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COMMUNICATION

High-Throughput Ligand Screening Enables the Enantioselective Conjugate Borylation of Cyclobutenones to Access Synthetically Versatile Tertiary Cyclobutylboronates

Helen A. Clement, Michele Boghi, Rory M. McDonald, Louise Bernier, Jotham W. Coe, William Farrell, Christopher J. Helal, Matthew R. Reese, Neal W. Sach, Jack C. Lee,* Dennis G. Hall*

Abstract: Cyclobutane rings are important in medicinal chemistry, yet few enantioselective methods exist to access this scaffold. In particular, cyclobutylboronates are receiving increasing attention in the literature due to the synthetic versatility of alkylboronic esters and the increasing role of boronic acids in drug discovery. Herein, a conjugate borylation of α-alkyl,β-aryl/alkyl cyclobutenones is developed leading to the first synthesis of enantioenriched tertiary cyclobutylboronates. Cyclobutanones with two stereogenic centers are obtained in good to high yield, with high enantioselectivity and diastereoselectivity. Vital to this advance are the development of a novel approach to unsymmetrically α,β-disubstituted cyclobutenone substrates and the use of a high-throughput chiral ligand screening platform. The synthetic utility of both the boronic ester and ketone functionalities is displayed, with remarkable chemoselectivity for either group being possible in this small ring scaffold.

Cyclobutane rings are embedded in the structure of numerous natural products and medicines (Figure 1).[1] In drug discovery, cyclobutyl moieties are often employed to impose spatial pharmacophore rigidification and have also been shown to be non-traditional bioisosteres of arenes.[2]

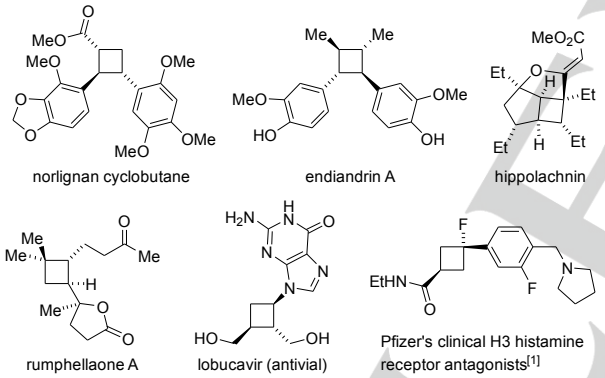

Figure 1. Examples of stereochemically complex cyclobutane-containing natural products and pharmaceutical drugs.

Compared to cyclopentane and cyclohexane homologs, much fewer synthetic methods exist to produce functionalized chiral cyclobutanes in high enantioselectivity.[3] Owing to the versatility of the boronyl substituent as a precursor to C–O, C–N, C–C and C–X bonds, there is significant interest in the development of efficient methods to prepare chiral cyclobutylboronates in optically enriched form. Moreover, the boronyl unit can be employed as a potential handle to install a cyclobutyl unit into a medicinal scaffold via transition metal catalyzed Suzuki-Miyaura cross-coupling or O–/N–arylation.[4] However, stereoselective methods to prepare optically enriched cyclobutylboronates are scarce and generally limited in scope.[5] Matteson and co-workers reported a multistep approach based on the stereospecific cyclization of a stabilized carbanion onto a chiral α-chloroalkylboronic ester.[6] Bach and co-workers reported the enantiofacial-selective photochemical [2+2] cycloaddition between an alkenylboronate and isoquinolone promoted by a stoichiometric chiral hydrogen-bonding template.[7] Reports of catalytic enantioselective methods are equally rare. A copper-catalyzed enantioselective formal hydroboration of symmetrical 2,3-disubstituted cyclobutenes was reported by Tortosa and co-workers (Figure 2a).[8] Because of its distinctive feature as a desymmetrization, this method is limited to symmetrically disubstituted cyclobutenes. Recently, Yu and co-workers described a directed catalytic enantioselective CH borylation of cyclobutyl carboxamides that provides cyclobutylboronates in high enantioselectivity with a distinct substitution pattern (Figure 2b).[9],[10] To develop a general, complementary approach to access cyclobutylboronates, we envisioned using a copper-catalyzed conjugate borylation of

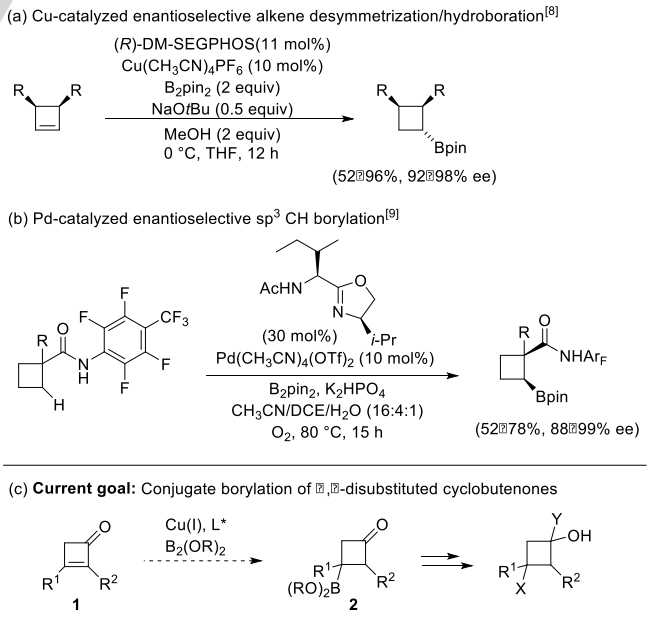

Figure 2. Known (a,b) and proposed (c) catalytic enantioselective methods to prepare cyclobutylboronates.

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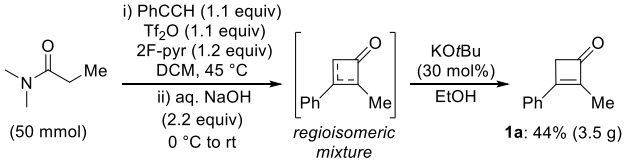
cyclobutenones. Pioneering work by Hosomi has shown that conjugate borylation provides an extremely efficient entry into optically enriched cyclopentyl- and cyclohexylboronates,[11] however the cyclobutane equivalent is lacking in the literature.[12,13] To address this void, we targeted the conjugate borylation of α,β-disubstituted cyclobutenones (Figure 2c), which would provide the first examples of enantioenriched tertiary cyclobutylboronates. Furthermore, it would also allow access to polysubstituted cyclobutanones, for which catalytic enantioselective approaches remain scarce.[14][15] The expected keto-boronate products can undergo bidirectional functionalizations, making them valuable medicinal chemistry intermediates.

Although enantioselective conjugate borylations of β-substituted cyclopentenones and cyclohexenones have been successfully realized,[13,16] the steric congestion in tetrasubstituted α,β-disubstituted enones makes their borylation a significant challenge. In fact, no example of catalytic enantioselective conjugate borylation of a tetrasubstituted alkene exists in the literature.[17] To surmount this challenge we envisioned using a ligand high-throughput screening (HTS) approach, since it has recently been demonstrated to be effective in addressing notoriously difficult cases of catalytic enantioselective hydrogenations of tetrasubstituted alkenes.[18] Herein, we report a successful application of this strategy, which provides richly-functionalized, optically enriched tertiary boronyl-cyclobutanones that can be transformed into new sub-classes of cyclobutanes by functionalization of the boronic ester and/or ketone groups.

Considering the importance of methylation in medicinal chemistry[19] and the structural simplicity of a methyl substituent, we were particularly interested in targeting the borylation of α-methyl-β-aryl/heteroaryl cyclobutenones using **1a** as a model substrate (Scheme 1). Although cyclobutenones have proven to be useful substrates in various contexts,[20] preparative methods for unsymmetrically disubstituted alkene derivatives were lacking in the literature. Inspired by pioneering work of Ghosez and co-workers,[21] cyclobutenone **1a** was prepared by a [2+2] cycloaddition between an amide-derived keteniminium intermediate and phenylacetylene, followed by an isomerization to the thermodynamically favored alkene.[22] The optimal conditions allowed for the synthesis of **1a** on a 50 mmol scale with a 44% yield over the three steps (Scheme 1). It should be noted that Jiao and co-workers recently described an elegant complementary synthesis of cyclobutenone **1a** using a novel triflic anhydride mediated [2+2] cycloaddition between activated acetonitrile and internal, unsymmetrically disubstituted alkynes.[23] Although Jiao's method features a mild work-up suitable for base-sensitive substituents, the approach of Scheme 1 allows the direct use of arylacetylene derivatives, which are more commercially prevalent than the corresponding internal alkynes.



Scheme 1. Preparation of α,β-disubstituted cyclobutenone **1a.**

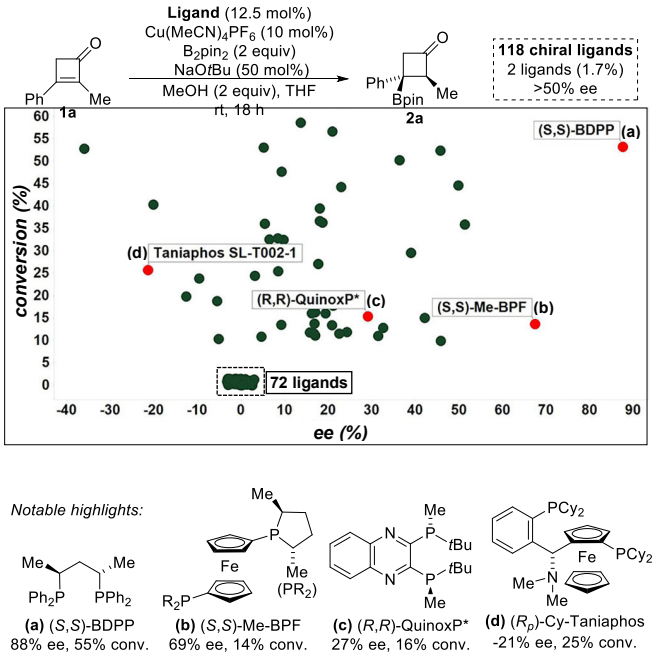


Figure 3. Summary of HTS results for ligand optimization. The data points are slightly skewed for visualization purposes.[24]

With an efficient access to **1a** developed, a HTS of a library of 118 chiral ligands was explored under pre-optimized conditions using $Cu(MeCN)_4PF_6$ as the catalyst with NaO*t*Bu as base in THF at 25 °C.[24],[25] By far, the highest enantioselectivity was obtained with (2*S*,4*S*)-2,4-bis(diphenylphosphino)pentane (BDPP) leading to the formation of **2a** as a single diastereomer in 55% conversion and 88% ee ((a), Fig. 3). Most of the remaining materials was leftover **1a**, leaving room for further optimization. The HTS results clearly highlight the notorious challenge provided by the cyclobutenone substrate (Figure 3). Out of 118 ligands, only two afforded over 50% ee, with the second best result having a low 15% conversion and 69% ee ((b), Fig. 3). Remarkably, Taniaphos and QuinoxP*, which were reported to be efficient ligand scaffolds for the copper-catalyzed borylation of cyclopentenones and cyclohexenones, were inadequate with cyclobutenone **1a** ((c) and (d), Fig. 3).[12],[13] Furthermore, over half of the ligands screened were found to give no conversion under the reaction conditions used (72 ligands, 61%).[24]

With an optimal ligand, validation of the HTS conditions and screening of the remaining reaction parameters were undertaken. Thus, when the reaction was performed at 0 °C with 5 mol% catalyst on a standard reaction scale (0.3 mmol), there was no loss of enantioselectivity with full consumption of cyclobutenone **1a** (entry 1). Increasing the steric bulk of the alcohol did not improve the diastereoselectivity, nor the enantioselectivity (entry 2). A less sterically hindered base resulted in a lower yield (entry 3), yet LiO*t*Bu produced a cleaner reaction and higher diastereoselectivity than its sodium equivalent. Aromatic solvents, such as toluene, were less efficient (entry 4), while acetonitrile resulted in a very clean

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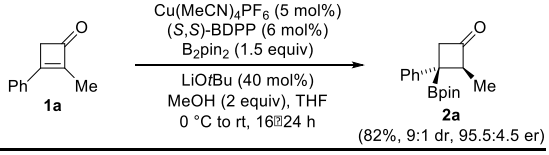
reaction with a high 17:1 dr, albeit with a lower conversion and enantioselectivity (entry 5). Changing the Cu(I) source to CuCl lowered the stereoselectivity (entry 6), as did using the more sterically bulky *m*-xyl-BDPP derivative (entry 7). Surprisingly, excess B_2pin_2 was detrimental to the yield with multiple unidentified side products forming (entry 8). Maintaining the reaction temperature at 0 °C did not result in any improvement to the enantioselectivity (entry 9). Finally, using the optimal parameters and 1.4 equivalents of B_2pin_2, the reaction was complete after 3 hours, providing more reproducible results

Table 1. Condition optimization for the conjugate borylation of cyclobutenone **1a**.



Entry	Changes from above	Yield of **2a**[a]	dr[b]	er[c]
1	NaO*t*Bu (50 mol%)	70%	7 : 1	96.0 : 4.0
2	Entry 1 with *i*PrOH instead of MeOH	68%	7 : 1	95.5 : 4.5
3	NaOMe (50 mol%)	57%	4 : 1	95.0 : 5.0
4	toluene	59%	10 : 1	94.5 : 5.5
5 [d]	MeCN	43%	17 : 1	83.5 : 16.5
6	CuCl	82%	9 : 1	92.5 : 7.5
7	(*R*,*R*)-*m*-xyl-BDPP	57%	6 : 1	14.5 : 85.5
8	2.0 equiv of B_2pin_2	28%	6 : 1	N.D.
9	0 °C reaction temp.	63%	7 : 1	95.0 : 5.0
10	**1.4 equiv B_2pin_2, 3 h, sealed vial**	**96%**	**16 : 1**	**95.0 : 5.0**

[a] ^{1}H NMR yield of the major diastereomer from the crude reaction mixture by integration of CH_2Br_2 as an internal standard. [b] dr was determined by relative ^{1}H NMR integration of the Me groups after the first column. [c] Enantiomeric ratios (er) are determined by chiral HPLC after isolation of a single diastereomer. [d] Only 62% conversion of **1a**. N.D. = not determined.

when a sealed vessel with a tight cap was used rather than a septum (entry 10). Overall, the optimized reaction allowed for formation of the desired borylated product **2a** in a high ^{1}H NMR yield (96%), with excellent diastereoselectivity (16:1 dr) and enantioselectivity (95.0:5.0 er). The absolute and relative configuration of cyclobutylboronate **2a** and other analogs was assigned based on the X-ray analysis of an optically enriched crystalline derivative of **2a** (cf. Scheme 2). Based on a control experiment demonstrating a lack of isomer equilibration, the observed diastereoselectivity is proposed to arise from a sterically-controlled, irreversible protodecupration away from the larger Bpin group (Figure 4).[24]

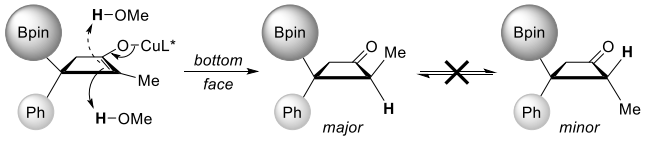
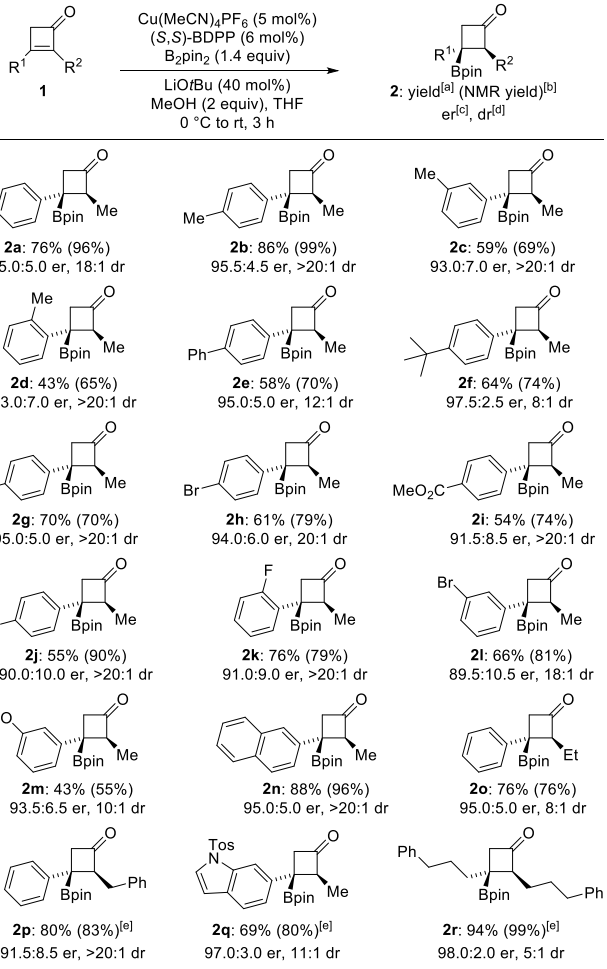


Figure 4. Proposed rationale for the observed diastereoselectivity.

A representative scope of the conjugate borylation is displayed in Table 2. In general, the isolated yields are moderate to high (44–88%). Screening of all three tolyl substrates showed the general steric effect of different substitution patterns – the reaction is not significantly affected by substitution at the *para* position; however, for both *meta* and *ortho* methyl substitution the enantioselectivity decreased slightly to 93.0:7.0 er (**2b–d**). Steric hindrance at the *para* position can be increased without erosion of enantioselectivity (**2e–h**), however electron withdrawing (**2i-k**) and *meta* substitution (**2l**, **2m**) led to lower levels of enantiomeric purity (89.5:10.5 to 93.5:6.5 er). Both β-2-naphthyl and α-ethyl substitution led to high yields and enantioselectivity of 95.0:5.0 er (**2n**, **2o**). In contrast, the enantioselectvity was eroded in the case of α-benzyl substitution (**2p**) to 91.5:8.5 er, but the dr remained high. Both heterocyclic (**2q**) and alkyl (**2r**) β-substituted enones (R^1) resulted in highly enantioenriched products in good diastereoselectivity. The single failed substrate was a *para*-cyanophenyl R^1 derivative, which gave protodeboronation as the major product.[24]

Table 2. Substrate scope of the stereoselective conjugate borylation.



[a] Isolated yield after column chromatography with water deactivated silica. [b] ^{1}H NMR yield of the major diastereomer from the crude reaction mixture by integration of CH_2Br_2 as an internal standard. [c] Determined by chiral HPLC after isolation of a single diastereomer. [d] dr was determined by relative ^{1}H NMR peak height of the Me groups after the first column. [e] 10 mol% $Cu(MeCN)_4PF_6$, 11 mol% (*S*,*S*)-BDPP.

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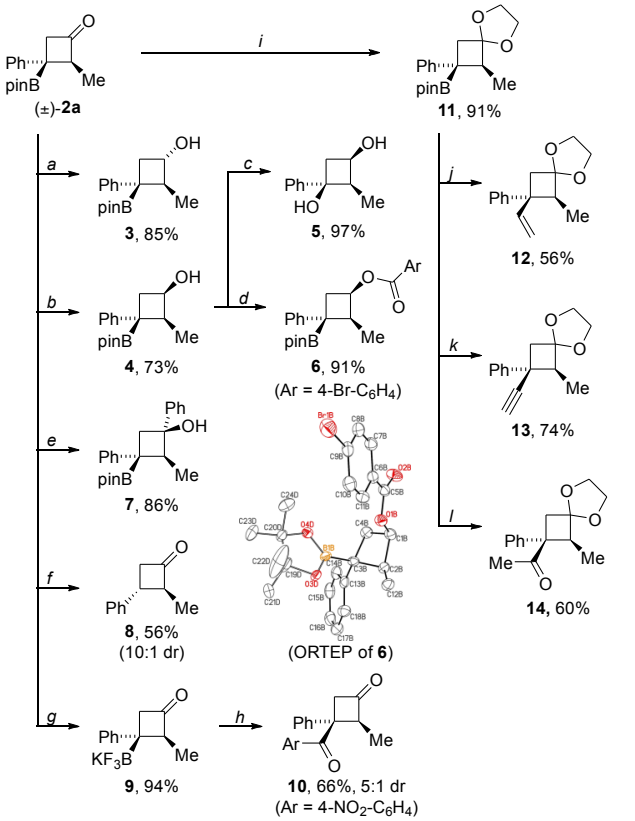
The synthetic potential and versatility of bifunctional cyclobutylboronates **2** is displayed in Scheme 2 with **2a** as a model substrate. Unless otherwise noted, all products were obtained as a single diastereomer according to ^{1}H NMR analysis. Remarkably, chemoselective functionalization of the ketone is possible without affecting the pinacol boronic ester. Divergent diastereoselectivity of the ketone reduction was accomplished by either using Luche conditions or L-selectride to obtain secondary alcohols **3** and **4** in 85% and 73% yield, respectively. Oxidation with sodium perborate resulted in diol **5** in high yield (97%), while benzoyl ester protection allowed for unambiguous stereochemical assignment of **6** by X-ray crystallography.[26] Furthermore, Grignard addition with phenylmagnesium bromide occurred cleanly to form tertiary alcohol **7** in 86% yield. Protodeboronation resulted in the formal *anti* cyclobutenone hydrogenation product **8** in moderate yield and 10:1 dr. The potassium trifluoroborate salt **9** was obtained in a high 94% yield and was found to be a suitable substrate for a rhodium catalyzed aldehyde addition to obtain diketone **10** as a mixture of diastereomers upon oxidation.[27] Alternatively, the corresponding ketal **11** can serve as a viable substrate for a number of carbon-carbon bond forming processes. Zweifel olefination, alkynylation and acetylation were possible in good to high yields (**12**–**14**), using previously



Scheme 2. Synthetic versatility of the cyclobutylboronate products. Reaction conditions: a) $NaBH_4$, $CeCl_3$●$7H_2O$, EtOH, -78 °C; b) L-selectride, THF, -78 °C; c) $NaBO_3$●$4H_2O$, THF/H_2O; d) 4-Br-BzCl, DMAP, Et_3N, DCM; e) PhMgBr, THF, 0 °C; f) Bu_4NF●$3H_2O$, toluene, 45 °C; g) KHF_2, MeCN/H_2O; h)(1) *p*NO_2-PhCHO, $[Rh(COD)Cl]_2$, dioxane/H_2O, 80 °C; (2) DMP, DCM i) PTSA●H_2O, $(HOCH_2)_2$, $HC(OMe)_3$, toluene; j) H_2C=CH-MgBr, THF, -78 °C; I_2, MeOH, -78 °C; NaOMe, -78 °C; k) (1) LiC(OCb)=CH_2, THF, -78 °C; I_2, MeOH, -78 °C; (2) LDA, THF, -78 °C; MeOH -20 °C; l) LiC(OEt)=CH_2, THF, - 78 °C; I_2; NaOMe, MeOH, -78 °C; NH_4Cl.

established stereoselective lithiation-1,2-boryl migration chemistry, which has been largely developed by Aggarwal and co-workers.[28]

In summary, a catalytic enantioselective approach to novel tertiary cyclobutylboronates by conjugate borylation of α-alkyl,β-aryl/alkyl cyclobutenones has been successfully developed. Keys to this advance include a new and practical access to unsymmetrically disubstituted cyclobutenones **1** and the application of HTS of 118 chiral ligands for efficient optimization of the desired reaction in up to 98:2 er. Both the ketone and boronic ester moieties in cyclobutylboronates **2** can be transformed orthogonally, in high stereoselectivity, to access novel cyclobutane scaffolds of potential pharmaceutical interest.

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Conflict of interest

L. B., J. W. C., W. F., C. J. H., M. R. R., N. W. S. and J. C. L. are employees of Pfizer Inc. and may own stocks in the company.

Keywords: asymmetric catalysis • cyclobutylboronates • cyclobutanones • conjugate borylation • cyclobutenones

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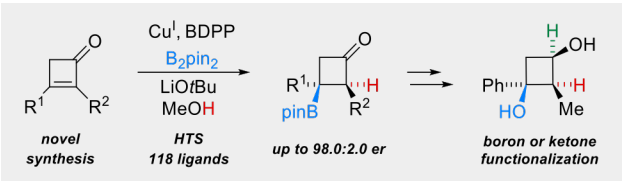

The conjugate borylation of α,β-disubstituted cyclobutenones allows access to tertiary cyclobutylboronates in up to 98:2 er with high diastereoselectivity. The synthetic versatility of the products is displayed by the orthogonal functionalization of both the ketone and boronic ester.

*Helen A. Clement, Michele Boghi, Rory M. McDonald, Louise Bernier, Jotham W. Coe, William Farrell, Christopher J. Helal, Matthew R. Reese, Neal W. Sach, Jack C. Lee, Dennis G. Hall**

Page No. – Page No.

High-Throughput Ligand Screening Enables the Enantioselective Conjugate Borylation of Cyclobutenones to Access Synthetically Versatile Tertiary Cyclobutylboronates

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