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Catalytic intermolecular allyl–allyl cross-couplings between alcohols and boronates†

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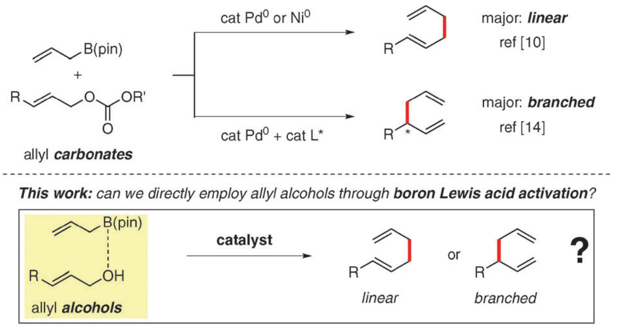
We developed catalytic intermolecular C(sp^3)–C(sp^3) cross-couplings between various allyl alcohols and allyl boronates, which proceeded smoothly in the presence of nickel(0) under mild conditions to form 1,5-dienes with excellent *linear*- and γ-selectivity; the use of boronates proved to be crucial in terms of reactivity.

Catalytic C–C bond formation with both high efficiency and selectivity is important in organic synthesis.[1] C(sp^3)–C(sp^3) cross-couplings are challenging, but useful reactions.[2] Allyl–allyl couplings provide straightforward access to 1,5-dienes, which are abundant in naturally occurring terpenes.[3] In addition, these compounds have proved to be important substrates in organic synthesis.[4] *Intermolecular unsymmetrical* C(sp^3)–C(sp^3) allyl–allyl couplings are significantly more challenging than *intramolecular* cyclizations;[5,6] only sporadic examples have been reported. These include allyl–allyl cross-couplings with *stoichiometric palladium complexes*,[7] *halides*, *acetates*, *carbonates*,[8] and *ethers*.[9] With few exceptions an excess of toxic reagents is required or harsh conditions are necessary. Another problem is the propensity of η^1-allyl–Pd intermediates to undergo β-hydride elimination. In addition, these reactions involve homo-coupling and moderate regioselectivities, leading to low yields and a limited scope.

To address these problems we recently developed cross-couplings between primary or secondary allyl carbonates and allyl *boronates* [Scheme 1; B(pin) = pinacolatoboron].[10] These reactions provided efficient access to various 1,5-dienes[11] with *linear* : *branched* ratios ranging in most cases from 4 : 1 to > 99 : 1. Allyl boronates are typically used for addition to C(sp^2) centers.[12] Thus, our earlier report[10] represents the first use of these nontoxic reagents in C(sp^3)–C(sp^3) cross-couplings.[11,13] More recently, Morken *et al.* developed a palladium-catalysed asymmetric version with *linear* : *branched* ratios ranging from 1 : 3 to 1 : > 20 (Scheme 1).[14] However, both methods[10,14] rely on the use of *carbonates*, which is a drawback in relation to step and atom economy. The direct use of allyl *alcohols* is more desirable. We hypothesized that we could address this issue by taking advantage of the *Lewis acidity of the trivalent boron atom* in allyl boronates. Lewis basic allyl alcohols may be activated by coordination to the intrinsically Lewis acidic boron atom, thereby transforming the hydroxyl moiety into a better leaving group (Scheme 1).[15] We report here catalytic intermolecular allyl–allyl cross-couplings between alcohols and boronates that proceed under remarkably mild conditions with excellent *linear*- and γ-selectivity.

We initially conducted a catalyst screening (10 mol%) for the reaction between the primary allyl alcohol **1a** and allyl boronate **2a** in toluene at room temperature for 12 h (Table 1). The use of $Pd(PPh_3)_4$[10] provided only traces of cross-coupled products in addition to the recovery of starting materials (Table 1, entry 1).

However, the use of $Ni(PPh_3)_4$ gave a particularly clean reaction with full conversion of **1a**. The *linear* 1,5-diene **3a** was formed in 94% yield, while the *branched* isomer **4a** was not detected (^{1}H NMR spectroscopy; entry 2). The central importance of phosphine ligation was confirmed by the use of $Ni(cod)_2$, which did not lead to any reaction (entry 3). We also examined the activity of main group 13 Lewis acids including indium(I) triflate,[13] but the desired cross-coupling did not occur (entries 4–7). No other catalyst used gave a reaction with **1a**.[16] Next, we screened allyl reagents other than **2a**. Somewhat unexpectedly, the use of the more Lewis acidic allyl borane **2b** under nickel(0) or indium(I)[17] catalysis provided only undesired reaction pathways (entries 8 and 9). Interestingly, the nickel(0)-catalysed reaction of allyl trifluoroborate **2c**



Scheme 1 Earlier studies with boronates and concept of the present work.

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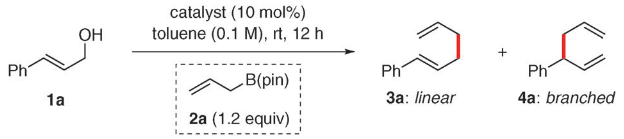
Table 1 Screening of catalysts and allyl reagents[16]



Entry	Allyl reagent	Catalyst	Yield[a] (%)	Ratio **3a** : **4a**[b]
1	**2a**	$Pd(PPh_3)_4$	Trace	—
2	**2a**	$Ni(PPh_3)_4$	94	> 99 : 1
3	**2a**	$Ni(cod)_2$	NR[c]	—
4	**2a**	$BF_3{\cdot}OEt_2$	ND[d]	—
5	**2a**	$GaCl_3$	ND[d]	—
6	**2a**	$In(OTf)_3$	ND[d]	—
7	**2a**	InOTf	NR[c]	—
8	**2b**	$Ni(PPh_3)_4$	ND[e]	—
9	**2b**	InOTf	ND[e]	—
10	**2c**	$Ni(PPh_3)_4$	41	9 : 1
11	**2d**	$Ni(PPh_3)_4$	NR[c]	—
12	**2e**	$Ni(PPh_3)_4$	NR[c]	—
13	**2f**	$Ni(PPh_3)_4$	NR[c]	—

[a] Isolated yields of 1,5-dienes after purification by PTLC. [b] Ratios **3a** : **4a** were determined for both crude mixtures and isolated products (^{1}H NMR spectroscopy). [c] NR = no reaction (^{1}H NMR spectroscopy). [d] ND = 1,5-dienes were not detected (^{1}H NMR spectroscopy); partial decomposition of **1a** and partial formation of Friedel–Crafts by-products. [e] ND = 1,5-dienes were not detected (^{1}H NMR spectroscopy); substantial decomposition of **1a** and **2b** as well as formation of Friedel–Crafts by-products (reactions in hexane, instead of toluene, provided mostly decomposition of **2b**).

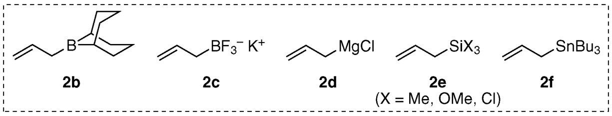
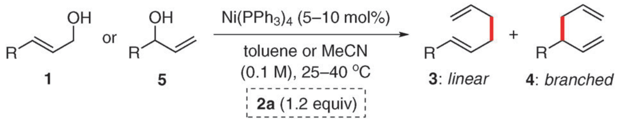
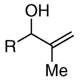
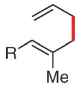
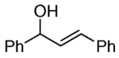
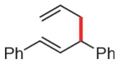
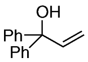
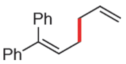


Table 2 Scope for allyl alcohols



Entry	Allyl alcohol	1,5-diene	Yield[a] (%)	Ratio **3** : **4**[b]
1	**1a**: R = Ph	**3a**: R = Ph	94	> 99 : 1
2	**5a**: R = Ph	**3a**: R = Ph	85	> 99 : 1
3	**5b**: R = 2-Naphthyl	**3b**: R = 2-Naphthyl	75	> 99 : 1
4	**1c**: R = 4-$MeOC_6H_4$	**3c**: R = 4-$MeOC_6H_4$	89	> 99 : 1
5	**5d**: R = 4-$Me_2NC_6H_4$	**3d**: R = 4-$Me_2NC_6H_4$	86	> 99 : 1
6	**5e**: R = 4-NCC_6H_4	**3e**: R = 4-NCC_6H_4	87	> 99 : 1
7	**5f**: R = 2-FC_6H_4	**3f**: R = 2-FC_6H_4	86	> 99 : 1
8	**5g**: R = 2-Furyl	**3g**: R = 2-Furyl	89	> 99 : 1
9	**5h**: R = 2-Thienyl	**3h**: R = 2-Thienyl	88	> 99 : 1
10	**5i**: R = 3-Pyridyl	**3i**: R = 3-Pyridyl	91	> 99 : 1
11[c]	**1j**: R = CH_2CH_2Ph	**3j**: R = CH_2CH_2Ph	78	4 : 1
				
12	**5k**: R = Ph	**3k**: R = Ph	86	> 99 : 1
13	**5l**: R = 4-$F_3CC_6H_4$	**3l**: R = 4-$F_3CC_6H_4$	87	> 99 : 1
14[d]	**5m** 	**3m** 	83	—
15[d]	**5n** 	**3n** 	79	> 99 : 1

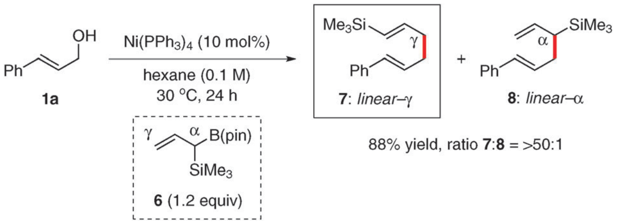
[a] Isolated yields of 1,5-dienes after purification by PTLC. [b] Ratios **3** : **4** were determined for both crude mixtures and isolated products (^{1}H NMR spectroscopy). [c] Solvent: hexane. [d] Temperature: 60 °C.

afforded the *linear* 1,5-diene **3a** as the major product, albeit in lower yield and with lower regioselectivity compared with the use of **2a** (entry 10). No other allyl reagent reacted under the mild experimental conditions (entries 11–13). Thus, we have identified a mild C–O bond activation for allyl alcohols that relies on the combined use of the moderately Lewis acidic allyl boronate reagent **2a** and an appropriate nickel(0) catalyst.[18,19] Two characteristic features are noteworthy. (1) This transformation displays an opposite reactivity profile for allyl boron-based reagents **2a** and **2b** as compared with our earlier related study.[17] (2) Control experiments with a mixture of 1,5-dienes **3a** and **4a** (ratio ~1 : 19) confirmed that a potential isomerization **4a** → **3a** *via* a Cope-type rearrangement[20] did not occur under the mild Ni(0) catalysis conditions; thus, the cross-coupling between **1a** and **2a** must have proceeded itself with exclusive *linear*-selectivity (formation of **3a**).

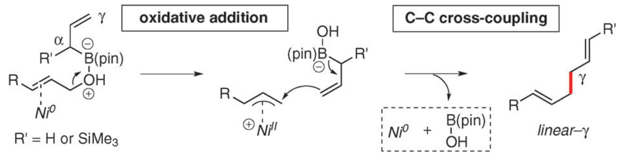
Next, we investigated the scope for primary and secondary allyl alcohols **1** and **5** under the optimized conditions (Table 2). A wide range of aromatic allyl alcohols were converted into the corresponding 1,5-dienes **3a–f** (entries 1–7). These reactions proceeded with high yields and exclusive *linear*-selectivity. This selectivity was observed in cases of both primary and secondary substrates (entry 1 *vs.* entry 2). While similar results were obtained with the heteroaromatic alcohols **5g–i** (entries 8–10),[21] the use of the aliphatic allyl alcohol **1j** gave lower selectivity (entry 11). The new protocol proved to be also effective for the β- and γ-substituted secondary allyl alcohols **5k–m** and the tertiary allyl alcohol **5n** (entries 12–15).

This new method was applicable to the selective formation of vinyl silanes (Scheme 2). The cross-coupling between allyl alcohol **1a** and α-silylallyl boronate **6** afforded almost exclusively the *linear*-γ-adduct **7**[10,22] in 88% yield. Only traces of the *linear*–α-adduct **8**[10,22] were detected, and neither *branched* cross-coupled or boron-containing products were found (^{1}H and ^{11}B NMR spectroscopy). This result underscores the significantly greater reactivity of boron relative to silicon, and highlights the synthetic potential[23] of this new allyl–allyl cross-coupling protocol.

Based on the observed *linear*-selectivity for both primary and secondary substrates (Table 1, entry 1 *vs.* entry 2) we propose



Scheme 2 Boron *vs.* silicon: *linear*-γ-selective cross-coupling with **6**.



Scheme 3 Proposed mechanism for *linear*-γ-selective cross-coupling.

dual activation of allyl alcohols with the nickel catalyst and the boronate reagent to generate π-allyl–nickel species as common reaction intermediates (oxidative addition; Scheme 3). Allyl–allyl cross-coupling would subsequently occur between the two sterically least congested carbon atoms of the electrophilic π-allyl–nickel and the nucleophilic allyl borate reagents. Thus, we favor a nontransmetalative pathway based on the observed excellent *linear*-γ-selectivity with **6**. However, we cannot exclude a 1,1′-reductive elimination of a generated bis(η^1-allyl)–nickel intermediate,[14] or similar transmetalative pathways.[22]

In summary, we have demonstrated nickel-catalysed intermolecular allyl–allyl cross-couplings between alcohols and boronates, and report here the first general use of allyl alcohols in this context.[21] The key to this facile C–O bond activation is the use of moderately Lewis acidic boron-based reagents combined with an appropriate nickel(0)–phosphine catalyst (dual activation).[19] The reactions proceeded under mild conditions with excellent *linear*- and γ-selectivity. This new protocol is applicable to the selective preparation of vinyl silanes,[23] and should therefore find great interest in organic chemistry. Further synthetic and mechanistic investigations are currently underway in our laboratories.

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