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# From Solution-Phase to Solid-Phase Enyne Metathesis: Crossover in the Relative Performance of Two Commonly Used Ruthenium Pre-Catalysts

**Dominic E. A. Brittain,[a, b] B. Lawrence Gray,[a, b] and Stuart L. Schreiber*[a]**

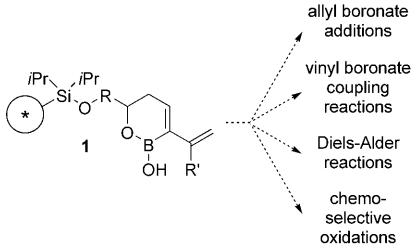
**Abstract:** A crossover in the ability of two distinct ruthenium-based metathesis pre-catalysts to effect the synthesis of dialkenylboronic esters in solution and on the solid-phase was observed. Specifically, while the Grubbs 2nd generation pre-catalyst **3** affords a greater degree of conversion to product than the Hoveyda–Grubbs pre-catalyst **2** in a solution-phase enyne-metathesis reaction, this trend is reversed in the solid-phase variant. Systematic investigation showed this trend to be general, regardless of variations in the homoallylic alcohol and alkynylboronic ester components of the reaction, as well as in the type of solid support employed. Experiments to determine a mechanistic hypothesis for this trend highlighted the significance of the ruthenium remaining bound to the substrate after metathetic rearrangement and found the presence of phosphine ligand to be detrimental to the success of the solid-phase reaction. Therefore, these results suggest an expanded role for phosphine-free pre-catalysts, such as **2**, in challenging solid-phase metathesis reactions.

**Keywords:** annulation · diversity-oriented synthesis · homogeneous catalysis · metathesis · solid-phase synthesis

## Introduction

The synthesis of complex molecules containing different skeletons and stereochemistries, and having chemical handles for appendages, is facilitating a small-molecule approach to understanding biology.[1] While this approach demonstrates a way in which chemistry can inform biology, the challenges met in designing and executing diversity-oriented synthesis (DOS) pathways can also inform chemistry itself. The necessary application of a broad range of substrates to a given transformation, combined with the parallel requirement of adapting a synthesis to the solid phase, can offer new insights into the scope and limitations of even well-known reagents.

Branching pathways, in which synthetic routes diverge from a common intermediate, represent a common method of generating skeletal diversity.[2] The potential of this approach has recently been highlighted through the development of methodology to access dialkenylboronic esters, intermediates with particularly abundant opportunities for branching.[3] In order to facilitate library synthesis based upon the annulation process from which these esters derive, in a way consistent with the use of the one-bead, one-stock solution approach to chemical genetics,[4] dialkenylboronic ester intermediates **1** needed to be synthesized while immobilized onto high-capacity polystyrene macrobeads (Scheme 1).[5] Unfortunately, although these intermediates were readily synthesised in solution via enyne metathesis,[6] early efforts to translate the reaction to the solid phase using support-bound homoallylic alcohols and Grubbs 1st or 2nd generation pre-catalysts (**4** and **3**,[7,8] respectively) gave low conversion levels; a frustrating result considering the ease of a related enyne metathesis involving a support-bound propargyl alcohol.[9] However, use of the Hoveyda–




Scheme 1. Branching pathways from dialkenylboronic esters.

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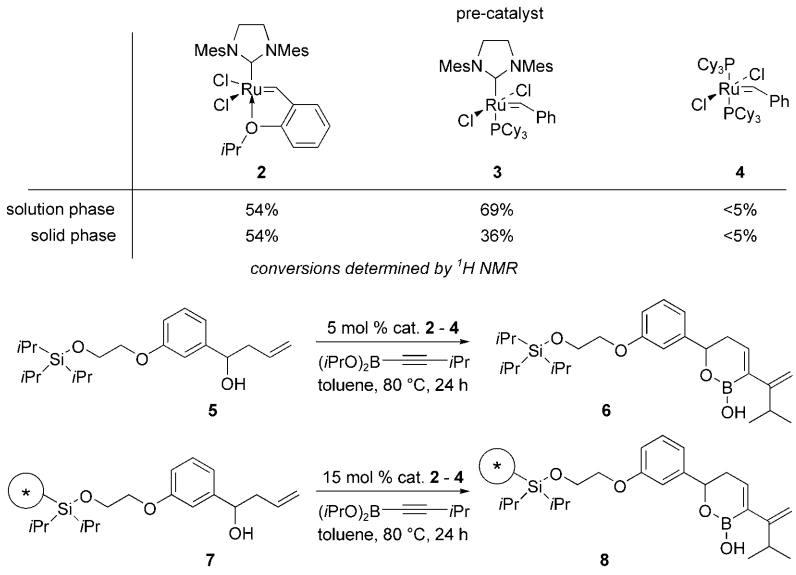
Grubbs pre-catalyst **2** resulted in a significant improvement,[10] a surprising result as initial catalyst screening in the solution phase showed it not to be the optimal catalyst for this transformation (Scheme 2). Intrigued by this crossover in activity, a systematic investigation was begun to probe the generality of this phenomenon and its mechanistic cause. In this communication, these results are presented along with the ensuing implication of an expanded role for pre-catalyst **2** in solid-phase metathesis reactions.

## Results and Discussion

**Effects of substrate, tether, and alkynylboronic ester**: The requisite homoallylic alcohols (**5**, **7**, **9**, **11**, **13**, **15**, **17**, **19**) were synthesized in two steps from the corresponding hydroxy-aldehyde, beginning either with formation of the triisopropylsilyl ether or attachment to polystyrene macrobeads through a diisopropylsilyl ether linkage, and subsequent aldehyde allylation. The metathesis reactions were then carried out in toluene at 80 °C, with pre-catalyst loadings below the levels needed for complete starting material consumption in order to maximize any observable differences in catalyst efficiency. For all solid-phase substrates (**7**, **11**, **15**, **19**) using alkynyl boronate **25**, the Hoveyda–Grubbs pre-catalyst **2** was found to exhibit the highest conversion levels (Table 1, 18–54 % higher than with pre-catalyst **3**); whereas for all corresponding solution-phase substrates (**5**, **9**, **13**, **17**), the Grubbs 2nd generation pre-catalyst **3** proved its superior or equal (Table 1, up to 27 % higher than with pre-catalyst **2**). Additional features to emerge from these data are as follows: 1) the trend is general for both aliphatic and phenolic attachments to silicon (compare entries 7–9 and 25–27 vs 10–12 and 28–30, for example) and tolerates changes in tether length;[11] 2) the spatial relationship of the tether to the homoallylic alcohol about the aromatic ring does not effect the trend (compare entries 4–6 and 22–24 vs 10–12 and 28–30, for example); 3) the Grubbs 1st generation pre-catalyst **4** showed negligible conversion levels in the solution-phase enyne metathesis reactions while retaining some activity for macrobead-bound compounds; 4) variation of the alkynylboronic esters did not effect the trend;[12] thus branched aliphatic (**25**), linear aliphatic (**26**), and heteroatom-containing alkynyl boronates (**27**),[13] were all more efficiently transformed by pre-catalyst **3** in the solution phase, and by pre-catalyst **2** on polystyrene macrobeads.

**Mechanistic considerations**: Having determined that the relative ability of pre-catalysts **2** and **3** to effect the desired enyne metathesis reaction crosses over on going from solution to solid phase, efforts were made to ascertain likely mechanistic origins. A broadly accepted mechanism that served to guide experimental design is illustrated in Scheme 3. Initial transesterification to generate a mixed organoboronic ester **28** was proposed, tethering the alkyne and alkene components together and facilitating subsequent metathesis.[14] Since the substrate contains a monosubstituted alkene and an internal alkyne, initial alkylidene exchange with the alkene rather than the alkyne component is more likely.[15] The resulting metal alkylidene **29** then undergoes a [2+2] cycloaddition with the triple bond to generate metallocyclobutene **30**, followed by a cycloreversion to give cyclic metal alkylidene **31** in a manner analogous to the accepted ring-closing metathesis mechanism.[16] A second alkylidene exchange reaction with a proximal alkene produces diene **32** and allows ruthenium to continue the catalytic cycle.

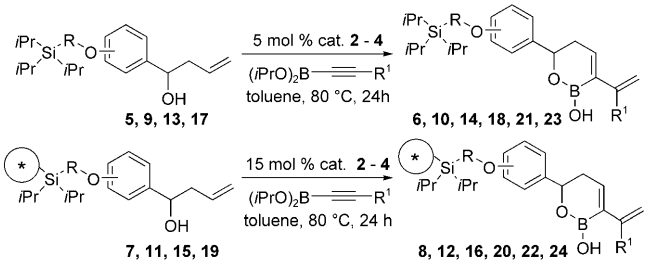
While there are numerous examples of metathesis reactions where either the catalyst or substrate has been immobilized to the solid phase,[17] the transition from solution to solid phase is often accompanied by complications, frequently requiring considerable reaction re-optimization.[18] In such instances, due to the slower reaction kinetics associated with an immobilized pre-catalyst or propagating carbene, catalyst decomposition probably competes with the desired transformation. With this hypothesis in mind, and using the proposed mechanism as a starting point, the conversion of metal alkylidene **31** to the diene **32** was identified as the likely turnover- and conversion-limiting step in the solid-phase variant of this reaction. This is based on the following features: 1) the generation of metal alkylidene **31** covalently attaches the metal species to the support, resulting in partial "site-isolation";[19] 2) metal alkylidene **31** requires an *inter*molecular reaction to liberate the




Scheme 2. Crossover in catalyst performance in solution and on the solid phase.

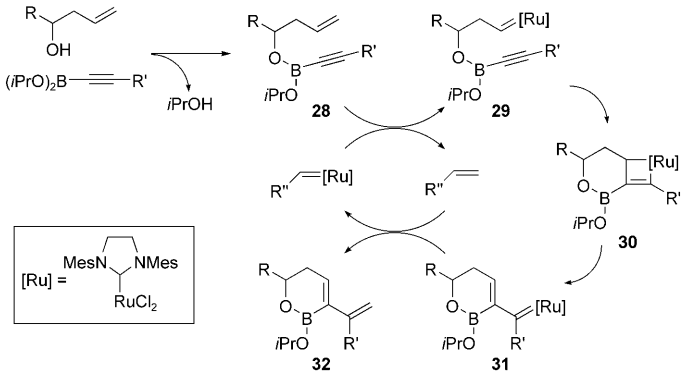
Table 1. Comparisons of catalytic efficiency for solution-phase and solid-phase boronic ester annulations.




| Cpd. | Substitution | R | $R^1$ [a] |
|---|---|---|---|
| **5-8** | *meta* | $OCH_2CH_2$ | *i*Pr |
| **9-12** | *meta* | - | *i*Pr |
| **13-16** | *para* | - | *i*Pr |
| **17-20** | *para* | $OCH_2CH_2$ | *i*Pr |
| **21**, **22** | *meta* | $OCH_2CH_2$ | *n*Bu |
| **23**, **24** | *meta* | $OCH_2CH_2$ | $CH_2OBn$ |

| Entry | Substrate | Boronate[b,c] | Pre-catalyst | Conversion [%][d] |
|---|---|---|---|---|
| 1 | **9** | **25** | **2** | 46 |
| 2 | **9** | **25** | **3** | 58 |
| 3 | **9** | **25** | **4** | < 5 |
| 4 | **5** | **25** | **2** | 54 |
| 5 | **5** | **25** | **3** | 69 |
| 6 | **5** | **25** | **4** | < 5 |
| 7 | **13** | **25** | **2** | 44 |
| 8 | **13** | **25** | **3** | 71 |
| 9 | **13** | **25** | **4** | < 5 |
| 10 | **17** | **25** | **2** | 18 |
| 11 | **17** | **25** | **3** | 42 |
| 12 | **17** | **25** | **4** | < 5 |
| 13 | **5** | **26** | **2** | 69 |
| 14 | **5** | **26** | **3** | 71 |
| 15 | **5** | **26** | **4** | < 5 |
| 16 | **5** | **27** | **2** | 17 |
| 17 | **5** | **27** | **3** | 22 |
| 18 | **5** | **27** | **4** | < 5 |
| 19 | **11** | **25** | **2** | 86 |
| 20 | **11** | **25** | **3** | 33 |
| 21 | **11** | **25** | **4** | 15 |
| 22 | **7** | **25** | **2** | 54 |
| 23 | **7** | **25** | **3** | 36 |
| 24 | **7** | **25** | **4** | < 5 |
| 25 | **15** | **25** | **2** | 60 |
| 26 | **15** | **25** | **3** | 34 |
| 27 | **15** | **25** | **4** | 17 |
| 28 | **19** | **25** | **2** | 66 |
| 29 | **19** | **25** | **3** | 26 |
| 30 | **19** | **25** | **4** | 12 |
| 31 | **7** | **26** | **2** | 51 |
| 32 | **7** | **26** | **3** | 8 |
| 33 | **7** | **26** | **4** | < 5 |
| 34 | **7** | **27** | **2** | 34 |
| 35 | **7** | **27** | **3** | 17 |
| 36 | **7** | **27** | **4** | < 5 |

[a] Not present in the homoallylic alcohol substrates. [b] $R^1 = i$Pr (**25**); $R^1 = n$Bu (**26**); $R^1 = CH_2OBn$ (**27**). [c] 1.9 equiv of alkynylboronic ester were used in all solution-phase reactions, 7.5 equiv of alkynylboronic ester were used in all solid-phase reactions. [d] Conversions were determined by $^1$H NMR and $^1$H MAS-NMR spectroscopy for solution-phase and immobilized substrates, respectively; see Experimental Section for details.

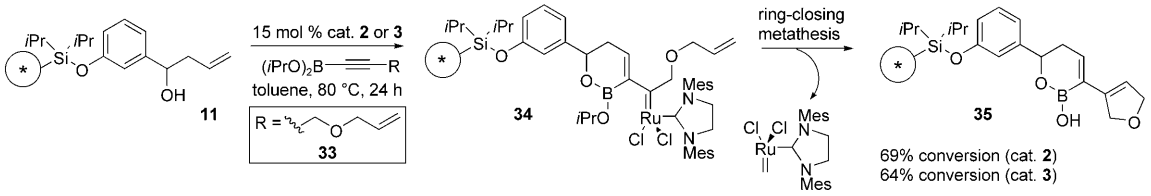



Scheme 3. Proposed mechanism and catalytic cycle for the boronic ester annulation. Reversible arrows are omitted for clarity.

metal and to allow it to continue the catalytic cycle;[20] 3) release of the metal might be expected to be especially challenging in enyne metathesis products such as **31**, due to possible metal coordination to one of the boronic ester oxygens in an analogous fashion to the metal coordination by the isopropoxy ligand in pre-catalyst **2**.

To test this hypothesis, a crossover experiment was designed to probe the extent to which free ruthenium carbene was present in solution. Treatment of resin-bound homoallylic alcohol **15** with 30 mol% pre-catalyst **3** in toluene at 40°C for 2 h, followed by transfer of the solution into a fresh batch of substrate and alkynyl boronate **25** showed less than 5% conversion in the second vessel. By contrast, a control experiment in which a solution of pre-catalyst **3** in toluene was heated at 40°C for 2 h in the *absence* of homoallylic alcohol **15** before transfer, gave an 85% conversion in the second vessel, thereby discounting catalyst decomposition as the determining factor. Further support for this mechanistic interpretation derives from the synthesis of alkynylboronate **33** and its use in the enyne-metathesis reaction with solid-phase homoallylic alcohol **11** to generate dialkenylboronate **35** (Scheme 4). The alkene functionality in the side chain of alkynylboronate **33** leads to a tandem enyne/ring-closing metathesis reaction, resulting in self-cleavage of the catalyst from the resin bound substrate, as illustrated by possible intermediate **34**. If detachment of the ruthenium from the solid support is impeding turnover in the previous experiments, this modification should improve the situation. Not only did this change increase conversions with both pre-catalysts **2** and **3**, it also brought them to a similar level (69% for pre-catalyst **2** vs 64% for pre-catalyst **3**), suggesting that the sequestration of the propagating carbene is no longer as important.

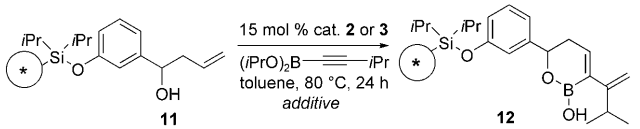
**Effects of additives on catalyst efficiency**: Although the evidence pointed to the release of ruthenium from the solid support as being critical to the reaction, it is not clear why one pre-catalyst should be preferred for the solution-phase reaction and the other for the solid-phase reaction, especially since both pre-catalysts generate identical 14-electron coordinatively unsaturated, propagating carbenes upon initia-




Scheme 4. Tandem enyne metathesis/ring-closing metathesis on the solid phase.

tion. Using support-bound homoallylic alcohol **11** and alkynylboronate **25**, it was hoped that an examination of the effects of some commonly used metathesis reaction additives might illuminate the origins of this difference (Table 2). Typically, additives promote catalysis either by preventing or breaking up unfavorable intramolecular ruthenium chelates,[21] or by acting as transient cross-metathesis partners to generate or to stabilize ruthenium methylidene through degenerate metathesis pathways.[22] Unfortunately, due to a variety of undesired side reactions that have been noted,[18h,o,23] the effectiveness of these additives can be unpredictable, somewhat limiting their utility as a panacea for failed metathesis reactions. Additionally, when using Lewis-acid additives, both substrates and products must be compatible. In fact, reaction of homoallylic alcohol **11**, alkynylboronate **25**, and pre-catalyst **3** in the presence of 25 mol% $Ti(OiPr)_4$ lowered the degree of conversion (entry 8), possibly due to an incompatibility with the alkynylboronic ester (the Lewis acid does not decompose product).[24,25] Styrene, which has been used as a beneficial olefin additive for pre-catalyst **4**, also resulted in lower conversion levels (entries 1–2). Since stilbene, the cross-metathesis product of styrene, is *not* inert towards pre-catalysts **2** and **3** (unlike pre-catalyst **4**), it is possible that styrene acts to decrease the concentration of highly active ruthenium methylidene here, thus retarding the reaction.[26] In contrast, it was discovered that running the reaction under an ambient pressure of *ethylene* resulted in a marked increase in the conversion with pre-catalyst **3** (entry 3, 77 vs 33% without ethylene), in line with the hypothesis that release of ruthenium from immobilized diene **31** represents the critical step in this transformation. It proved important to introduce the ethylene only *after* the reaction was initiated (20 min after pre-catalyst addition), since pre-treatment of pre-catalyst with ethylene seriously reduced conversion levels (entry 4). With a means of improving conversion levels in reactions using pre-catalyst **3** on the solid phase, a complementary way of repressing the reaction in the presence of pre-catalyst **2** was sought. Indeed, conducting the reaction of homoallylic alcohol **11** and alkynylboronate **25** with pre-catalyst **2** in the presence of tricyclohexylphosphine drastically reduced conversion levels (entry 6, 29 vs 86% without $PCy_3$ at 15 mol% catalyst loading).[27] The effect was only observed when the ruthenium was saturated with the phosphine (at least one equivalent relative to pre-catalyst) or premixed with the additive. A reasonable hypothesis to account for these observations is that the transition from the reaction of solution-phase homoallylic alcohols to those bound to the solid phase reduces the ease with which the 14-electron ruthenium intermediate **31** can co-ordinate an alkene to continue the catalytic cycle. Since the tricyclohexylphosphine ligand, when present, can also compete with any alkenes for the free co-ordination site on intermediate **31**,[28] the use of a phosphine-free pre-catalyst **2** ameliorates the situation. While this mirrors the observations seen in improving cross metathesis reactions involving electron-poor alkenes (e.g. acrylonitrile) by using phosphine-free pre-catalysts or phosphine scavengers,[29] and the subsequent suggestions of phosphine reassociation inhibiting the catalytic cycle,[30] to the best of our knowledge, these results constitute the first documented example of the benefit of phosphine-free conditions to a solid-phase ruthenium carbene metathesis reaction.

Table 2. Effect of additives on solid-phase boronic ester annulations.



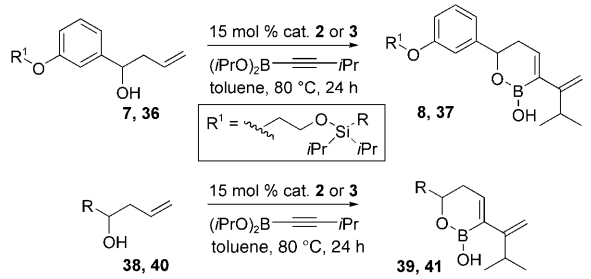

| Entry | Pre-catalyst | Additive[a] | Quantity | Conversion [%][b] |
|---|---|---|---|---|
| 1 | **3** | styrene | 15 mol% | 32 |
| 2 | **3** | styrene | 15 mol%[c] | <5 |
| 3 | **3** | ethylene | 1 atm | 77 |
| 4 | **3** | ethylene | 1 atm[c] | 10 |
| 5 | **2**[d] | $PCy_3$ | 15 mol% | 86 |
| 6 | **2**[d] | $PCy_3$ | 100 mol% | 29 |
| 7 | **2**[d] | $PCy_3$ | 15 mol%[c] | 36 |
| 8 | **3** | $Ti(OiPr)_4$ | 15 mol% | 21 |

[a] $PCy_3$ = tricyclohexylphosphine. [b] Conversions were determined using $^1H$ MAS-NMR spectroscopy. [c] additive mixed with pre-catalyst prior to addition of substrate. [d] 30 mol% pre-catalyst loading was used.

**Variation of the solid support**: Curious as to whether this new reactivity pattern was a general solid-phase phenomenon or specific to polystyrene macrobeads, the enyne metathesis was performed with the two pre-catalysts **2** and **3** on homoallylic alcohols bound to different solid-phase platforms. As shown in Table 3, Synphase lantern bound homoallylic alcohol **36** also undergoes metathesis markedly better with pre-catalyst **2** (entries 3–4, 25% higher conversion).[31] The trend is also significant with the substrate derived from allylation of formyl polystyrene. In this case, the effect of small variations in percentage cross-linking (1 vs 2% DVB) was examined and found to make only a slight difference in the magnitude of the trend (entries 5–8). Despite the variance in absolute conversion levels, the fact that pre-catalyst

Table 3. Effect of polymer support on catalytic efficiency.




| Entry | Substrate | Pre-catalyst | R[a] | Conversion [%][b] |
|---|---|---|---|---|
| 1 | **7** | **2** | polystyrene macrobead | 54 |
| 2 | **7** | **3** | polystyrene macrobead | 36 |
| 3 | **36** | **2** | synphase lantern | 74 |
| 4 | **36** | **3** | synphase lantern | 49 |
| 5 | **38** | **2** | 1% DVB 100–200 mesh polystyrene | 49 |
| 6 | **38** | **3** | 1% DVB 100–200 mesh polystyrene | 8 |
| 7 | **40** | **2** | 2% DVB 100–200 mesh polystyrene | 31 |
| 8 | **40** | **3** | 2% DVB 100–200 mesh polystyrene | 16 |

[a] Description of and purchasing information for the various polymer supports can be found in the Experimental Section. [b] Conversions were determined using $^1$H MAS-NMR spectroscopy.

**2** was superior in cases covering different polymer constitution, bead size, tether length and degree of cross-linking, suggests the observed trend is a relatively general solid-phase phenomenon.[32] Although facilitating site-site interactions could also be considered as an approach to improving certain difficult solid-phase metathesis reactions, whether through the use of minimally cross-linked or high-loading resins etc., this approach could also lead to intermolecular covalent bond formation instead.[33] In these cases, using a phosphine-free catalyst, such as pre-catalyst **2**, that maximizes the chance that a site-site interaction will lead to a productive release and transfer of ruthenium, constitutes a potentially simple and useful alternative solution.[34]

## Conclusion

This study provides an example of how efforts in diversity-oriented synthesis can bring to light unexpected complexities in chemistry, allowing practical solutions to emerge for intransigent reactions. While the realization of the branching potential of dialkenylboronates has now been made possible through the application of the findings described, it is also hoped that they will prove useful in enabling other unrelated but equally problematic metathesis reactions to be applied to the solid phase through the use of phosphine-free pre-catalysts. The full exploitation of this methodology towards a library of complex and diverse small molecules is currently underway.

## Experimental Section

**General techniques**: Except as otherwise noted, reactions were carried out under nitrogen with dry, freshly purified solvents. Solvents were purified by passage through a column of activated alumina (A-2) and supported copper redox catalyst (Q-5 reactant). NMR spectra were recorded at either 500 or 300 MHz for all solution phase compounds using a Varian I-500 or a Varian M-300 instrument, respectively. $^1$H NMR chemical shifts are reported relative to residual $CHCl_3$ (7.26 ppm). $^{13}$C NMR data were recorded at 125 or 100 MHz for all solution phase compounds using a Varian I-500 or a Varian M-400 instrument, respectively. $^{13}$C chemical shifts are reported relative to the central line of $CDCl_3$ (77.0 ppm). MAS-NMR spectra were recorded at 600 MHz for all compounds immobilized to the solid phase using a Varian INOVA I-600 instrument equipped with nanoprobe. Infrared spectra were recorded using a Perkin–Elmer FT-IR spectrometer (thin film or neat, as indicated). Mass spectra were obtained with JEOL AX 505, JEOL SX-102 and Micromass ESI-LCT spectrometers. 1% divinylbenzene crosslinked formyl polystyrene (0.9 mmol g$^{-1}$) was purchased from Aldrich and dried in vacuo prior to use. 2% divinylbenzene crosslinked formyl polystyrene (2.5 mmol g$^{-1}$) was purchased from Aldrich and dried in vacuo prior to use. Information concerning polystyrene macrobeads and Synphase lanterns is contained in the relevant references, cited in the paper.

**Representative procedure for solution-phase allylation**

**Reaction sequence used for the generation of 5**: 3-(2-Hydroxyethoxy)-benzaldehyde (1.01 g, 6.09 mmol) was placed into a flame-dried round-bottom flask equipped with magnetic stirrer and dissolved in THF (10 mL). Imidazole (1.45 g, 21.31 mmol) was added with rapid stirring and, after complete dissolution, triisopropylsilyl chloride (1.95 mL, 9.14 mmol) was introduced. After 22 h, the reaction was quenched with saturated, aqueous $NaHCO_3$ (7 mL) and diluted with water. The mixture was extracted with $CH_2Cl_2$ (3×30 mL) and combined organics were washed with water and brine (50 mL portions). After drying over $MgSO_4$, the organics were filtered, concentrated in vacuo to afford the desired silylated alcohol (1.96 g, 6.09 mmol), which was transferred to a flame-dried round-bottom flask equipped with magnetic stirrer and dissolved in THF (20 mL). The resultant solution was cooled to −78 °C and allylmagnesium bromide (12.18 mL, 12.18 mmol) was added dropwise over 10 min. The mixture was allowed to come to ambient temperature overnight and was then slowly quenched with saturated, aqueous $NaHCO_3$ and diluted with water. Extraction with $CH_2Cl_2$ (3×80 mL) was followed by washing of combined organics with water and brine (100 mL portions). Drying over $MgSO_4$, filtration and concentration in vacuo gave a crude oil which was purified by silica chromatography (hexanes/$Et_2O$ 6:1) to give **5** as a clear oil (2.10 g, 5.76 mmol, 94%).

**1-{3-[2-(Triisopropylsilanyloxy)-ethoxy]-phenyl}-but-3-en-1-ol (5)**: $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 7.25 (t, $J$=8.3 Hz, 1H), 6.94 (s, 1H), 6.94–6.92 (m, 1H), 6.84–6.82 (m, 1H), 5.86–5.77 (m, 1H), 5.16–5.15 (m, 2H), 4.71 (dd, $J$=7.8, 5.4 Hz, 1H), 4.09–4.03 (m, 4H), 2.56–2.46 (m, 2H), 1.98 (br s, 1H), 1.21–1.11 (m, 3H), 1.09 (d, $J$=5.9 Hz, 18H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 159.1, 145.5, 134.4, 129.4, 118.4, 118.1, 113.6, 112.0, 73.2, 69.3, 62.2, 43.8, 17.9, 12.0; IR (neat): $\tilde{\nu}$ = 3405, 3077, 2933, 2862, 2728, 2359, 1641, 1600, 1585, 1487, 1461, 1446, 1385, 1369, 1318, 1262, 1128, 1062, 1010, 995, 964, 918, 882, 785, 749, 682, 656 cm$^{-1}$; HRMS (ApCI): $m/z$: calcd for $C_{21}H_{36}O_3Si+NH_4$: 382.2778; found: 382.2769 [$M+NH_4^+$].

**1-{4-[2-(Triisopropylsilanyloxy)-ethoxy]-phenyl}-but-3-en-1-ol (17)**: $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 7.27 (d, $J$=8.3 Hz, 2H), 6.90 (d, $J$=8.8 Hz, 2H), 5.80 (dddd, $J$=17.2, 10.0, 7.3, 7.1 Hz, 1H), 5.14 (app s, 1H), 5.14 (d, $J$=27.3 Hz, 1H), 4.70–4.67 (m, 1H), 4.07–4.04 (m, 4H), 2.51–2.48 (m, 2H), 2.02 (br s, 1H), 1.19–1.08 (m, 21H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 158.4, 136.0, 134.6, 127.0, 118.1, 114.4, 73.0, 69.3, 62.2, 43.7, 17.9, 12.0; IR (neat): $\tilde{\nu}$ = 3397, 3074, 2941, 2866, 1640, 1611, 1586, 1512, 1463, 1383, 1302, 1248, 1173, 1132, 1066, 996, 962, 916, 882, 831, 744, 681 cm$^{-1}$; HRMS (ApCI): $m/z$: calcd for $C_{21}H_{36}O_3Si+NH_4$: 382.2778; found: 382.2776 [$M+NH_4^+$].

**1-[3-(Triisopropylsilanyloxy)-phenyl]-but-3-en-1-ol (9)**: $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 7.19 (t, $J$ = 2.8 Hz, 1H), 6.92 (d, $J$ = 7.8 Hz, 1H), 6.89 (s, 1H), 6.80–6.78 (m, 1H), 5.80 (dddd, $J$ = 16.3, 13.8, 7.3, 7.1 Hz, 1H), 5.14–5.13 (m, 2H), 4.69 (dd, $J$ = 3.7, 2.7 Hz, 1H), 2.51–2.47 (m, 2H), 2.05–1.60 (brs, 1H), 1.26 (sept, $J$ = 3.9 Hz, 3H), 1.10 (d, $J$ = 3.7 Hz, 18H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 158.0, 145.5, 134.4, 129.3, 118.9, 118.4, 118.3, 117.3, 73.1, 43.8, 17.9, 12.6; IR (neat): $\tilde{\nu}$ = 3376, 3076, 2944, 2893, 2867, 1642, 1603, 1586, 1484, 1464, 1443, 1385, 1280, 1155, 1058, 1004, 960, 915, 882, 832, 788, 682 cm$^{-1}$; HRMS (ApCI): $m/z$: calcd for $C_{19}H_{32}O_2Si+NH_4$: 338.2516; found: 338.2494 $[M+NH_4]^+$.

**1-[4-(Triisopropylsilanyloxy)-phenyl]-but-3-en-1-ol (13)**: $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 7.20 (d, $J$ = 8.3 Hz, 2H), 6.86 (d, $J$ = 8.8 Hz, 2H), 5.79 (dddd, $J$ = 17.2, 10.2, 7.3, 7.1 Hz, 1H), 5.13–5.12 (m, 1H), 5.13 (d, $J$ = 23.9 Hz, 1H), 4.67 (appt, $J$ = 6.4 Hz, 1H), 2.49 (appt, $J$ = 6.8 Hz, 2H), 1.99 (s, 1H), 1.24 (septet, $J$ = 7.8 Hz, 3H), 1.10 (d, $J$ = 7.3 Hz, 18H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 155.7; 136.6, 134.9, 127.2, 120.0, 118.4, 73.3, 44.0, 18.1, 12.9; IR (neat): $\tilde{\nu}$ = 3358, 2944, 2867, 1641, 1608, 1510, 1464, 1387, 1266, 1168, 1056, 997, 913, 883, 838, 683 cm$^{-1}$; HRMS (ApCI): $m/z$: calcd for $C_{19}H_{32}O_2Si+NH_4$: 338.2516; found: 338.2523 $[M+NH_4^+]$.

**Representative procedure for solid-phase allylation**

**Reaction sequence used for the generation of 15**: A flame-dried, 5 mL tapered flask was charged with macrobeads (58.1 mg, 1.3 mmol g$^{-1}$, 0.075 mmol) functionalized with the appropriate substituted benzaldehyde and THF (1.5 mL) was added. The beads were allowed to swell at ambient temperature for 10 min before the flask was cooled to −78 °C and allylmagnesium bromide (0.75 mL, 0.750 mmol, 10.0 equiv) added dropwise. A stream of argon that was bubbled through it agitated the mixture. After 6 h at −78 °C, the mixture was warmed to 23 °C and agitated on a rotary shaker for 19 h. $CH_2Cl_2$ (3 mL) was added, causing the beads to float, and they were transferred to a plastic fritted column. Beads were rinsed successively with THF (3×), THF/$H_2O$ (3:1, 3×), THF/$H_2O$ (1:1, 3×), THF/$H_2O$ (1:3, 3×), $H_2O$ (3×), $CH_3OH$ (3×), THF/$H_2O$ (1:1, 3×), THF (3×), $CH_2Cl_2$ (3×), $CHCl_3$ (3×), and $CDCl_3$ (1×). The beads were then dried for 24 h in vacuo to afford immobilized homoallylic alcohol **15** (53.0 mg).

**Macrobead-bound 1-[4-(diisopropylsilanyloxy)-phenyl]-but-3-en-1-ol (15)**: MAS $^1$H NMR (600 MHz, $CDCl_3$/$CD_3OD$ 9:1): $\delta$ = 7.1–6.2 (m, 4H + polymer), 5.7–5.6 (brs, 1H), 5.0–4.9 (m, 2H), 4.6–4.5 (brs, 1H), 4.3–4.2 (brs, polymer), 2.5–2.3 (brs, 2H), 1.8–1.0 (m, polymer), 1.0–0.8 (brs, 14H).

**Representative procedure for comparative studies in the solution phase**

**Reaction using Hoveyda–Grubbs pre-catalyst 2**: To a solution of the alkynylboronic ester **25** (55.0 mg, 0.280 mmol) in toluene (0.25 mL) was added the homoallylic alcohol **5** (53.8 mg, 0.148 mmol) as a solution in toluene (0.2 mL), and residual homoallylic alcohol was introduced with two additional toluene rinses (2×0.15 mL). After 5 min, catalyst **2** (4.6 mg, 5 mol %) was introduced as a solid. The vessel was purged with argon, then heated at 80 °C for 24 h. The crude reaction mixture was cooled to 23 °C, then concentrated in vacuo, giving a dark brown oil, which was taken up in $CDCl_3$ and assayed by $^1$H NMR at 500 MHz, using increased relaxation time. Conversions are measured relative to the dienyl proton at 6.6 ppm in the alkenyl boronic ester and the two alkene protons at 5.1–5.2 ppm in the homoallylic alcohol. The crude mixture was then purified by flash column chromatography (silica gel; eluted with hexanes/diethyl ether 25:1) to give the pure cyclic dialkenylboronic acid **6**.

**Reaction using Grubbs pre-catalyst 3**: To a solution of the alkynylboronic ester **25** (61.2 mg, 0.312 mmol) in toluene (0.25 mL) was added the homoallylic alcohol **5** (59.9 mg, 0.164 mmol) as a solution in toluene (0.2 mL), and residual homoallylic alcohol was introduced with two additional toluene rinses (2×0.15 mL). After 5 min, catalyst **3** (7.0 mg, 5 mol %) was introduced as a solid. The vessel was purged with argon, then heated at 80 °C for 24 h. The crude reaction mixture was cooled to 23 °C, then concentrated in vacuo, giving a dark brown oil, which was taken up in $CDCl_3$ and assayed by $^1$H NMR at 500 MHz, using increased relaxation time. Conversions are measured relative to the alkene proton at 6.6 ppm in the alkenyl boronic ester and the two alkene protons at 5.1–5.2 ppm in the homoallylic alcohol. The crude mixture was then purified by flash column chromatography ($SiO_2$; eluted with hexanes/diethyl ether 25:1) to give the pure cyclic dialkenylboronic acid **6**.

**3-(1-Isopropyl-vinyl)-6-{4-[2-(triisopropylsilanyloxy)-ethoxy]-phenyl}-5,6-dihydro[1,2]oxaborinin-2-ol (18)**: $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 7.19 (d, $J$ = 8.3 Hz, 2H), 6.79 (d, $J$ = 8.8 Hz, 2H), 6.51 (dd, $J$ = 4.6, 2.4 Hz, 1H), 4.92 (dd, $J$ = 11.5, 4.4 Hz, 1H), 4.86 (s, 1H), 4.70 (s, 1H), 3.96 (d, $J$ = 6.8 Hz, 2H), 3.93 (d, $J$ = 6.3 Hz, 2H), 3.23 (s, 1H), 2.48–2.54 (m, 1H), 2.39 (ddd, $J$ = 17.7, 5.9, 4.4 Hz, 1H), 2.29 (ddd, $J$ = 17.6, 11.5, 2.9 Hz, 1H), 0.95–0.96 (m, 21H), 0.92 (d, $J$ = 6.8 Hz, 3H), 0.88 (d, $J$ = 6.8 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 158.2, 156.3, 141.3, 135.2, 126.6, 114.3, 108.0, 74.6, 69.3, 62.2, 36.6, 31.4, 22.5, 17.7, 13.8, 11.8; IR (neat): $\tilde{\nu}$ = 3401, 2942, 2867, 1613, 1513, 1463, 1384, 1318, 1304, 1249, 1174, 1133, 1068, 1014, 996, 964, 918, 883, 829, 743, 682, 658 cm$^{-1}$; HRMS (TOF MS ES+): $m/z$: calcd for $C_{26}H_{43}BO_4Si$: 459.3102; found: 459.3105 $[M+H^+]$.

**3-(1-Isopropyl-vinyl)-6-{3-[2-(triisopropylsilanyloxy)-ethoxy]-phenyl}-5,6-dihydro[1,2]oxaborinin-2-ol (6)**: $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 7.19 (t, $J$ = 7.8 Hz, 1H), 6.94 (brs, 1H), 6.86 (d, $J$ = 7.8 Hz, 1H), 6.77 (dd, $J$ = 8.1, 2.0 Hz, 1H), 6.61 (dd, $J$ = 6.1, 2.4 Hz, 1H), 5.03 (dd, $J$ = 12.0, 3.9 Hz, 1H), 4.84 (d, $J$ = 1.9 Hz, 1H), 4.73 (s, 1H), 4.04–4.00 (m, 4H), 3.35 (s, 1H), 2.64–2.60 (m, 1H), 2.44 (ddd, $J$ = 17.6, 6.4, 3.9 Hz, 1H), 2.32 (ddd, $J$ = 17.6, 12.2, 2.4 Hz, 1H), 1.12–1.06 (m, 3H), 1.06–0.99 (m, 21H), 0.96 (d, J = 6.8, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 159.1, 158.7, 142.1, 129.5, 129.3, 117.9, 113.9, 111.2, 107.6, 75.3, 69.3, 62.4, 37.2, 31.7, 22.2, 18.1, 12.7, 12.2; IR (neat): $\tilde{\nu}$ = 3374, 2933, 2862, 1600, 1456, 1380, 1313, 1262, 1123, 1067, 1015, 995, 882 cm$^{-1}$; LRMS (TOF MS ES+): $m/z$: calcd for $C_{26}H_{43}BO_4Si+NH_4$: 476.3; found: 476.3 $[M+NH_4^+]$.

**3-(1-Butyl-vinyl)-6-{3-[2-(triisopropylsilanyloxy)-ethoxy]-phenyl}-5,6-dihydro-[1,2]oxaborinin-2-ol (21)**: $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 7.18 (t, $J$ = 8.1 Hz, 1H), 6.91–6.88 (m, 1H), 6.76 (dd, $J$ = 8.4, 2.6 Hz, 1H), 6.61 (dd, $J$ = 6.2, 2.6 Hz, 1H), 5.12 (d, $J$ = 2.2 Hz, 1H), 4.97 (dd, $J$ = 11.7, 3.7 Hz, 1H), 4.81 (s, 1H), 4.00–3.96 (m, 4H), 2.45 (ddd, $J$ = 17.6, 6.2, 4.0 Hz, 1H), 2.33 (ddd, $J$ = 17.6, 11.9, 2.6 Hz, 1H), 2.20–2.15 (m, 2H), 1.33–1.17 (m, 6H), 1.07–0.99 (m, 21H), 0.82 (t, $J$ = 7.32 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 159.2, 149.2, 144.9, 141.2, 129.5, 118.0, 113.3, 112.4, 112.1, 74.8, 69.4, 62.4, 36.8, 34.6, 30.7, 22.6, 18.0, 14.0, 12.1; IR (thin film from $CDCl_3$): $\tilde{\nu}$ = 3412, 2930, 2868, 1726, 1598, 1454, 1383, 1311, 1260, 1121, 1065, 1014, 993, 962, 880, 772, 736 cm$^{-1}$; LRMS (TOF MS ES+): $m/z$: calcd for $C_{27}H_{45}BO_4Si+NH_4$: 490.3; found: 490.3 $[M+NH_4^+]$.

**3-(1-Isopropyl-vinyl)-6-[4-(triisopropylsilanyloxy)-phenyl]-5,6-dihydro-[1,2]oxaborinin-2-ol (14)**: $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 7.15 (d, $J$ = 8.3 Hz, 2H), 6.77 (d, $J$ = 8.8 Hz, 2H), 6.54–6.53 (m, 1H), 4.94 (dd, $J$ = 11.5, 3.4 Hz, 1H), 4.88 (s, 1H), 4.73 (s, 1H), 3.26 (s, 1H), 2.53 (sept, $J$ = 6.8 Hz, 1H), 2.40 (ddd, $J$ = 17.5, 5.1, 4.4 Hz, 1H), 2.34–2.28 (m, 1H), 1.16 (sept, $J$ = 7.8 Hz, 3H), 1.00 (d, $J$ = 7.3 Hz, 18H), 0.94 (m, 3H), 0.90 (m, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 156.4, 155.2, 141.3, 135.5, 126.5, 119.6, 108.1, 74.6, 36.6, 31.2, 22.0, 21.6, 17.8, 12.6 cm$^{-1}$; IR (thin film from $CDCl_3$): $\tilde{\nu}$ = 3422, 2945, 2867, 1010, 1512, 1463, 1383, 1318, 1264, 1168, 1093, 1014, 914, 884, 833, 683 cm$^{-1}$; LRMS (TOF MS ES+): $m/z$: calcd for $C_{24}H_{39}BO_3Si$: 416.3; found: 416.3 $[M+H^+]$.

**3-(1-Isopropyl-vinyl)-6-[3-(triisopropylsilanyloxy)-phenyl]-5,6-dihydro-[1,2]oxaborinin-2-ol (10)**: $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.14 (t, $J$ = 8.0 Hz, 1H), 6.92–6.87 (m, 2H), 6.74 (dd, $J$ = 8.2, 1.5 Hz, 1H), 6.58 (app d, $J$ = 3.3 Hz, 1H), 4.99 (dd, $J$ = 11.5, 3.7 Hz, 1H), 4.94 (s, 1H), 4.78 (s, 1H), 2.60–2.54 (m, 1H), 2.50–2.43 (m, 1H), 2.35–2.28 (m, 1H), 1.24–1.14 (m, 3H), 1.03 (d, $J$ = 7.7 Hz, 18H), 0.99 (d, $J$ = 6.6 Hz, 3H), 0.94 (d, $J$ = 7.0 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 156.5, 156.2, 144.8, 141.4, 129.3, 119.0, 118.2, 117.1, 108.4, 74.8, 36.8, 31.4, 22.2, 21.8, 18.0, 12.8; IR (thin film from $CDCl_3$): $\tilde{\nu}$ = 3878, 2923, 2867, 1605, 1585, 1485, 1463, 1381, 1314, 1282, 1154, 1077, 1005, 877, 841, 785, 728, 682 cm$^{-1}$; LRMS (TOF MS ES+): $m/z$: calcd for $C_{24}H_{39}BO_3Si$: 416.3; observed 416.3 $[M+H^+]$.

**Representative procedure for comparative studies on the solid phase**

**Reaction using Hoveyda–Grubbs pre-catalyst 2**: To the alkynylboronic ester **25** (12.7 mg, 0.065 mmol) was added the macrobead bound homoallylic alcohol **15** (6.6 mg, 1.3 mmol g$^{-1}$) in one portion, with the beads noticeably swelling. Toluene (0.25 mL) was added, and the beads were al-

lowed to swell further for 5 min. Catalyst **2** (0.8 mg, 15 mol%) was then introduced as a solid. The vessel was purged with argon, then heated at 80°C for 24 h. The crude reaction mixture was cooled to 23°C, and $CH_2Cl_2$ (1 mL) was added, causing the macrobeads to float. These were taken up into a pipette and moved to a fritted column for washing. Beads were rinsed successively with THF (3×), THF/$H_2O$ (3:1, 3×), THF/$H_2O$ (1:1, 3×), THF/$H_2O$ (1:3, 3×), $H_2O$ (3×), $CH_3OH$ (3×), THF/$H_2O$ (1:1, 3×), THF (3×), $CH_2Cl_2$ (3×), $CHCl_3$ (3×), and $CDCl_3$ (1×) before drying under reduced pressure for >4 h. 6–7 macrobeads were then removed and swollen in 9:1 $CDCl_3$:$CD_3OD$ for analysis by MAS-NMR. Conversions are measured by integration of selected alkene protons (**15**: 5.65 ppm; **16**: 4.75 ppm).

**Reaction using Grubbs pre-catalyst 3**: To the alkynylboronic ester **25** (16.3 mg, 0.083 mmol) was added the macrobead bound homoallylic alcohol **15** (8.5 mg, 1.3 mmol g$^{-1}$) in one portion, with the beads noticeably swelling. Toluene (0.35 mL) was added, and the beads were allowed to swell further for 5 min. Catalyst **3** (1.4 mg, 15 mol%) was then introduced as a solid. The vessel was purged with argon, then heated at 80°C for 24 h. The crude reaction mixture was cooled to 23°C, and $CH_2Cl_2$ (1 mL) was added, causing the macrobeads to float. These were taken up into a pipette and moved to a fritted column for washing. Beads were rinsed successively with THF (3×), THF/$H_2O$ (3:1, 3×), THF/$H_2O$ (1:1, 3×), THF/$H_2O$ (1:3, 3×), $H_2O$ (3×), $CH_3OH$ (3×), THF/$H_2O$ (1:1, 3×), THF (3×), $CH_2Cl_2$ (3×), $CHCl_3$ (3×), and $CDCl_3$ (1×) before drying under reduced pressure for >4 h. 6–7 macrobeads were then removed and swollen in 9:1 $CDCl_3$:$CD_3OD$ for analysis by MAS-NMR. Conversions are measured by integration of selected alkene protons (**15**: 5.65 ppm; **16**: 4.75 ppm).

**Representative procedure for the crossover experiment**: To the alkynylboronic ester **25** (7.5 mg, 0.038 mmol, 7.5 equiv) was added the macrobead bound homoallylic alcohol **15** (3.9 mg, 1.3 mmol g$^{-1}$, 1.0 equiv) in one portion, with the beads noticeably swelling. Toluene (0.15 mL) was added, and the beads were allowed to swell further for 5 min. Catalyst **3** (1.3 mg, 30 mol%) was then introduced as a solid. The vessel was purged with argon, then heated at 40°C for 2 h. The crude reaction mixture was cooled to 23°C, and the solution was transferred to another reaction vessel containing a freshly prepared mixture of alkynylboronic ester **25** (6.8 mg, 0.035 mmol, 7.5 equiv) and macrobead bound homoallylic alcohol **15** (3.6 mg, 1.3 mmol g$^{-1}$, 1.0 equiv). This vessel was purged with argon, then heated at 40°C for 24 h, then cooled to ambient temperature. Both batches of macrobeads were suspended in $CH_2Cl_2$ (1 mL), taken up into a pipette and moved to a fritted column for separate washing. Beads were rinsed successively with THF (3×), THF/$H_2O$ (3:1, 3×), THF/$H_2O$ (1:1, 3×), THF/$H_2O$ (1:3, 3×), $H_2O$ (3×), $CH_3OH$ (3×), THF/$H_2O$ (1:1, 3×), THF (3×), $CH_2Cl_2$ (3×), $CHCl_3$ (3×), and $CDCl_3$ (1×) before drying under reduced pressure for >4 h. 6–7 macrobeads were then removed and swollen in $CDCl_3$/$CD_3OD$ 9:1 for analysis by MAS-NMR.

**Representative procedure for the crossover control experiment**: Catalyst **3** (8.1 mg) was added as a solid to a solution of the alkynylboronic ester **25** (6.1 mg, 0.031 mmol) in toluene (1.0 mL). The vessel was purged with argon, then heated at 40°C for 2 h. The crude reaction mixture was cooled to 23°C, and an aliquot (0.13 mL, corresponding to 1.1 mg catalyst) was removed by syringe under argon and transferred to another reaction vessel containing a freshly prepared mixture of alkynylboronic ester **25** (6.1 mg, 0.031 mmol, 7.5 equiv) and macrobead bound homoallylic alcohol **15** (3.2 mg, 1.3 mmol g$^{-1}$, 1.0 equiv). This vessel was purged with argon, then heated at 40°C for 24 h. The crude reaction mixture was cooled to 23°C, and $CH_2Cl_2$ (1 mL) was added, causing the macrobeads to float. These were taken up into a pipette and moved to a fritted column for washing. Beads were rinsed successively with THF (3×), THF/$H_2O$ (3:1, 3×), THF/$H_2O$ (1:1, 3×), THF/$H_2O$ (1:3, 3×), $H_2O$ (3×), $CH_3OH$ (3×), THF/$H_2O$ (1:1, 3×), THF (3×), $CH_2Cl_2$ (3×), $CHCl_3$ (3×), and $CDCl_3$ (1×) before drying under reduced pressure for >4 h. 6–7 macrobeads were then removed and swollen in $CDCl_3$/$CD_3OD$ 9:1 for analysis by MAS-NMR.

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