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# Rh-Catalyzed Decarbonylative Cross-coupling Between *o*-Carboranes and Twisted Amides: A Regioselective, Additive-free and Concise Late-stage Carboranylation

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Dedicated to the 100th anniversary of the School of Chemistry and Chemical Engineering, Nanjing University。

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**Abstract:** The convenient cross-coupling of $sp^2$ or $sp^3$ carbons with a specific boron vertex on carborane cage represents significant synthetic values and insurmountable challenges. In this work, we report a Rh-catalyzed reaction between *o*-carborane and *N*-acyl-glutarimides to construct various $B_{cage}$−C bonds. Under the optimized condition, the removable imine directing group (DG) leads to B(3)- or B(3,6)−C couplings, while the pyridyl DG leads to B(3,5)−Ar coupling. In particular, an unexpected rearrangement of amide reagent is observed in pyridyl directed B(4)−C($sp^3$) formation. This scalable protocol has many advantages, including easy access, the use of cheap and widely available coupling agents, no requirement of an external ligand, base or oxidant, high efficiency, and a broad substrate scope. Leveraging the $Rh^I$ dimer and twisted amides, this method enables straightforward access to diversely substituted and therapeutically important carborane derivatives at boron site, and provides a highly valuable vista for carborane-based drug screening.

## Introduction

Transition-metal-catalyzed carbon-carbon and carbon-heteroatom bond-forming reactions have had a major impact on the practice of organic synthesis and have been mainstays of modern drug discovery.[1] Alone these lines, cross-coupling based on carboxylic acids or activated carboxylic acids are well and rapidly investigated in recent years, owing to the abundant, commercially available, non-toxic and bench-stable nature of carboxylic acids and corresponding derivatives. In 2015, Szostak developed *N*-acyl-glutarimide reagents, whose reactivity is driven by disruption of the amide resonance. Since then twisted amides have been employed in coupling reactions, and less additives are necessary in most cases, which makes them ideal surrogates of halides.[2]

The icosahedral *closo*-$[C_nB_{12-n}H_{12}]_{n-2}$ (n = 0, 1, 2) clusters have been extensively studied in the polyhedral borane family.[3] Owing to the 3D aromaticity, steric hindrance, unique electronic properties, and non-classical interactions, the icosahedral boron clusters play a prominent role in materials science,[4] uranium capture,[5] catalysis,[6] radiotherapy,[7] and also work as a good model for physical organic chemistry investigation.[8] On the other hand, the carboranyl is a useful scaffold in drug design.[9] As an unique electron-adjusting steric group,[10] it has been shown that the replacement of an aromatic ring with the B(3)-gratified carboranyl, other than C-gratified carboranyl, can improve the potency of lidocaine (Figure 1A).[11] As an analog of phenyl, the future investigation of superior therapeutics or antibiotics would greatly benefit from approaches that permit access to a larger chemical space of diversely substituted carboranyl derivatives. However, synthetic access to densely functionalized carboranyl-fused molecules is still challenging, especially for B(3,6) functionalization at late-stage. This is because the ten inert BH units locate in a similarly chemical atmosphere, and B(3,6)−H units are the most electronic deficient.[12] Traditionally some precursors for B(3)−C coupling were employed (Figure 1B). From a synthetic standpoint, these precursors are hard to prepare, most often via a multi-step chemical sequences[13] and toxic[13a, 13d] or explosive[13b, 13c] syntheses. In addition, precursor **1** is sensitive to oxygen as well as moisture, and diazonium salt **3** is not stable.

Direct B(3)−C coupling via B−H activation would be advantageous for the step-economic synthesis of carboranyl-based arenes, alkenes or alkanes. The organometallic B(3,6)−H activation was well investigated by Hawthorne,[14] Herbhold,[15] Xie,[16] Jin[17] and our group[18]. In recent years, several B(3)−C coupling without directing group has been disclosed (Figure 1C, left),[19] while the limited substrate scope impeded their further applications. Since either B(3) or B(4) is adjacent to cage carbons and the carbon vertex itself is easy to be decorated comparing with other boron vertices, Xie,[20] Duttwyler,[21] Ackermann[22] and Che[23] and our lab[24] installed DGs on cage carbon that a series B−C coupling products were generated. Among them, the carboxylic acid, imine, “transient” imine, bidentate amide DGs resulted in B(4)- or B(4,5)−C formation. These results implicated that the other $C_{cage}$ should be blocked by alkyl or aryl to guarantee good yield and B(4) selectivity.[24b, 25] Ackerman reported the amide directed construction of B(3)- or B(3,4)−Ar,[22] while Che realized the syntheses of B(3,6)−C coupling compounds by irremovable $PAr_2$ DG (Figure 1C, right).[23] In most cases,


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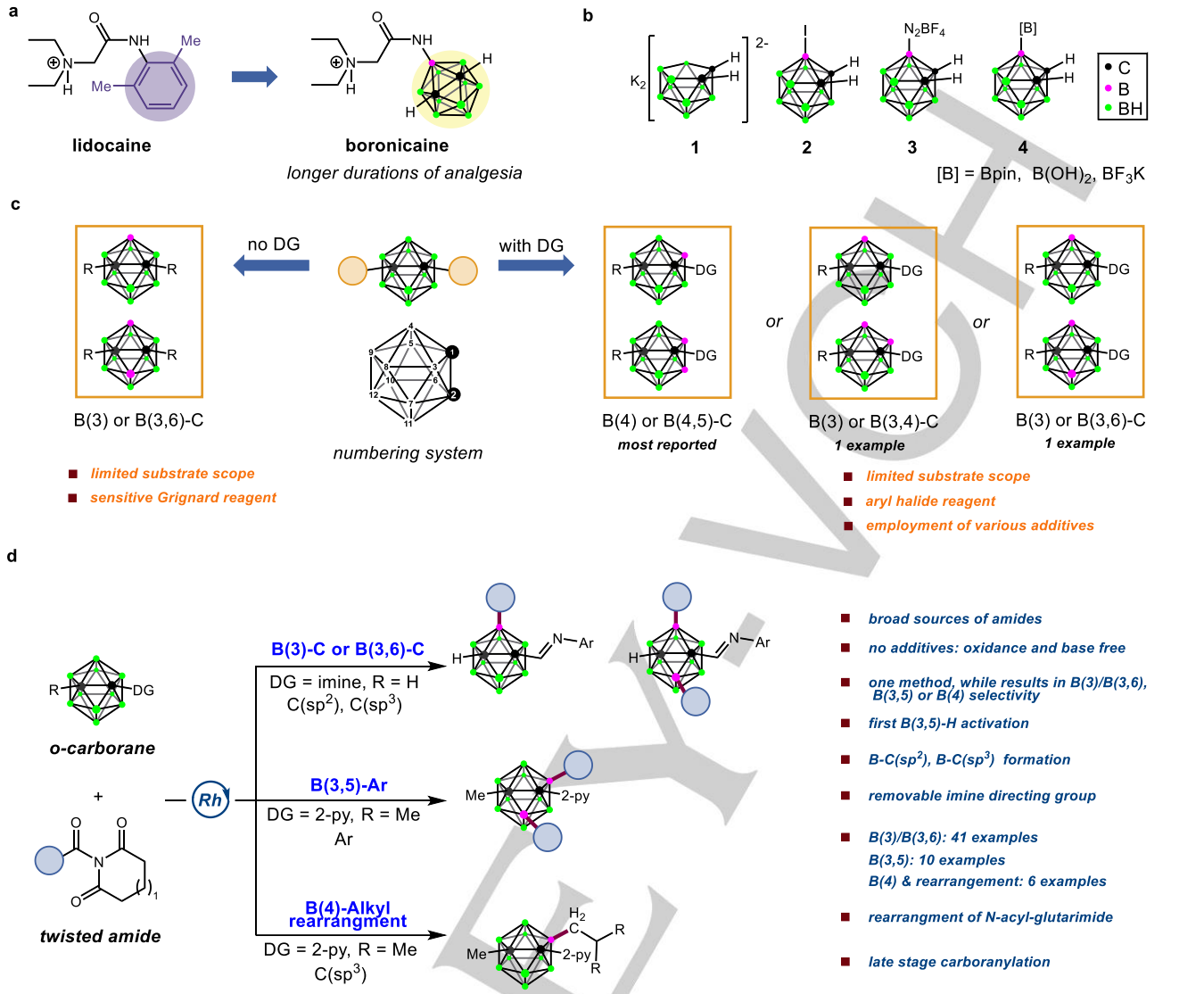


**Figure 1.** Background of the utilities and reactivities of *o*-carborane. **a**, B(3)-tethered bioactive small-molecule. **b**, Classical B(3) precursors for B(3)-C bond construction. **c**, Recently disclosed strategies for B(3)-C coupling via B-H activation. **d**, This work: Rh-catalyzed decarbonylative cross-coupling between *o*-carboranes and twisted amides.

aryl bromide or aryl iodide works as the aryl source. But different from C−H activation, the B−O or B−halide by-product, which was observed in our previous work and recent work reported by Che, can be generated due to the stronger bond energy of B−O, B−Br, or B−I bonds.[20b, 23, 24c] In addition, the weakly reductive *o*-carborane is sensitive to strong oxidants, and deboranation may happen when bases exist in reaction system. Thus, we are looking for a base-, halide-, and oxygen-free, redox neutral, soluble condition and a surrogate of halide reagent with a good availability should be taken into consideration. Apart from the considerations above, we hope to find a way to construct diverse B−C($sp^2$), B−C($sp^3$) by only one method. We herein report the Rh-catalyzed decarbonylative cross-coupling between *o*-carboranes and twisted amides (Figure 1D). By employing removable imine DG, B−C($sp^2$) and B−C($sp^3$) couplings are realized with a B(3) or B(3,6) selectivity. By employing 2-pyridyl DG, the coupling between B−Ar with an unreported B(3,5) selectivity are realized. In addition, an unanticipated rearrangement of third ordered alkyl was observed in pyridyl directed B(4)−C($sp^3$) coupling, which is in sharp contrast to corresponding fashion in C−H activation.[26] The broad availability of amide, good solubility and additive free condition enable preparation of carboranylated (at boron site) organic scaffolds, which may vastly boost medicinal discovery.

## Results and Discussion

After extensive investigation, we have discovered the reaction conditions to achieve our goal (see Table S1). Enlighted by Szostak's rhodium catalysis, treatment of *o*-carborane with imine DG (1.0 equiv) and *N*-acyl-glutarimides (2.2 equiv) in presence of 5 mol% $[Rh(cod)Cl]_2$ in toluene (0.2 M) at 150 °C for 24 hours afforded the corresponding product **5** in 93% overall yield. The robustness of this decarbonylative B(3)−C coupling is illustrated in the synthesis of 40 products (Figure 2). In general, *N*-acyl-glutarimides possessing electron-withdrawing groups (EWG) at the *para*-position worked very well (**9**-**18**), although electron-donating groups (EDG) (**6**-**8**) also gave moderate yields. When



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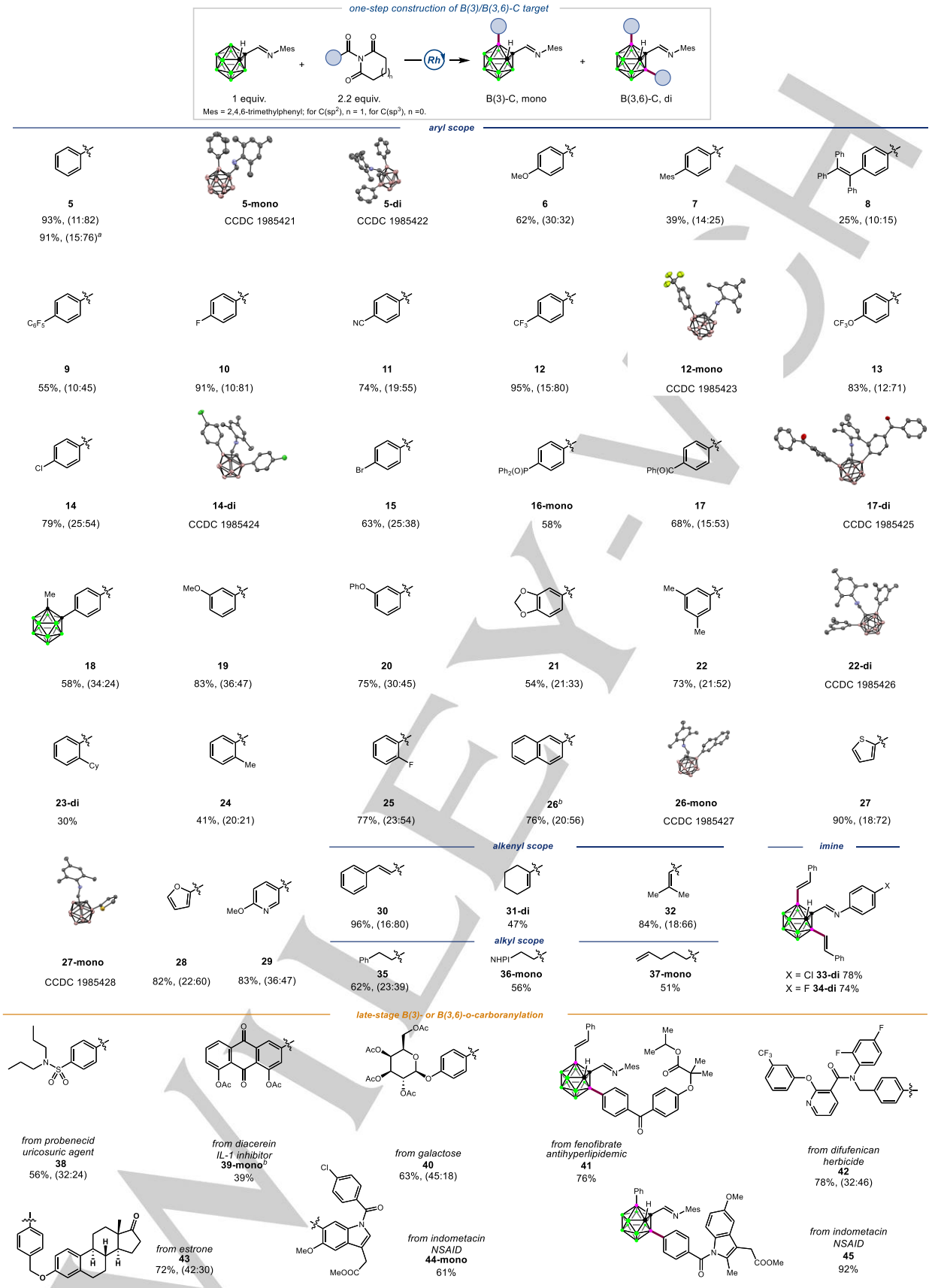


**Figure 2.** Scope of twisted amides. Reaction condition: The reaction is typically performed with *o*-carbonrane starting material (0.2 mmol), twisted amide (0.44 mmol, 2.2 equiv), $[Rh(cod)Cl_2]_2$ (0.01 mol, 0.05 equiv), toluene (1 mL) under argon at 150 °C heating for 24 hours. Isolated yields unless otherwise noted. [a] 1.0-gram scale. [b] $[Rh(cod)Cl_2]_2$ (0.02 mol, 0.1 equiv)



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methoxyl, phenoxyl and methyl groups were installed on *meta*-position of *N*-acyl-glutarimides, we eventually obtained **19**-**22** in good yields. Figure 2 outlines the influence of steric effect at the *ortho*-position. The larger steric hindered groups, such as cyclohexyl and methyl, impeded the formation of **23** and **24**, whereas the less steric hindered fluoride availed a good yield of **25**. Naphthyl was tolerated but required increased loading in catalyst to achieve similar efficiency (**26**). Furthermore, either heteroaromatic thienyl (**27**), furyl (**28**) pyridyl (**29**) or alkenyls (**30**-**34**) performed well in the cross-coupling with B(3)-*o*-carboranyl under the optimized conditions. When 2,4,6-trimethylpheyl (Mes) group of imine DG was substituted by 4-fluorophenyl (**33**) or 4-chlorophenyl (**34**), the yield is not influenced. To date, the C($sp^3$)−B(3) coupling has been exceedingly challenging. Harnessing alkyl amide precursors, we were delighted to find that the C($sp^3$)−B(3) couplings displayed moderate yields (**35**-**37**) under the same condition. As pointed out by Buchwald, the structurally complex substrates typically encountered in applied settings often contain functional groups or substructures that can inhibit catalyst turnover or participate in unproductive side reactions.[27] On the other hand, several molecules with increased physiological activities after transition-metal introduced late-stage C−H arylation have been surveyed.[28] As a good analog of phenyl ring, the three-dimentional carboranyl group opens up new prospects for drug design.[11] To this end, the impressive regioselectivity of our reaction furnishes the unique opportunity to pursue late-stage carboranylation of bioactive molecules with diverse functionalities.[29] A diverse array of substrates that derived from natural products or drugs were also subjected to this protocol. The coordinative oxygen and nitrogen containing molecules were easily converted into the corresponding B(3)−C($sp^2$) coupling products (**38**-**45**). Complex steroidal derivatives proved to be exceptional coupling products with the notoriously sensitive ketone functional group left unperturbed in the coupling (**43**). Notably, other amide bond was not affected, and no transformation was observed on potentially competing C−H bonds under the standard condition (**42**), further supporting that the ideal selectivity and practicability of this method. It is worth noting that two different positions of indomethacin can be functionalized by B(3)-*o*-carboranyl in this method (**44**, **45**). To explore this methodology, we have managed to prepare two unsymmetrical B(3,6) disubstituted carboranes (**41**, **45**). Therefore, we have achieved the coupling between B(3)-*o*-carboranyl with diverse aryl, alkenyl or alkyl just by using the simple rhodium catalytic system, which may benefit for screening of B(3)-*o*-carboranyl fused bio-active molecules.

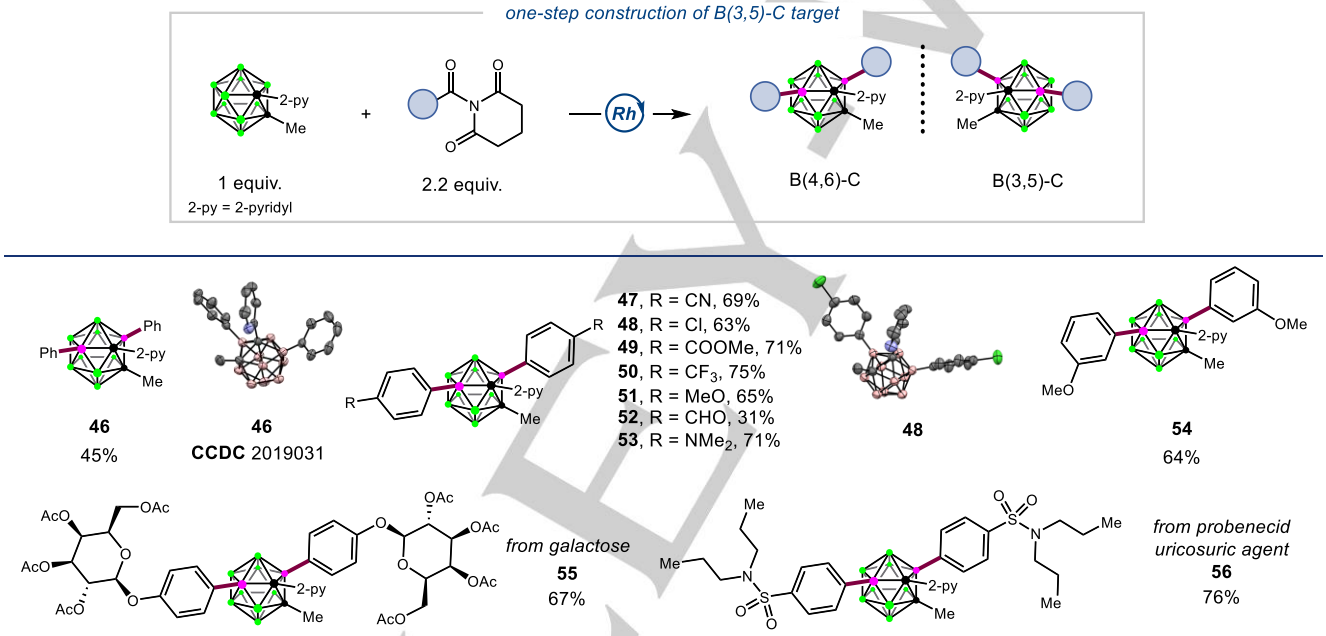


**Figure 3.** Pyridyl directed B(3,5)-Ar coupling. Racemic mixtures were acquired, while only one configuration, B(4,6) diaryl product, is displayed in this figure.

In our previous work, we have realized pyridyl-directed Rh-catalyzed *o*-carborane B(3)- or B(3,6)–H acyloxylation. We therefore speculated that pyridyl DG can lead to a B(3) or B(3,6)−Ar coupling as well (Figure 3). Under the optimized condition, 1-methyl-2-(2-pyridyl)-*o*-carborane (1 equiv), *N*-acyl-glutarimides (2.2 equiv) and 5 mol% $[Rh(cod)Cl]_2$ were mixed. To our surprise, the di-substituted products show an unreported B(3,5) selectivity. The electronic efficient seldom influences the yield, compared with the imine directed B(3)- or B(3,6)−C coupling. EWGs such as cyano group (**47**), chloride (**48**), ester (**49**), trifluoromethyl (**50**), formyl (**52**) resulted in moderate to good yields. While good yields were also obtained for EDG containing products (**51**, **53**). Good yields were acquired when *meta*-substituted substrate (**54**) was tested. Drug motif, such as probenecid or galactose, can be gratified on B(3,5) positions as well (**55**, **56**). 1-methyl-2-(2-pyridyl)-*o*-carborane is a prochiral molecule, in the absence of chiral catalysts or chiral ligands the racemic mixtures were required (see Section 6 in SI). In Figure 3, only one configuration is displayed. When methyl group on carbon vertex was changed to a larger hindered phenyl group, no reaction took place (see Section 5 in SI).

As both are severely steric hindered groups, the cross-coupling between *o*-carboranyl and *tert*-C($sp^3$) is formidable. Insisting on our investigation of cross-coupling of *o*-carborane and twisted amides, we finally found the third order *N*-acyl-glutarimide with a methyl group can facilitate the coupling. Nevertheless, the reaction is different from the similar case in C−H activation.[30] The *tert*-butyl precursor furnished a *t*-Bu to the *ortho*-C−H bond of 2-phynelpyridine (see Section 7 in SI), whereas the compound **57** was proven to be an isobutyl substituted *o*-carborane derivative with B(4) selectivity. To our best knowledge, the cross-coupling which accompanies with rearrangement of twisted amide's scaffold have not been observed before. Besides, this coupling is also different from recently reported coupling between *t*-Bu and B(4) via a nucleophilic substitution.[19b] We considered that the large steric hindrance of *o*-carboranyl and third order C($sp^3$) center is the primary cause for the unique rearrangement. The simple description for this unanticipated rearrangement displays in Figure 4. There is a big repulsion between *o*-carboranyl and the third ordered alkyl group. After *β*-H elimination and subsequent 1,2-migratory insertion,[31] the repulsion releases, and the product is generated after reductive elimination. This protocol runs well for



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*N*-acyl-glutarimides with a methyl group on the third ordered carbons (**57**-**61**) including Gemfibrozil, an antihyperlipidemic drug. Without chiral catalysts and chiral ligands, the products are racemic as well.

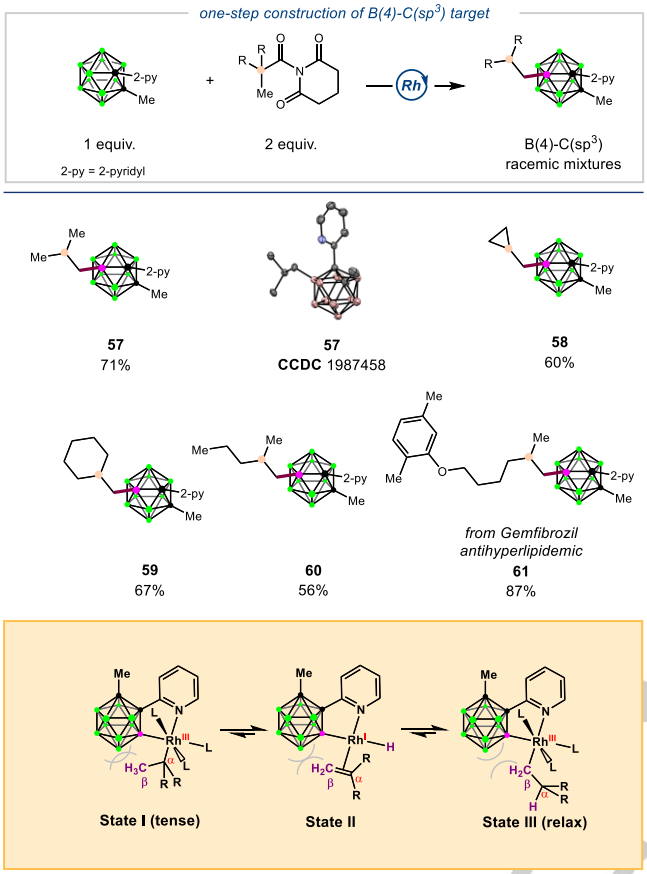


**Figure 4.** Pyridyl directed B(4)−C(sp³) coupling accompanied with rearrangement of *N*-acyl-glutarimides. Racemic mixtures were acquired, while only one configuration is displayed in this figure.

Many transformations were also employed to expand the utilities of this carboranylation method (Figure 5). This protocol has a good chemical orthogonality. Either arylation under Suzuki coupling condition (**62**) or reduction of the cyano group is a case in point (**63**). The imine group can be transferred to corresponding aldehyde in the first step (**64**), and the aldehyde group can be cleaved by potassium permanganate afterwards (**65**). It came as no surprise that the unblocked cage carbon site can be methylated well (**66**). By the treatment of trifluoroacetic acid, compound **66** can be converted into a *nido*-carborane derivative **67**. At last, to test the practicality of this method, gram scale reactions were carried out to give **5** with only a slight decrease in yield (Figure 2).

To better understand the B(3)−H selectivity rather than B(4)−H or C−H selectivity in imine directing system, we commenced on mechanistic study based on density functional theory (DFT). DFT calculations have been conducted to elucidate the catalytic cycle of this reaction. The calculated reaction pathways are summarized in Figure 6, in which carborane **68** and 1-benzoylpiperidine-2,6-dione are selected as a model system. The reaction starts at the coordination of **68** and rhodium to form **Int1**.

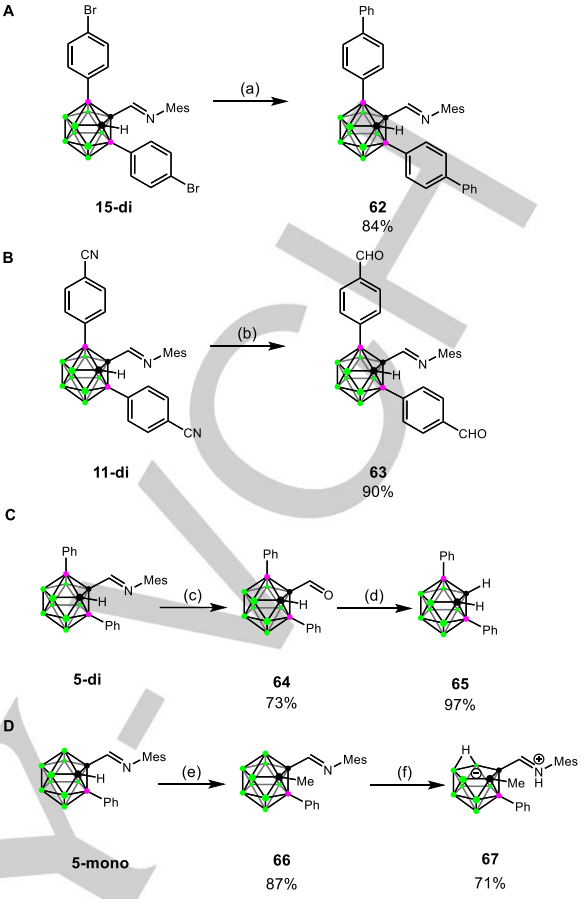


**Figure 5.** Synthetic utilities. (a) $Pd(PPh_3)_4$ (10 mol%), $Na_2CO_3$ (2 equiv), toluene-$H_2O$-EtOH (5:5:1, 0.05 M), Ar, 100 °C, 24 hrs; (b) DIBAL-H (3 equiv), DCM (0.1 M), Ar, -40 °C, 5 hrs; (c) TFA (10 equiv), dioxane-$H_2O$ (1:1, 0.1 M), 100 °C, 2 hrs; (d) $KMnO_4$ (1 equiv), $Na_2HPO_4$ (1 equiv), THF-$H_2O$ (1:1, 0.03 M), r. t., 12 hrs; (e) KHMDS (1.2 equiv), r.t., Ar, 0.5 hr; then MeI (2 equiv), r.t. 3 hrs; (f) TFA (10 equiv), dioxane-$H_2O$ (1:1, 0.1 M), 100 °C, 2 hrs.

Preferential oxidative addition of B(3)−H then takes place, followed by reductive elimination of HCl to achieve the B−H activation. Reaction pathways with amide oxidative addition prior to B−H activation are also investigated and found energetically unfavorable (for details, see Section 10 in SI). Afterward, 1-benzoylpiperidine-2,6-dione exchanges with cod ligand, then undergoes oxidative addition with a rate-determining 38.7 kcal $mol^{-1}$ barrier.[32] The corresponding B(4)-carboranyl transition state **TS3-B(4)** is 4.5 kcal $mol^{-1}$ higher in energy than **TS3**, in accordance with regiospecific B(3) carboranylation. Subsequently, HCl exchanges with glutarimide ligand, followed by decarbonylation and reductive elimination to finish the cross-coupling. Pathways without decarbonylation are found to require a much higher barrier (for details, see Section 10 in SI). To finish the reaction, cod re-enters the coordination sphere to expel CO, affording **Int1-Ph** as the resting state of this system. The second catalytic cycle can start either from **Int1-Ph** to form symmetric disubstituted *o*-carborane or **Int1** to generate the mono one. Calculations indicate that the former pathway is energetically slightly favorable. This agrees with the experimentally observed di-functionalization tendency of carborane **68**.

To better understand the origin of B(3)-selectivity of this carboranylation, rate-determining transition states **TS3** and **TS3-**



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**B(4)** are further investigated. The main difference of these two transition states is the different coordination mode of carboranyl ligands. Therefore, carboranyl ligands **L-TS3** and **L-TS3-B(4)** are separated from the corresponding transition states, following by calculations of their single-point energy and NBO atomic charge analysis (Figure 7). The relative energy ( $\Delta E_{sol}$) of two transition states is 4.1 kcal mol$^{-1}$. Since the $\Delta E_{sol}$ of carboranyl ligands (3.3 kcal mol$^{-1}$) has a comparable value, the energy difference in ligand indeed contributes dominantly to $\Delta E_{sol}$ of transition states, which leads to the final regioselectivity. From NBO analysis, it is shown that **L-TS3** locates less negative charge at the carboranyl B(3) site. This can be explained as B(3) is adjacent to two more electronegative carbon atom, and therefore, a better charge delocalization is achieved. To coordinate with Rh, the carboranyl B atom and imine N atom in ligand are close to each other, resulting in the repulsion between negative charges. The more charge-delocalized ligand **L-TS3** experiences less repulsion, which causes it to be energetically more favorable than **L-TS3-B(4)**.

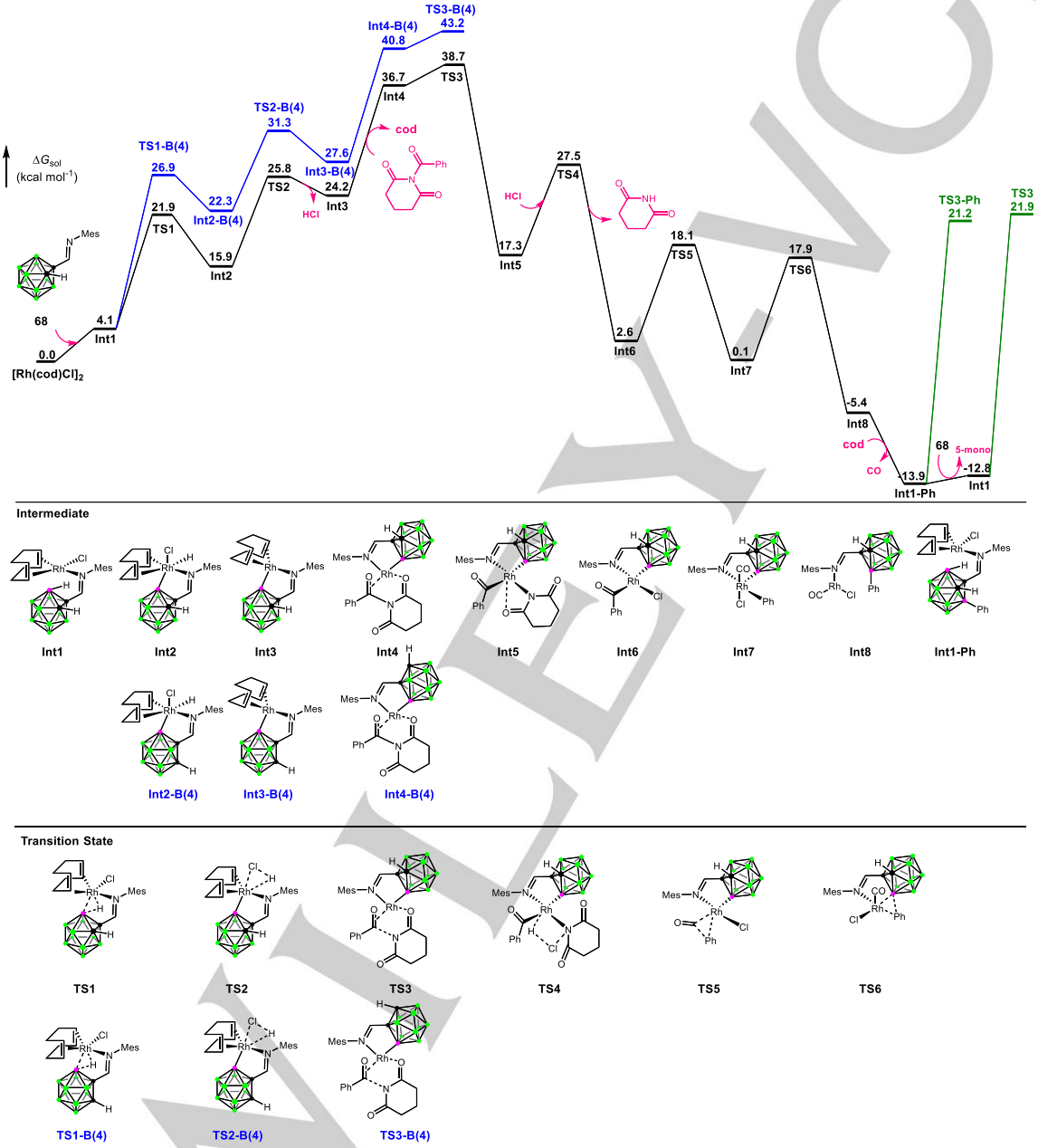


**Figure 6.** DFT-computed pathways for the Rh-catalyzed reaction between substrates **68** and 1-benzoylpiperidine-2,6-dione. Numbers associated with each name are Gibbs free energies in kcal·mol$^{-1}$. Transition states and intermediates in blue describe Rh−B(4) connection, the black ones describe Rh−B(3) connection.



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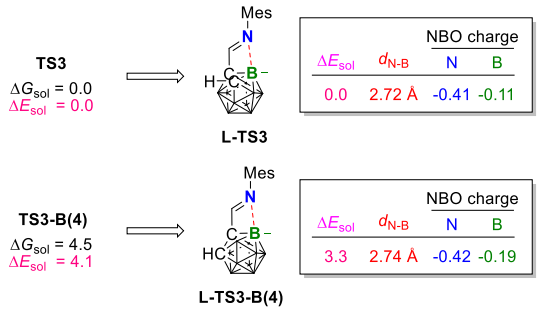


**Figure 7.** Single-point electronic energy (in kcal mol$^{-1}$), N-B distance and NBO charge analysis of B(3) and B(4) carboranyl ligands isolated from **TS3** and **TS3-B(4)**, respectively.

## Conclusion

In summary, we have described a new cross-electrophile carboranylation by using *N*-acyl-glutarimide as a coupling partner. B(3) and B(4) selectivity could be adjusted by directing group and substrate precisely. This reaction enables a precise, rapid and scalable carboranylation with simple reagents under a redox neutral and base free condition, thus making it a practical approach for late stage carboranylation. In particular, the rearrangement of twisted amide indicates some differences between carborane and classical organic functionality. Furthermore, the boron vertex can be installed even on drug scaffolds, which paves the way for pharmaceutical investigation based on carboranylated drugs.

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**Keywords:** carborane • rhodium • C–N activation • B–H activation • late stage

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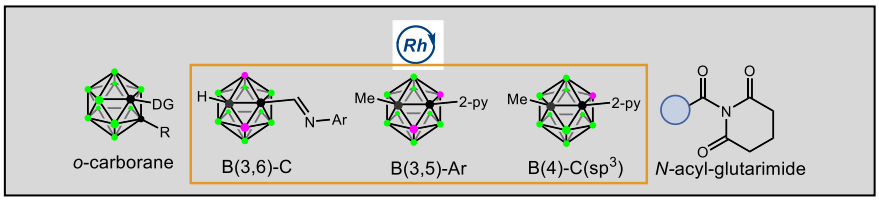


Rh catalysis enables cross- coupling between *o*-carborane and twisted amide. A series of regioselective B(3,6)-C, B(3,5)-Ar and B(4)-C($sp^3$) coupling products have been obtained. The operationally simple reaction gives rise to diverse carboranyl-fused organic motifs and accommodates late-stage diversification, which may pave a new way for medicinal investigations.

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