A One-Pot Cross-Metathesis/Allylboration Reaction: A Three-Component Coupling for the Synthesis of Functionalized Homoallylic Alcohols[**]

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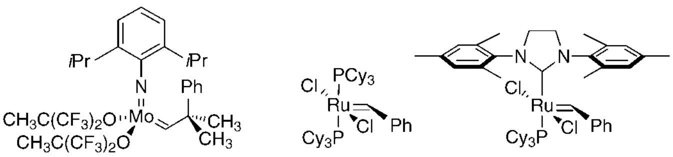
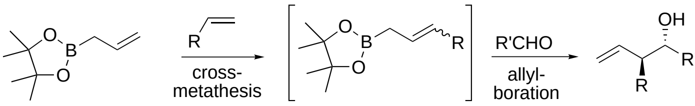
The development of methods for the chemo- and stereoselective formation of carbon–carbon bonds remains a primary goal of organometallic and organic chemistry. The olefin metathesis reaction[1] has become such a method, partly as a result of the development of well-defined transition metal alkylidene catalysts, such as the molybdenum alkylidene **1**[2] and the ruthenium benzylidene **2** (Scheme 1).[3] In particular, **2** is characterized by its remarkable stability to various functional groups and activity under mild reaction conditions. Recently, olefin cross-metathesis has emerged as a versatile method for the synthesis of functionalized acyclic structures.[1, 4] The discovery of highly active N-heterocyclic carbene-containing catalysts,[5] for example, **3**,[6] has advanced the utility of cross-metathesis, thus allowing the synthesis of small molecules with a wide range of pendant functional groups, including α,β-unsaturated carbonyl compounds,[7] styrenes,[8] vinyl and allyl phosphonates,[9] vinyl[7] and allyl silanes,[10] vinyloxiranes,[7] and trisubstituted olefins.[11] Consequently, olefin cross-metathesis presents a unique opportunity to introduce reactive functional groups, not as structural elements, but for use in subsequent mechanistically distinct carbon–carbon bond-forming reactions.



1 **2** **3**

Scheme 1. Olefin metathesis catalysts.

The allylation of aldehydes with allyl boron reagents is an excellent method for the stereoselective synthesis of homoallylic alcohols and is widely used in organic synthesis.[12] Studies by the groups of Hoffmann,[13] Roush,[14] and Brown[15] provided a detailed understanding of this transformation and resulted in the development of high-yielding, enantio- and diastereoselective allylboration protocols.[13–15] Despite decades of interest, the accessibility of functionalized allyl boron reagents remains limited. Traditionally, these complexes are prepared by allylmetal addition to haloboranes[16] or trialkoxy boranes,[14a] vinylmetal addition to halomethyl boranes,[17] or by hydroboration of 1,3-dienes;[18] methods that may be incompatible with complex substrates and/or many desirable functional groups. Recently, allyl boronates have been prepared by using transition metal mediated processes,[19] yet these methods are limited in their substrate scope[19b–d] or require stoichiometric amounts of tin reagents,[19a] and there remains no general method for the construction of allyl boronates with allylic functionality. Olefin metathesis appears ideally suited to address this problem. Herein we report a one-pot cross-metathesis/allylboration sequence that affords densely functionalized homoallylic alcohols (Scheme 2). This three-component coupling reaction combines two orthogonal, chemoselective, and mild carbon–carbon bond-forming reactions and demonstrates the power of olefin metathesis for the preparation of novel and highly reactive reagents.



4 **5** **6**

Scheme 2. One-pot cross-metathesis/allylation reaction.

The dimerization of pinacol allyl boronate (**4**)[20] was investigated to determine its compatibility with catalysts **2** and **3**. Treatment of **4** with catalyst **2** (5 mol%) in dichloromethane (0.2 N) at 40 °C for 12 h furnished the corresponding dimer **5** ($R = CH_2B[OC(CH_3)_2C(CH_3)_2O]$) as the major product in a 1.5:1 *E*:*Z* mixture. To our surprise, attempts to dimerize **4** by using the more active catalyst **3** gave only trace amounts of the desired dimer, thus generating a complex mixture of products, composed, in part, of vinyl boronates formed by olefin isomerization.[21]

Auspiciously, the inclusion of an olefin cross partner in the above reactions results in productive cross-metathesis to afford functionalized allyl boronates **5**. This finding demonstrates that productive cross-metathesis with either **2** or **3** is competitive with the olefin isomerization discussed above. Although these reactions may be monitored by means of thin-layer chromatography, significant hydrolysis of the boronate esters **5** occurs during purification by silica gel chromatography. However, addition of an aldehyde to the crude cross-metathesis reaction mixtures furnishes the corresponding homoallylic alcohols **6**, thus revealing that purification of the intermediates **5** is unnecessary and that the catalysts do not interfere with allylboration. This one-pot protocol has been applied to the preparation of a variety of functionalized homoallylic alcohols (Tables 1–3).[22]

The effects of varying the catalyst and the relative stoichiometries of the components of the cross-metathesis/allylation reaction were explored by using (*Z*)-1,4-diacetoxy-2-butene and benzaldehyde (Table 1).[23] *E* allyl boronates afford *anti*[24] products with high diastereoselectivity,[13b] and catalyst **3** is more *E* selective than catalyst **2** in olefin metathesis reactions,[1, 25] thus suggesting that catalyst **3** may

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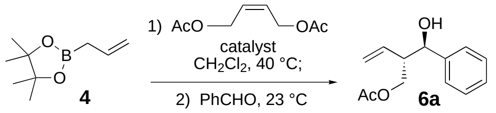
provide homoallylic alcohol **6a** with greater *anti* selectivity. Not only does this prediction hold true, but the yield of **6a** is significantly greater when catalyst **3** is used (Table 1, entries 1 and 2). The catalyst loading could be reduced to 2 mol% (Table 1, entry 3) without affecting the yield or the diastereoselectivity. The fact that alcohol **6a** is formed in 57% yield when using stoichiometric amounts of the cross partner (Table 1, entry 4), greater than is expected statistically (50%), suggests that the mixed cross product **5** (R=CH_2OAc) is favored over the respective symmetrical dimers. Interestingly, with benzaldehyde as the limiting reagent (Table 1, entry 5), the yield of **6a** is undiminished (75%), which implies that the cross-metathesis step is not yield-determining in this case.

Table 1. Cross-metathesis/allylation with pinacol allylboronate (**4**) and (*Z*)-1,4-diacetoxy-2-butene.



Entry	Cross partner [equiv]	Benzaldehyde [equiv]	Catalyst (mol%)	Yield [%]	*anti*:*syn*[a]
1	3	1.5	**2** (5)	32	1.8:1
2	3	1.5	**3** (5)	75	4.5:1
3	3	1.5	**3** (2)	75	4.5:1
4	0.5	1.5	**3** (5)	57	4.7:1
5	3	0.75	**3** (5)	75	4.5:1

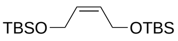
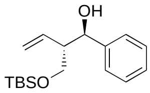
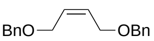
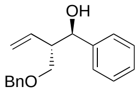
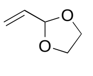
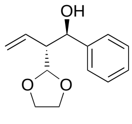
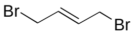
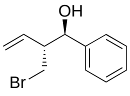
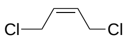
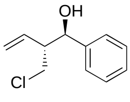
[a] Ratios determined by means of ^1H NMR spectroscopy.

Homoallylic alcohols with protected hydroxymethyl,[26] protected aldehyde and halomethyl side chains may be prepared efficiently by using the developed protocol (Table 2). As stated above, a decrease in the catalyst loading does not affect the overall chemical yield (Table 2, entries 2–5), and only in entry 2 is a noticeable decrease in the *anti*:*syn* ratio observed. Silyl[27] and benzyl allylic ethers are efficiently transformed into the corresponding homoallylic alcohols **6b** and **6c**, respectively, thus allowing facile tuning of the olefinic substrate to conform with preexisting protecting group strategies (Table 2, entries 1 and 2). 2-Vinyl-1,3-dioxolane is effectively converted into alcohol **6d** in 69% yield as a single diastereomer (Table 2, entry 3), in agreement with the expectation that increasing steric bulk at the allylic carbon atom would favor the formation of *trans* olefins.[28] In contrast, terminal olefins that lack allylic functional groups are poor substrates for this reaction and afford products in low yields and with lower *anti*:*syn* ratios.

The direct incorporation of a halomethyl group by allylboration (or by the related aldol addition reaction) had not previously been reported. The current protocol allows the synthesis of bromomethyl (Table 2, entry 4) and chloromethyl (Table 2, entry 5) allylation products **6e** and **6f**, respectively, in good yields from the corresponding 1,4-dihalo-2-butenes.[29] This sequence effectively constitutes the first preparation of a β-halo anion equivalent, thus allowing the synthesis of halogenated targets that would require several steps to prepare by traditional methods.

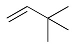
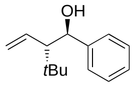
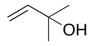
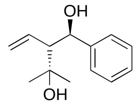
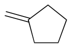
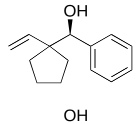
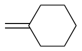
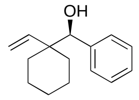
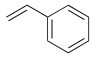
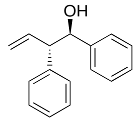
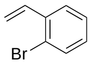
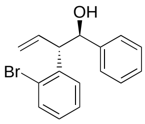
In light of the moderate *anti*:*syn* ratios obtained with smaller allylic functional groups, we explored olefinic substrates known to form predominantly *trans* products in cross-metathesis reactions (Table 3). Neopentyl olefins (Table 3, entries 1 and 2),[30] 1,1-disubstituted olefins that ultimately afford products containing quaternary centers (Table 3, entries 3 and 4), and styrenes (Table 3, entries 5 and 6) are successful in this sequence. For these substrates, a decrease in the loading of catalyst **3** lowers the yield of **6g** considerably (Table 3, entry 1). Importantly, the loading of the terminal olefin component in these cases is increased significantly beyond that used in the previous examples. This requirement

Table 2. Cross-metathesis/allylation reactions with functionalized olefins.

Entry	Cross partner	**3** [mol%]	Yield [%]	*anti*:*syn*[a]	Product
1		5	44–67	4:1	 **6b**
2		5 2	60 63	4.7:1 3.2:1	 **6c**
3		5 2	68 69	>20:1 >20:1	 **6d**
4		5 2	73 72	3.8:1 3.6:1	 **6e**
5		5 2	78 79	4.9:1 4.6:1	 **6f**

[a] Ratios determined by means of ^1H NMR spectroscopy.

Table 3. Cross-metathesis/allylation with hindered olefins and styrenes.

Entry	Cross partner	Equiv	**3** [mol %]	Yield [%]	Product[a]
1		5	5	35	 **6g**
		20[b]	5	51	
		30[b]	2	17	
2		3	5	49	 **6h**
		10	5	58	
3		10	5	34	 **6i**
		20[b]	5	66	
4		20[b]	5	45	 **6j**
5		5	5	25	 **6k**
6		10	5	60	 **6l**

[a] All products formed in >20:1 *anti*:*syn* ratio (determined by means of ^{1}H NMR spectroscopy). [b] The cross partner was used as solvent.

results from the formation of vinyl boronates through olefin isomerization (see above) becoming competitive with productive cross-metathesis for these less reactive cross partners.[31]

In conclusion, the successful application of olefin cross-metathesis to the preparation of functionalized allyl boronate reagents has resulted in a one-pot three-component coupling procedure for the synthesis of functionalized homoallylic alcohols. Of particular interest is the direct incorporation of halomethyl side chains, as can be seen in the previously unknown γ-halo allyl boronates **6e** and **6f**. This methodology highlights the utility of olefin metathesis for the synthesis of highly functionalized and reactive reagents that would be challenging or impossible to prepare by traditional methods.

Experimental Section

General procedure: A flame-dried round-bottomed flask was charged with **4** (1 equiv) and the olefin cross partner (3.0 equiv). A rubber septum was attached, dichloromethane was added (0.2–0.3 N in **4**), and argon was bubbled through the resultant solution for 10 min. Under a stream of argon, **3** (0.050 equiv) was added to the degassed solution as a solid. A reflux condenser was attached immediately, and the entire system was flushed with argon for 2 min. The colored solution was then heated at reflux for 2–12 h, and the reaction was monitored by thin-layer chromatography. Upon consumption of **4**, the aldehyde (1.5 equiv) was added to the reaction mixture through a syringe, and the resultant solution was stirred at 23 °C for 12–48 h. The solution was concentrated in vacuo, and the residue was purified by means of silica gel chromatography to afford **6**. Characterization data for **6a**–**6l** are given in the Supporting Information.

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[20] Pinacol allyl boronate was employed for its ease of synthesis and stability to elevated temperature and to long-term storage.

[21] Olefin isomerization has been observed during ring-closing metathesis reactions with ruthenium benzylidene catalysts; see: a) A. Fürstner, O. R. Thiel, L. Ackermann, H.-J. Schanz, S. P. Nolan, *J. Org. Chem.* **2000**, *65*, 2204; b) S. S. Kiderman, J. H. van Maarseveen, H. E. Schoemaker, H. Hiemstra, F. P. J. T. Rutjes, *Org. Lett.* **2001**, *3*, 2045; c) L. A. Paquette, I. Efremov, *J. Am. Chem. Soc.* **2001**, *123*, 4492.

[22] Varying the reaction temperature (23 °C or 60 °C) or the solvent did not increase the yield or the *anti*:*syn* ratio of the products.

[23] Our investigation focused on the synthesis of allyl boronate reagents by means of olefin metathesis, not on the effect of the aldehyde component, which has been aptly studied elsewhere. Therefore, for

consistency, benzaldehyde was used exclusively as the aldehyde component in these reactions.

[24] *Anti* refers to the relative stereochemistry of the hydroxy and side-chain groups, for example, product **6a** as drawn.

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[26] Wuts et al. were first to prepare the analogous THP-protected (THP = tetrahydropyran) hydroxymethyl products by means of allylboration; see ref. [17b].

[27] This substrate isomerizes to the corresponding silyl enol ether under the reaction conditions, resulting in the varying yields of **6b**: C. W. Lee, R. H. Grubbs, unpublished results.

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[29] Alcohol **6e** was synthesized in only 36% yield with a 2:1 *anti*:*syn* ratio when allyl bromide was used as the cross partner.

[30] A. K. Chatterjee, R. H. Grubbs, unpublished results.

[31] This is in stark contrast to previous studies in which hindered olefins could be used in nearly equal stoichiometric amounts with terminal olefins as a result of the slow dimerization of the hindered substrates; see ref. [11].

Electrodeposition of Redox Polymers and Co-Electrodeposition of Enzymes by Coordinative Crosslinking[**]

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The electrodeposition of metals and electron- or hole-conducting polymers proceeds through forming metallic or covalent bonds, respectively. We show here that films of hydrated redox polymers can also be electrodeposited. Electron conduction in redox polymers derives of the mobility of their segments. When the polymers are hydrated, their mobile segments randomly collide. Upon colliding, reduced mobile segments transfer electrons to oxidized ones.[1–9] The electrodeposition of redox polymers results of the formation of coordinative bonds that crosslink the chains.

The electrodeposited polymers were water soluble and comprised backbone-bound ligands and Os^{2+}/Os^{3+} complexes with exchangeable Cl^- ions in their inner coordination sphere. When the polymers were adsorbed on electrodes and were electroreduced, they were crosslinked by ligand exchange: about 5–10% of the labile Cl^- ions of the Os complexes of one polymer chain were exchanged by the more strongly coordinating pyridine or imidazole functions of neighboring chains.

It is well known that transition metal ions exchange ligands when electroreduced and/or electrooxidized.[10–14] It is also known that upon illumination the redox polymer formed by coordinating $[Ru(bpy)_2Cl]^+/[Ru(bpy)_2Cl]^{2+}$ to poly(4-vinylpyridine) exchanges its inner-sphere chloride with water, perchlorate or acetonitrile.[15] Here we show that when the initially reversibly adsorbed water-soluble redox polymers are electrochemically cycled, they are irreversibly crosslinked and are thereby irreversibly electrodeposited. The resulting films conduct electrons when they are hydrated, and their redox segments are mobile enough to collide, even though they are tethered to the crosslinked polymer. The deposition is rapid (200 s) and takes place at 25 °C in aqueous solutions at neutral pH. As the crosslinking caused by ligand exchange proceeds under mild conditions, dissolved enzymes with amine or heterocyclic nitrogen functions coordinating transition metals are conveniently co-electrodeposited. Substrates of the enzymes are electrocatalytically oxidized/reduced on the resulting "wired enzyme" electrodes.[16, 17]

The ligand exchange, and therefore the electrodeposition, takes place only when the surface coverage by the precursor redox polymer is high. When the precursor polymer does not densely cover the surface, the likelihood of finding neighboring chains at distances short enough for ligand exchange is small. Chloride, a weakly coordinating anionic ligand, is exchanged when Os^{3+} is electroreduced to Os^{2+} thereby diminishing the coulombic component of the binding energy. As the rate of interchain ligand exchange increases with the surface density of the chain containing the exchanged ligand and with that of the chain containing the exchanging ligand, it scales superlinearly with the surface density of the adsorbed polymer. At high surface coverage, the crosslinking is expected to be rapid and at low coverage it is expected to be negligible. The surface density of adsorbed redox polycations can be modulated on vitreous carbon electrodes through their oxidation, because oxidation of the carbon surface adds polycation-binding carboxylate and phenolate functions.[18]

On vitreous carbon electrodes that were pre-oxidized in plasma (air, 1 Torr, 5 min) the redox polymers were electrodeposited under exceptionally mild conditions, merely by cycling the electrodes between −150 and +150 mV vs the polymer's redox potential. When the vitreous carbon electrodes were not oxidized in plasma, the electrodeposition required electrooxidation of their surfaces and did not proceed unless the electrodes were cycled to greater than +0.4 V prior to applying the crosslinking reducing potential. The rate of deposition increased when the oxidizing potential was raised up to 0.8 V (vs Ag/AgCl; Figure 1). Thus, the purpose of the oxidative half cycle, where the electrode surface is oxidized, is to increase the surface density of the redox polymer prior to its crosslinking in the reductive half cycle.

Crosslinked films of redox polymer **I** (Scheme 1) were irreversibly electrodeposited from redox polymer solutions in PBS (0.5–1.0 mg mL^{-1} polymer, pH 7.1, 20 mM phosphate buffer, 0.1 M NaCl solution). In the 200-s process the potential was stepped 50 times between −0.3 (2 s) and +0.8 V (2 s). A sequence of the applied square potential waves is illustrated in

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