarbofunctionalization, reductive dialkylation, reductive alkylarylation, alkylborate synthesis

Introduction

Olefins are fundamental chemicals in organic synthesis. They frequently occur in natural products, are produced in enormous quantities in the petroleum industry, and are prepared through a variety of synthetic methods in the laboratory. The reactive double bonds make
olefins attractive substrates for high-complexity synthesis. Among the well-developed olefin functionalization strategies, the newly developed reductive dicarbofunctionalization has already been proven to be a powerful and straightforward method (Scheme 1a). For example, Nevado and co-workers realized nickel-catalyzed intermolecular olefin reductive alkylation, in which one C(sp\textsuperscript{3})-C(sp\textsuperscript{3}) bond and one C(sp\textsuperscript{3})-C(sp\textsuperscript{2}) bond were formed. Chu and co-workers reported an example of intermolecular olefin reductive carboacylation with fluoroalkyl iodides and acyl chlorides. However, the development of important dialkylation processes is relatively limited and still relies on organometallics that are sensitive to many functional groups.

Recently, dicarbofunctionalization of commercially available vinyl boronates has been applied to the diversified synthesis of alkylborates. For example, Morken, Studer and Aggarwal independently achieved functionalization of a vinylboronate complex using an organolithium reagent and another electrophile (Scheme 1b). Most recently, the electrophile-nucleophile dicarbofunctionalization of a vinyl boronate has been achieved with appropriate radical precursor (Scheme 1c). In addition, hydroalkylation and hydroarylation of alkenyl boronic esters has also been realized. Despite these great successes, general and modular methods to access versatile alkylborates without using any organometallic reagents are still desirable. With our focus on olefin reductive coupling and alkylborate synthesis, we set out to realize the regioselective dicarbofunctionalization of vinyl boronates, taking advantage of nickel-catalyzed reductive coupling and classical Giese-type addition. Herein, we report a three-component olefin reductive dicarbofunctionalization for constructing densely functionalized alkylborates, specifically, nickel-catalyzed reductive dialkylation and alkylarylation of vinyl boronates with a variety of alkyl bromides and aryl iodides (Scheme 1d). This reaction shows good coupling efficiency,
excellent functional group compatibility, and a high degree of regioselectivity. From the point of view of versatile alkylborate transformations, this reaction might find a number of applications in modular and convergent synthesis of complex, densely functionalized compounds.

**Scheme 1. Dicarbofunctionalization of Vinyl Boronates to Access Alkylborates**

\[ \text{B}_2\text{pin}_2 = \text{bis(pinacolato)diboron. B}_2\text{neop}_2 = \text{bis(neopentyl glycolato)diboron. Tf} = \text{triflyl. Nu} = \text{nucleophile. E} = \text{electrophile.} \]

**Results and Discussion**

We began this study with the synthesis of alkylborate 4 through the proposed dialkylation (Table 1). We systematically screened all the reaction parameters (see the Supporting Information for more details), and desired product 4 was obtained in 88% gas chromatography (GC) yield and 83% isolated yield in the presence of NiBr\(_2\)(diglyme), a dipyrazolpyridine ligand (L), a Mn(0) reductant, and a NaI additive in DMAc (entry 1). A number of other nitrogen-containing ligands were compared: all bidentate ligands, bipyridine (L\(_1\) and L\(_2\)), pyridine-oxazoline (L\(_3\)), and bioxazoline (L\(_4\)) were inefficient; tridentate tripyridine (L\(_5\)) yielded only a small amount of the desired products; and pyridine-oxazoline ligands (L\(_6\) and L\(_7\)) produced moderate yields. In the absence of nickel catalysts or ligands, dialkylation could not proceed (entry 2). Other nickel sources, including NiCl\(_2\)(PPh\(_3\))\(_2\), Nil\(_2\), and Ni(COD)\(_2\) could also be used instead of NiBr\(_2\)(diglyme); however, they
led to different decreases in coupling efficiency (entry 3). Metal Zn$^{13c, 16}$ and diboron$^{13b, 17}$ were potential reductants for this transformation (entries 4-6),$^{18}$ but our previously used nickel-silane reductive system$^{13a, 13d}$ was incompetent (entry 7). Amide solvents were critical: DMF and NMP resulted in comparable yields (entry 8) to that of DMAc (optimal conditions), but the reaction was completely inhibited in THF, 1,4-dioxane, CH$_3$CN, and DMSO (entry 9). The performance of primary alkyl iodide 5 was barely satisfactory (entry 10), and a significant amount of homocoupling product 6 was observed. Tertiary alkyl bromides were irreplaceable: the corresponding iodides and chlorides provided no dialkylation product (entry 11), even in the presence of activator reagents (entry 12). Finally, the iodide ion additive and ratio of starting material were also carefully selected (entries 13-16).

**Table 1. Optimization of the Reaction Conditions**

| entry | deviation from standard conditions | yield (%) |
|-------|------------------------------------|-----------|
| 1     | none                               | 88        |
| 2     | w/o NiBr$_2$(diglyme) or w/o L     | N.R.      |
| 3     | NiCl$_2$(PPh$_3$)$_2$, NiI$_2$, or Ni(COD)$_2$ instead of NiBr$_2$(diglyme) | 49-83     |
| 4     | 3.0 eq. Zn instead of Mn           | 76        |
| 5     | 3.0 eq. B$_2$pin$_2$ and 3.0 eq. LiOMe instead of Mn | 44        |
| 6     | 3.0 eq. B$_2$pin$_2$ and 3.0 eq. K$_3$PO$_4$ instead of Mn | 50        |
| 7     | 3.0 eq. DEMS and 3.0 eq. Na$_2$CO$_3$ instead of Mn | 11        |
| 8     | DMF, or NMP instead of DMAc        | 72-87     |
| 9     | THF, 1,4-Dioxane, CH$_3$CN, or DMSO instead of DMAc | <2        |
| 10    | 5 instead of 3                      | 54        |
| 11    | tBuI or tBuCl instead of tBuBr     | <2        |
| 12    | tBuCl with 20% Cp$_2$TiCl$_3$ instead of tBuBr | <2        |
| 13    | 30% TBAI instead of 50% NaI         | 82        |
| 14    | 20% NaI instead of 50% NaI          | 45        |
| 15    | ratio of 1 : 2 : 3 = 1 : 1 : 1 instead of 1 : 2 : 2 | 52        |
| 16    | ratio of 1 : 2 : 3 = 1 : 1.5 : 2 instead of 1 : 2 : 2 | 76        |
With suitable conditions in hand, we set out to evaluate the scope of this olefin dialkylation reaction. As shown in Scheme 2, a variety of primary alkyl bromides delivered desired products 7-25 in moderate to good yields (60-84%). Because of mild reductive cross-

\[\text{Product 7-25} \]
coupling conditions, this reaction exhibited good compatibility with a wide range of synthetically useful functional groups, such as ester (4), ether (7-8), aryl fluoride (10), trifluoromethyl (11), and trifluoromethoxy (12) groups. Satisfactory chemoselectivity was observed in compounds 13-15; in these cases, aryl chlorides and bromides were proven to be less reactive than alkyl bromides. This chemoselectivity provided a profitable platform for further manipulations at the surviving aryl electrophilic sites. Both base-sensitive ketone (16) and cyano (17) groups and acid-sensitive acetal (18) groups posed no problem during this transformation. Several heterocycles such as phthalimide (19), thiophene (20), furan (21), morpholine (22), and indole (23) moieties, were well tolerated. Finally, this reaction also performed well in the presence of amide-possessing N-H bonds (24) and unprotected alcohol (25) groups.

Scheme 3. Substrate Scope of Tertiary Alkyl Bromides

The versatility of this reaction was further demonstrated in terms of the tertiary alkyl partners (Scheme 3). Both acyclic (26-30) and cyclic (31-33) tertiary alkyl bromides were successfully converted to the desired products. With respect to the acyclic substrates, dramatically different steric hindrances only resulted in a slight influence on the coupling
efficiencies. Finally, tertiary alkyl bromides containing ester (32), ether (33), acetal (34), and \(C(sp^3)\)-Cl (35) groups were indeed good substrates during the transformation and afforded the corresponding products with moderate to good isolated yields.

**Scheme 4. Substrate Scope of Olefin Reductive Alkylarylation**

* Conditions: as shown in Table 1, entry 1, without NaI, 0.2 mmol scale. Isolated yield.

Although the primary focus of this study was olefin reductive dialkylation, the optimized conditions could also be extended to alkylarylation (Scheme 4). Benzylic boronates were obtained conveniently with the simultaneous formation of one aryl-alkyl bond and one alkyl-alkyl bond.\(^{19}\) With respect to aryl coupling partners, both electron-donating (36) and electron-withdrawing (37-39) substituents were well tolerated in the meta- and para-positions and afforded the corresponding products in moderate (39–50%) isolated yields. In addition, this transformation is orthogonal to classical Suzuki cross-coupling procedures, as the \(C(sp^3)\)-B bond remained intact in substrate 40. Finally, different tertiary alkyl bromides were also explored (41-43), in which the desired alkylarylation products were delivered smoothly.

**Scheme 5. Synthetic Applications**

* Conditions: as shown in Table 1, entry 1, without NaI, 0.2 mmol scale. Isolated yield.
In a scale-up reaction, we successfully obtained reductive dialkylation product 9 with a satisfactory 84% isolated yield (Scheme 5a), which highlights the practicality of this new alkylborate synthetic method. Combined with versatile alkylborate transformations, our method provided a modular strategy for the synthesis of densely functionalized compounds (Scheme 5b). For example, structurally complicated alcohols (45-46), diaryl alkanes (47-48), and alkyl iodide (49) were created via such an assembly-line synthetic route. Finally, we used this method for the late-stage functionalization of complex natural products and drug molecules (Scheme 5c). The efficient conversion of glucose (50), indomethacin (51), and oleanic acid (52) derivatives to the desired products demonstrated a high degree of tolerance to diverse functional groups.

Scheme 6. Mechanistic Probes
To examine the reaction mechanism, we carried out competition experiments (Scheme 6a). 4-Bromobut-1-ene (53) was subjected to standard conditions, and desired product 54 was obtained in 63% isolated yield, with the terminal alkene group retained. In the competition reaction between vinyl boronate (1) and dec-1-ene (55), the vinyl boronate dialkylation product (4) was formed in 70% GC yield. However, the dialkylation product (56) of dec-1-ene was not observed, with 77% recovery of the starting material dec-1-ene (55). The competition reaction between vinyl boronate (1) and acrylamide (57) was also conducted, and both the vinyl boronate dialkylation product (9) and the acrylamide alkylation product (58) were observed. Thus, electron-deficient olefins were more reactive in this reaction, and no reaction occurred for the electron-rich olefins. In addition, tertiary alkyl bromides exhibited higher radical addition reactivity than the primary alkyl bromides (see Supporting Information for more details). The radical clock experiment was tested using...
(bromomethyl)cyclopropane (60), and we obtained only ring opening product 54 in 42% yield, which revealed the radical activation of primary alkyl bromides (Scheme 6b). Finally, the nonmetallic reductant TDAE was used instead of Mn(0) and resulted in a decent 25% GC yield. We deduced that the activation of alkyl bromides was a single-electron-transfer (SET) process, but not the in situ formation of alkylmanganese reagents (Scheme 6c).

**Conclusion**

We reported a convenient method to access highly functionalized alkylborates through nickel-catalyzed olefin reductive dialkylation and alkylarylation of vinyl boronates. A variety of alkyl bromides and aryl iodides were converted to the corresponding products with both good coupling efficiency and excellent functional group compatibility. This reaction is practical and useful in the late-stage modification of complex natural products and the modular synthesis of densely functionalized compounds. Our next challenge is the improvement of stereochemical control.20

**Supporting Information**

Supporting Information is available and includes detailed experimental procedures and spectral data.

**Conflict of Interest**

There is no conflict of interest to report.

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20. A moderate 40% enantiomeric excess was obtained using a pyridine-oxazoline ligand.

**Table of Contents Graphic**
