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Homogeneous Catalysis

Ca^{II}-Catalyzed Alkenylation of Alcohols with Vinylboronic Acids

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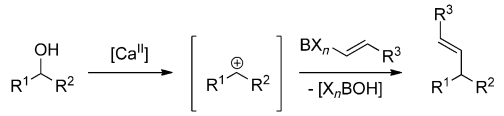
Abstract: Direct alkenylation of a variety of alcohols with vinylboronic acids has been accomplished using the air-stable calcium(II) complex $Ca(NTf_2)_2$ under mild conditions with short reaction times. For reluctant transformations, an ammonium salt was used as an additive to circumvent the reactivity issue.

Cross-coupling reactions are of paramount importance to provide access to highly diverse molecules.[1] Among the different cross-coupling partners, boronic acids are very popular reagents because they are readily available, easy-to-handle solids, weakly toxic, and compatible with a broad range of functional groups.[2] On the other hand, the synthesis of the second coupling partner (an organohalide for instance) often requires several tedious steps. The cross-coupling bears also its own limitations due to the use of a transition-metal complex as the catalyst, which can be expensive, toxic, difficult to prepare, and sensitive to oxygen and moisture. Regarding the substrates, it would be especially appealing to use readily available alcohols for C–C bond-forming transformations with boronic acids. However, the poor leaving ability of the hydroxyl group remains a major impediment. Over the last decade, several groups have reported a few transition-metal-catalyzed cross-couplings of allyl alcohols with arylboronic acids.[3,4] The transition-metal-catalyzed cross-coupling of alcohols with vinylboronic acids has also been sporadically reported.[5,6,7] Most of these approaches involve the formation of π-allyl metal complexes, yet, the versatility of this process remains to be demonstrated. Currently, there are only a few methods reported for the direct alkenylation of alcohols using simple styrene derivatives or vinyl silanes by the formation of a carbocation intermediate; however, these methods require either harsh conditions, long reaction times, or suffer from a limited substrate scope.[8,9] For these reasons, a general and mild reaction between alcohols and vinylboronic acids that avoids the use of noble transition-metals would be even more elegant. In this regard, calcium(II) salts display a high affinity towards alcohols to generate carbocation intermediates,[10] so they could be relevant catalysts for new C–C bond-forming reactions. They are air- and moisture-stable and also weakly toxic. Herein, we describe our preliminary investigations towards a calcium(II)-catalyzed alkenylation of a wide range of allyl, propargyl, and benzyl alcohols, with a series of vinylboronic acids and related reactants (Scheme 1).



Scheme 1. Alkenylation of alcohols with vinylboron derivatives.

We first investigated the reactivity of vinylbenzyl alcohol **1a** with (*E*)-styrylboronic acid **2a** (Table 1). While the use of $Ca(OTf)_2$ did not lead to any reaction (Table 1, entry 1), we were pleased to find that, with $Ca(NTf_2)_2$,[11] the linear product **3a** was formed selectively in 73% yield after 30 min at room temperature in CH_2Cl_2 (entry 2). It is noteworthy that the same result was obtained under argon or in air using distilled CH_2Cl_2. In addition, the branched cross-coupled product **3′′a** was not detected, which can be explained by the steric hindrance at the benzylic position. The use of nitromethane, 1,4-dioxane, or acetone as a solvent significantly decreased the reactivity leading to lower yields or no reaction (entries 3–5). Other Group 2 metal salts such as $Mg(NTf_2)_2$ and $Ba(NTf_2)_2$ were also tested, but the reaction proceeded at a slower rate and **3a** was isolated in 55 and 30% yield, respectively (entries 6 and 7). We, then, examined the influence of additives (entries 8–10). Several reports have recently shown that the use of ammonium or potassium salts, such as nBu_4NBF_4, nBu_4NPF_6, or KPF_6,[12] could be beneficial to reactions involving $Ca(NTf_2)_2$ as a catalyst. Indeed, the ammonium or potassium salts of weakly coordinating anions can promote an anion metathesis to generate the heteroleptic complex $Ca(NTf_2)(X)$ ($X=BF_4$, PF_6), which is more Lewis acidic than $Ca(NTf_2)_2$.[11f] Surprisingly, the reaction was less efficient and proceeded at a slower rate (entries 8–10). Moreover, **3a** was obtained admixed with the conjugated diene **3′a**, which was not detected in our previous experiments. On the other hand, the use of the Brønsted acid $HNTf_2$ as the catalyst led to a significant decrease of the yield (entry 11). A control experiment, carried out in the absence of $Ca(NTf_2)_2$, led to the recovery of the starting materials (entry 12). The coupling was also tested with other boron reagents, which promoted either the decomposition of the alcohol (BPin, entry 13), led to a complex mixture (BF_3K, entry 14),

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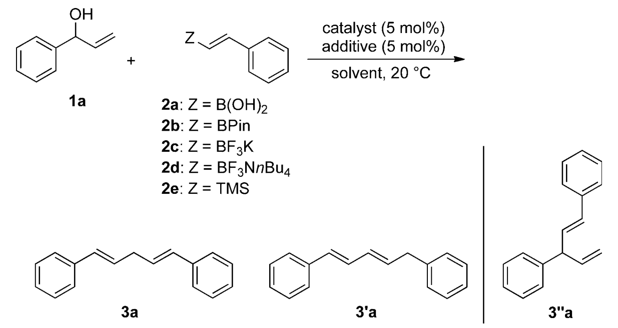
Table 1. Alkenylation of vinylbenzyl alcohol **1a** with the (*E*)-styrylboron and -styrylsilicon derivatives **2a**–**e**: optimizations of reaction conditions.

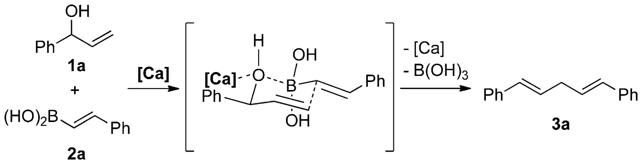


Entry	Catalyst	Additive	2	Solvent	*t* [min]	Yield of **3a** [%]
1	$Ca(OTf)_2$	–	**2a**	CH_2Cl_2	120	NR
2	$Ca(NTf_2)_2$	–	**2a**	CH_2Cl_2	30	73
3	$Ca(NTf_2)_2$	–	**2a**	$MeNO_2$	30	35
4	$Ca(NTf_2)_2$	–	**2a**	1,4-dioxane	120	NR
5	$Ca(NTf_2)_2$	–	**2a**	acetone	60	NR
6	$Mg(NTf_2)_2$	–	**2a**	CH_2Cl_2	60	55
7	$Ba(NTf_2)_2$	–	**2a**	CH_2Cl_2	120	30
8	$Ca(NTf_2)_2$	nBu_4NBF_4	**2a**	CH_2Cl_2	50	55[b]
9	$Ca(NTf_2)_2$	KPF_6	**2a**	CH_2Cl_2	30	58[b]
10	$Ca(NTf_2)_2$	nBu_4NPF_6	**2a**	CH_2Cl_2	85	57[b]
11	$HNTf_2$	–	**2a**	CH_2Cl_2	15	15
12	–	–	**2a**	CH_2Cl_2	60	NR
13	$Ca(NTf_2)_2$	–	**2b**	CH_2Cl_2	50	–
14	$Ca(NTf_2)_2$	–	**2c**	CH_2Cl_2	60	–
15	$Ca(NTf_2)_2$	–	**2d**	CH_2Cl_2	120	NR
16	$Ca(NTf_2)_2$	–	**2e**	CH_2Cl_2	60	NR
17	$Ca(NTf_2)_2$	nBu_4NBF_4	**2e**	CH_2Cl_2	60	65

[a] Reaction conditions: **1a** (1 equiv) and organoboron (or organosilicon) derivative **2** (2 equiv) in the indicated solvent (0.1 M) in the presence of the catalyst (5 mol%) with/or without additive (5 mol%). [b] The compound **3a** is admixed with **3′a** (ratio 3:1 to 4:1).

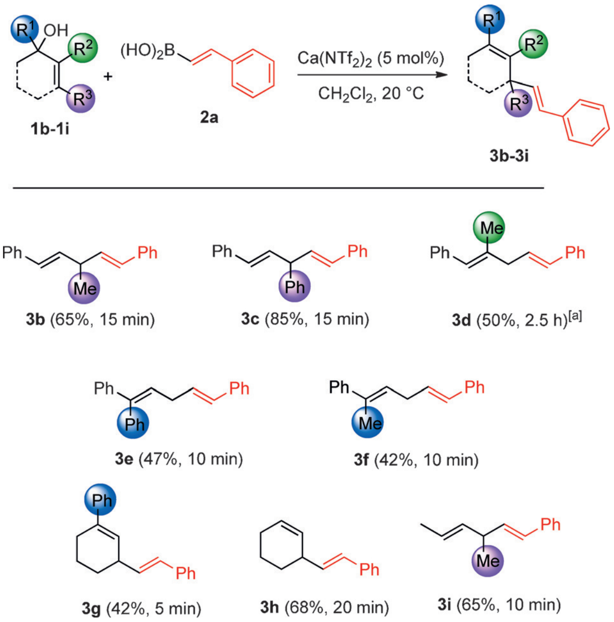
or did not react (BF_3NnBu_4, entry 15).[12] Finally, the reaction was attempted with (*E*)-styrylsilane **2e**, a substrate that has already been used by Niggemann et al. for a few calcium-catalyzed alkenylation of alcohols.[8d] In the absence of additive, no reaction was observed (entry 16). In this case, the use of an ammonium salt was necessary to achieve the reaction (entry 17).

Despite their low intrinsic nucleophilicity, organoboronic acids have recently emerged as promising nucleophiles in transition-metal-free C–C bond-forming reactions.[13] In our case, the efficiency of the reaction might be explained by a synergistic activation of the hydroxyl group by calcium and the boronic acid to form a more reactive boron-tethered nucleophile by a six-membered transition state (Scheme 2). As a result, vinylboronic acids would be more reactive than vinylsilanes, boron being more oxophilic than silicon.



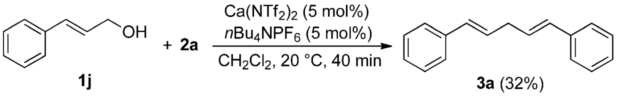
Scheme 2. Proposed transition state in the Ca^{II}-catalyzed alkenylation of vinylbenzyl alcohol **1a** with (*E*)-styrylboronic acid **2a**.

With these optimized conditions, we turned our attention to the reactivity of various secondary and tertiary allyl alcohols with **2a** (Scheme 3). The alkenylation gave rise to linear products in good yields within 10–20 min at room temperature. The only exception concerned compound **1d** (R^1 = Ph, R^2 = Me, R^3 = H), which required heating at a more elevated temperature (30 °C) for a longer reaction time (4 h), presumably for steric reasons. Remarkably, even 2-cyclohexen-1-ol (**1h**) and (*E*)-pent-3-en-2-ol (**1i**), which are not activated by a phenyl group, proved to be compatible substrates.

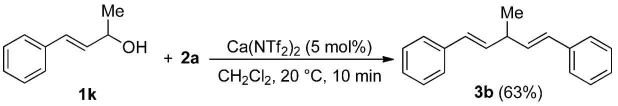


Scheme 3. Alkenylation of allyl alcohols **1b**–**i** with (*E*)-styrylboronic acid **2a**. Reaction conditions: **1b**–**i** (1 equiv) and **2a** (2 equiv) in CH_2Cl_2 (0.1 M) in the presence of $Ca(NTf_2)_2$ (5 mol%). [a] The reaction was carried out at 30 °C for 4 h.

The 1,4-diene **3a** could also be obtained from the less reactive cinnamyl alcohol **1j** and **2a**, yet in this case reinforcement of the Lewis acidity of the calcium complex was necessary. However, even by adding nBu_4NPF_6, the yield did not exceed 32% [Eq. (1)]. On the other hand, in the case of substrate **1k**, which displays an additional methyl group, the use of nBu_4NPF_6 was not required [Eq. (2)], and the 1,4-diene **3b** was generated in 63% yield, similar to that of allyl alcohol **1b** (see Scheme 3).

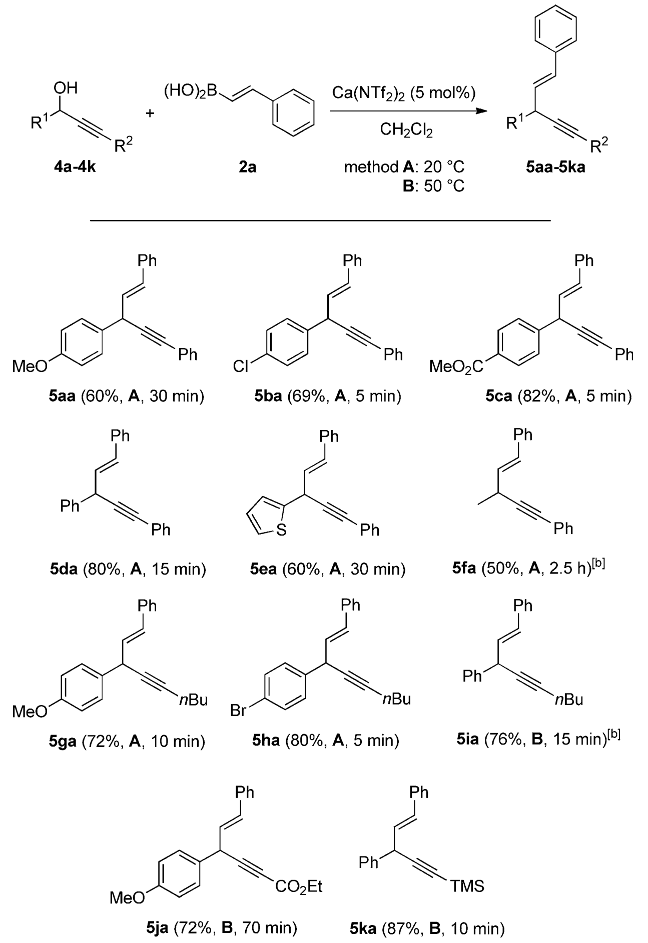


(1)

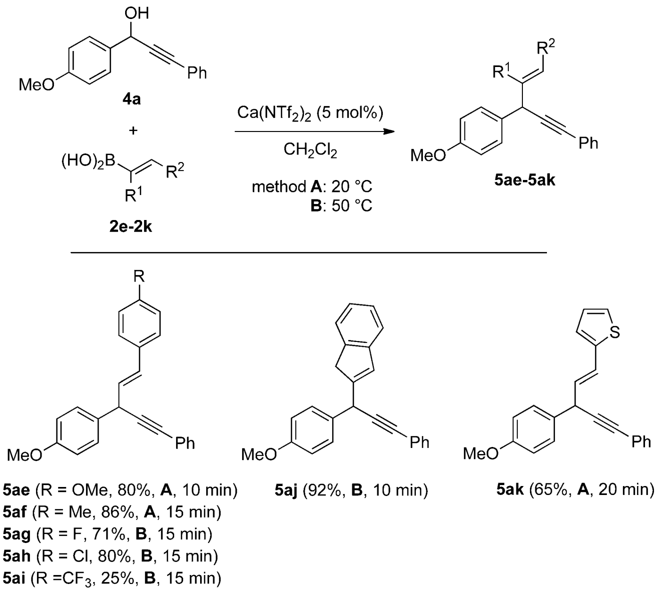


(2)

Then, we examined the reactivity of propargyl alcohols with styrylboronic acids (Scheme 4). Gratifyingly, the transformation was compatible with a broad substrate scope and led to the corresponding products in good yields within 5 to 30 min. Interestingly, with phenylpropargyl alcohols bearing electron-withdrawing Cl and CO_2Me substituents at the *para* position (**5 ba** and **5 ca**), the reaction proved to be faster than with an electron-donating OMe group (**5 aa**). The reaction was also efficient in the absence of substitution at this position (**5 da**), and can be applied to 2-thienyl- and alkylpropargyl alcohols to give compounds **5 ea** and **5 fa** in 60 and 50% yields. However, in the latter case, it was necessary to introduce $n\mathrm{Bu_4NPF_6}$ in the reaction mixture. We, then, explored the influence of the substitution at the alkyne moiety and noticed that the reaction is not only compatible with a phenyl, but also with alkyl (**5 ga**—**ia**), ester (**5 ja**), or trimethylsilyl groups (**5 ka**). In the latter two cases, the reaction did not take place below 50 °C.



Scheme 4. Alkenylation of propargyl alcohols **4 a**–**k** with (*E*)-styrylboronic acid **2 a**. [a] Reaction conditions: **4 a**–**k** (1 equiv) and **2 a** (2 equiv) in CH_2Cl_2 (0.1 M) in the presence of $Ca(NTf_2)_2$ (5 mol%) at the indicated temperature. [b] The reaction was carried out in the presence of 5 mol% of $n\mathrm{Bu_4NPF_6}$, otherwise, no reaction was observed.

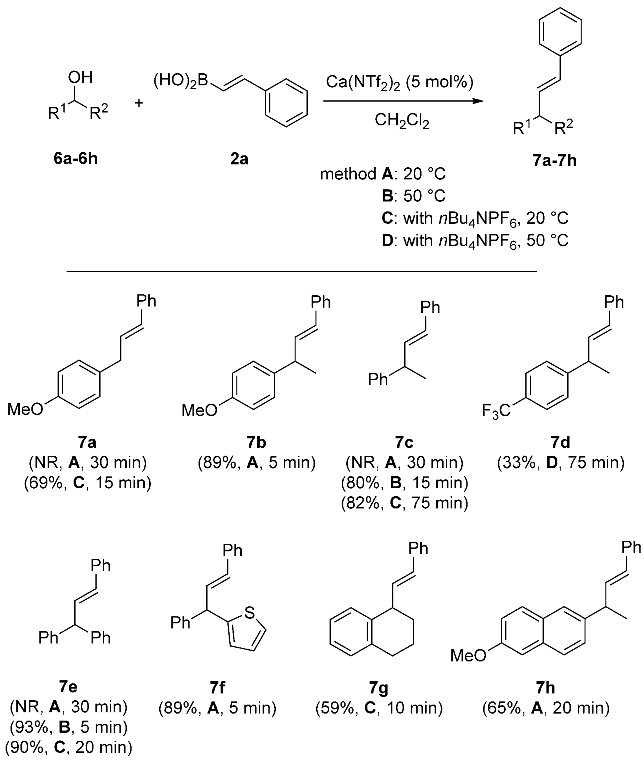


Scheme 5. Cross-Coupling of phenylpropargyl alcohol **4 a** with styrylboronic acids **2 e**–**k**. [a] Reaction conditions: **4 a** (1 equiv) and **2 e**–**k** (2 equiv) in CH_2Cl_2 (0.1 M) in the presence of $Ca(NTf_2)_2$ (5 mol%) at the indicated temperature.

Various styrylboronic acids were also tested with phenylpropargyl alcohol **4 a** (Scheme 5). While the presence of the electron-rich OMe and Me groups did not affect the reactivity (**5 ae** and **5 af**), no reaction occurred at room temperature with moderately electron-withdrawing F and Cl substituents. Nevertheless, the desired compounds could be obtained at 50 °C in good yields (**5 ag** and **5 ah**). In the case of substrate **2 i**, containing a strong electron-withdrawing CF_3 substituent at the *para* position of the phenyl group, the product **5 ai** was obtained in a moderate yield of 25%.[14] The more hindered substrate 2-indenylboronic acid **2 j** or the heteroaromatic vinylboronic acid **2 k** could also be employed to prepare the coupling products **5 aj** and **5 ak** in 92 and 65% yields.

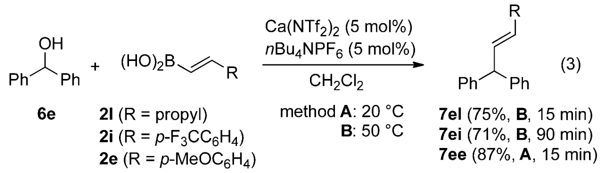
Next, we sought to investigate the reactivity of simple benzyl alcohols (Scheme 6). In general, the desired products were obtained in good yields. However, it is important to note that no reaction occurred at room temperature, when $n\mathrm{Bu_4NPF_6}$ was omitted, with the exception of **6 b** and **6 h**. At elevated temperature (50 °C), the reaction could be conducted without $n\mathrm{Bu_4NPF_6}$ to furnish the corresponding products in high yields (**7 c** and **7 e**). A strong electron-withdrawing CF_3 substituent at the *para* position was also used to generate **7 d** in a moderate 33% yield. The reaction was compatible with the cyclic benzyl alcohol **6 g** to give the desired product in 59% yield within 10 min. To illustrate the synthetic utility of this method, we prepared a key precursor of the anti-inflammatory drug (±)-naproxen. The cross-coupling reaction of 1-(6-methoxynaphthalen-2-yl)ethanol **10** with (*E*)-styrylboronic acid **2 a** generated compound **11** in 65% yield, which could lead to (±)-naproxen after a simple oxidation.[15]

Of particular interest, the reaction of benzyl alcohols was also possible with less reactive vinylboronic acids, that is, those substituted by an alkyl or a trifluoromethyl group [Eq. (3)]. For example, the reaction of the benzhydrol **6 e** with **2 l** and **2 i** provided the corresponding products in 75 and 71% yields, respectively, but had to be carried out at 50 °C. A *para*-methoxy-

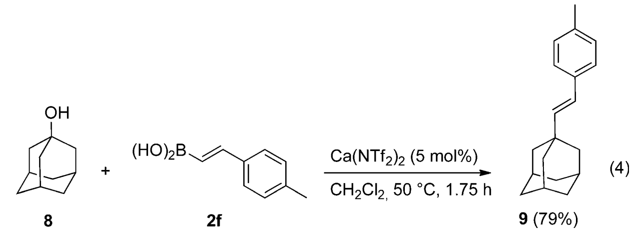


Scheme 6. Alkenylation of benzyl alcohols **6a**–**h** with (*E*)-styrylboronic acid **2a**. [a] Reaction conditions: **6a**–**h** (1 equiv) and **2a** (2 equiv) in CH_2Cl_2 (0.1 м) in the presence of $Ca(NTf_2)_2$ (5 mol %) with/or without nBu_4NPF_6 (5 mol %) at the indicated temperature.

phenyl, however, allowed the reaction to proceed at room temperature to generate compound **7ee** in 87 % yield.



Finally, we noticed that 1-adamantanol could also be used as a coupling partner to deliver product **9** in 79 % yield at 50 °C [Eq. (4)].



We have developed a highly efficient method for C–C bond-forming reactions based on a calcium-catalyzed direct coupling of alcohols with vinylboronic acids. In addition, the reagents and the catalytic system have the advantage of being stable easy-to-handle compounds and commercially available. This new protocol has a broad applicability and allows a straightforward access to a great diversity of alkenes, dienes, and enynes under mild conditions without taking special precautions.

Experimental Section

General procedure for the calcium-catalyzed alkenylation of alcohols with vinylboronic acids

Alcohol (0.25 mmol, 1 equiv), vinylboronic acid (0.5 mmol, 2 equiv), $Ca(NTf_2)_2$ (5 mol %), and nBu_4NPF_6 (5 mol %) (when indicated) were charged (in air) in a 10 mL screw-cap vial equipped with a stir bar. Distilled dichloromethane (2.5 mL, 0.1 м) was added and the tube was sealed. The reaction mixture was stirred at the indicated temperature until TLC analysis showed full conversion. Then, the crude product was purified by flash column chromatography using different gradients of pentane and ethyl acetate.

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Keywords: alcohol · calcium · cross-coupling · homogeneous catalysis · vinylboronic acid

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