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Calcium-Catalyzed Direct Coupling of Alcohols with Organosilanes

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A calcium-catalyzed direct substitution of π-activated alcohols with different organosilanes under very mild reaction conditions is presented. The high reactivity of the calcium catalyst allows efficient conversion of secondary and tertiary allylic, secondary benzylic, and tertiary propargylic alcohols with allyltrimethylsilane at room temperature. Furthermore, the first direct substitution of an alcohol with (*E*)- as well as (*Z*)-alkenylsilanes was achieved under mild reaction conditions.

Introduction

Precious metals, playing a critical role in many homogeneously catalyzed reactions, are becoming increasingly rare and consequently more expensive as we use up natural resources. Therefore, the search for alternative catalysts is nowadays of more significance. The potential application of early main group metals as catalysts has remained a widely underexplored research field, despite the apparent ecological and economical benefits. Among other alkaline earth metals, calcium seems to be an ideal main group metal catalyst,[1] as it is essentially free of toxicity, very cheap, and the fifth most frequent element of the earth crust. We recently reported a novel calcium-based, highly Lewis acidic catalyst system for the dehydration of benzylic, allylic, and propargylic alcohols and their subsequent reaction with nucleophilic arenes under very mild reaction conditions.[2,3] We have now turned our attention towards catalytic C–C bond formation with water-tolerant organometallic reagents. The general utility of unsaturated organosilicon compounds as carbanion surrogates is well recognized. Numerous scientific efforts devoted to the exploration of these comparatively stable and environmentally benign organometallic reagents have led to their establishment as a valuable instrument in the synthetic tool box. The use of alcohols as electrophilic coupling partners in C–C bond-formation reactions with these very mild organometallic reagents appears beneficial in several ways. Silanol is formed as the only byproduct during the reaction. The transformation of the hydroxy group into a better leaving group such as the corresponding halide, carboxylate, carbonate, phosphate, or related compounds is unnecessary. Consequently, overall salt loads, being a common accompaniment of metal organic reactions, are substantially reduced. The direct addition of allyltrimethylsilane to alcohols in the presence of Lewis[4] or Brønsted[5] acids has been investigated by other groups. However, many of these transformations suffer from significant drawbacks such as harsh reaction conditions, prolonged reaction times, and low functional group compatibility. In further pursuit of our efforts towards the development of main group metal-catalyzed reactions for organic synthesis, as an alternative to traditionally used transition-metal-catalyzed transformations, we herein report the direct substitution of π-activated alcohols with silicon-based carbanion surrogates.

Results and Discussion

Initially, we attempted the allylation of methyl cinnamyl alcohol (**1**) with allyltrimethylsilane (**2**) in the presence of our calcium-based catalyst system consisting of $Ca(NTf_2)_2$ (5 mol-%) and Bu_4NPF_6 (5 mol-%). The reaction proceeded smoothly at room temperature in dichloromethane to give the desired allylated product after 1 h as a 2.7:1 mixture of regioisomers **3a/3b** in 76% yield. To improve the regioselectivity and the yield of the transformation, we investigated the effect of various additives (Table 1). In the presence of tetrabutylammonium hexafluorosilicate or tetraphenylborate, the reactivity of the catalyst was inhibited (Table 1, Entries 2 and 3). The tetrapentafluorophenylborate anion based additive increased the yield at the expense of regioselectivity (Table 1, Entry 4). In presence of the hexafluoroantimonate salt, the outcome of the reaction was comparable to that of the initial attempt with hexafluorophosphate (Table 1, Entry 5 vs. 1). The best results were obtained by using tetrabutylammonium tetrafluoroborate (Table 1, Entry 6). In an earlier publication, we already discussed the role of the additive as a precursor for the formation of the catalytic species by anion exchange.[6] Unfortunately, the formation of the catalytically active $CaNTf_2BF_4$ species proved less efficient under the reaction conditions starting

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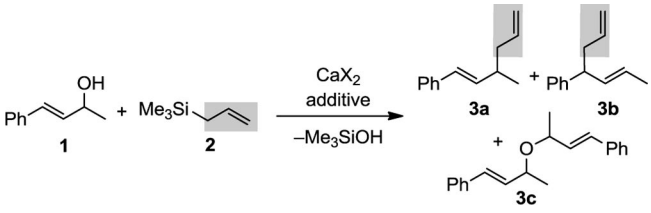
from commercially available $Ca(BF_4)_2$ and Bu_4NNTf_2 (Table 1, Entry 7). As for previously described calcium-catalyzed reactions, dichloromethane proved to be the most suitable solvent for the allylation of alcohols. The transformation is incomplete and stops after the intermediary formation of ether **3c** in stronger coordinating, ethereal solvents (Table 1, Entries 8 and 9).[6] The reaction in toluene, giving only slightly poorer results than those obtained in dichloromethane, represents a potential alternative (Table 1, Entry 10) where non-halogenated solvents are mandatory.

Table 1. Optimization of the reaction conditions.[a]

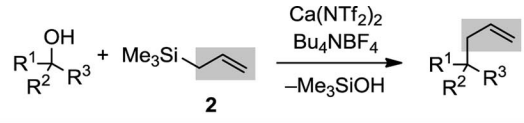


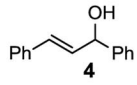
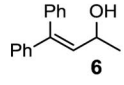
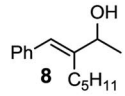
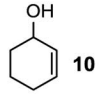
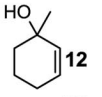
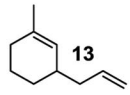
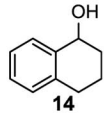
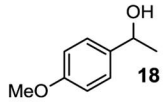
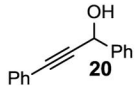
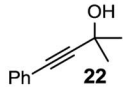
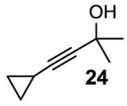
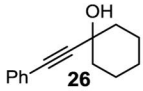
Entry	CaX_2	Additive	**3a/3b/3c**[b]	*t* [h]	Yield[c] [%]
1	$Ca(NTf_2)_2$	Bu_4NPF_6	2.7:1:0	1	76
2	$Ca(NTf_2)_2$	$(Bu_4N)_2SiF_6$	–	16	–
3	$Ca(NTf_2)_2$	Bu_4NBPh_4	–	16	–
4	$Ca(NTf_2)_2$	$PhMe_2NHB(C_6F_5)_4$	2:1:0	1	98
5	$Ca(NTf_2)_2$	Bu_4NSbF_6	2.7:1:0	1	75
6	$Ca(NTf_2)_2$	Bu_4NBF_4	2.7:1:0	1	91
7	$Ca(BF_4)_2$	Bu_4NNTf_2	2.4:1:0.3	1	69
8[d]	$Ca(NTf_2)_2$	Bu_4NBF_4	4:1:7	1	23
9[e]	$Ca(NTf_2)_2$	Bu_4NBF_4	1:0:5	1	9
10[f]	$Ca(NTf_2)_2$	Bu_4NBF_4	2.7:1:0	1	84
11[g]	$Ca(NTf_2)_2$	Bu_4NBF_4	2.7:1:5	1	30

[a] CaX_2 (5 mol-%) and the additive (5 mol-%) were added at room temperature to allyl alcohol **1** (0.5 mmol) and allylsilane **2** (1.5 mmol) in CH_2Cl_2 (1 mL), and the mixture was stirred for the time indicated. [b] Ratio determined by GC analysis. [c] Isolated yield. [d] Reaction run in Et_2O. [e] Reaction run in THF. [f] Reaction run in toluene. [g] Reaction run in hexane.

To explore the generality and scope of the reaction, a series of different alcohols was allylated under the optimized reaction conditions (Table 2). The transformation of secondary allylic alcohols with **2** afforded the desired products in good yields after 1 h at room temperature. The addition of the allyl anion surrogate occurred regioselectively in the case of alcohols **4**, **6**, and **10** (Table 2, Entries 1, 3 and 4), and only product **9** was obtained as a 6.2:1 mixture of regioisomers **9a/9b** (Table 2, Entry 3; Supporting Information). In analogy with previously investigated calcium-catalyzed reactions,[3,6] tertiary allylic alcohol **12** reacted with complete isomerization of the double bond to yield product **13**. The allylation of secondary benzylic alcohols gave the desired products in good yields and selectivities (Table 2, Entries 6–9). The transformation of tertiary benzylic alcohols was hampered by a competing background reaction, affording the corresponding olefins by irreversible elimination of H_2O. Therefore, the desired reaction products were formed in unsatisfactory yields. The same elimination reaction occurred during the conversion of tertiary propargylic alcohols. Fortunately, the use of a greater excess of the nucleophile (5 equiv.) was sufficient to suppress the undesired elimination to an extent that moderate yields of the allylated products were obtained (Table 2, Entries 10–12). As for previously described calcium-catalyzed transfor-

Table 2. Allylation of different alcohols with allyltrimethylsilane (**2**).[a]



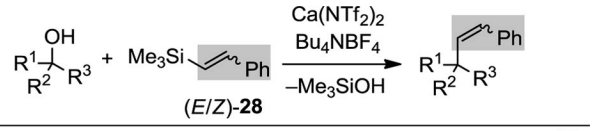
Entry	Alcohol	Product	*t* [h]	Yield[b] [%]
1	 **4**	**5**	1	82
2	 **6**	**7**	1	81
3	 **8**	**9**[c]	1	77
4	 **10**	**11**	1	64
5	 **12**	 **13**	1	72
6	 **14**	**15**	1	82
7	 **16**	**17**	1	52
8	 **18**	**19**	1	83
9	 **20**	**21**	1	72
10[d]	 **22**	**23**	1	46
11[d]	 **24**	**25**	1	58
12[d]	 **26**	**27**	1	45

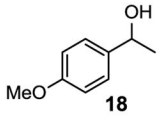
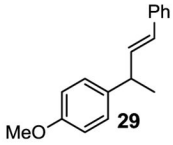
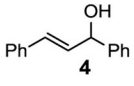
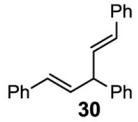
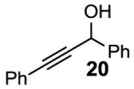
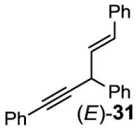
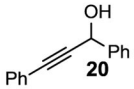
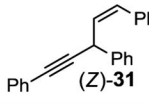
[a] $Ca(NTf_2)_2$ (5 mol-%) and Bu_4NBF_4 (5 mol-%) were added at room temperature to the alcohol (0.5 mmol) and allylsilane **2** (1.5 mmol) in CH_2Cl_2 (1 mL), and the mixture was stirred for the time indicated. [b] Isolated yield. [c] Mixture of regioisomers 6.2:1 (see Supporting Information). [d] 2.5 mmol of **2** was used.

mations, primary alcohols as well as aliphatic alcohols that do not bear a π-activating moiety were unsuitable substrates even at elevated temperatures.

Despite the prosperity of the commonly used allylsilanes,[7] the potential of other unsaturated organosilicon compounds such as vinylsilanes received only little attention.[8] This is undoubtedly due to the much lower inherent nucleophilicity of these species. Therefore, we were very pleased to find that vinylsilanes, such as **28**, were suitable nucleophilic coupling partners for the calcium-catalyzed substitution of alcohols under our optimized reaction conditions (Table 3). Due to the lower reactivity of these silanes, the reaction of the intermediary formed carbocation with the silyl nucleophile is assumed to be comparatively slow. Thus, only alcohols that provide well-stabilized carbocations were suitable for this transformation, as they have a lower propensity to partake in undesired side reactions such as eliminations and polymerizations. Electron-rich secondary benzylic alcohols **18**, **4**, and **20** reacted readily with (*E*)-2-phenyl-1-trimethylsilylethylene [(*E*)-**28**] to afford desired products **29**, **30**, and (*E*)-**31** within 1 h at room temperature in good to moderate yields with complete retention of the double bond geometry (Table 3, Entries 1–3). To the best of our knowledge this is the first time that an alcohol was demonstrated to react with an alkenylsilane under conditions below 80 °C. Furthermore, vinylsilane (*Z*)-**28**, which has shown no nucleophilicity in previously described reactions,[8] readily reacted with alcohol **20** to provide desired product (*Z*)-**31**, again with complete retention of the double bond geometry.

Table 3. Alkenylation of alcohols.[a]



Entry	Alcohol	Product	*t* [h]	Yield[b] [%]
1			1	62
2			1	61
3			1	79
4			1	69

[a] $Ca(NTf_2)_2$ (5 mol-%) and Bu_4NBF_4 (5 mol-%) were added at room temperature to the alcohol (0.5 mmol) and alkenylsilane **28** (1.5 mmol) in CH_2Cl_2 (1 mL), and the mixture was stirred for the time indicated. [b] Isolated yield.

Conclusions

In summary, we have developed a new and efficient calcium-catalyzed direct coupling of π-activated alcohols with different types of silyl-based carbanion surrogates under very mild reaction conditions. The high reactivity of the calcium catalyst allows efficient conversion of secondary and tertiary allylic, secondary benzylic, as well as tertiary propargylic alcohols with allyltrimethylsilane. Furthermore, the first direct substitution of an alcohol with (*E*)- as well as (*Z*)-alkenylsilanes was achieved under mild reaction conditions. Typical reactions proceed at room temperature, with no added strong acids or bases, and special precautions for exclusion of moisture or air are not unnecessary.

Experimental Section

Typical Procedure: To a solution of the alcohol (0.5 mmol) and the organosilane (1.5 mmol) dissolved in dichloromethane (1 mL) was added Bu_4NBF_4 (5 mol-%) and $Ca(NTf_2)_2$ (5 mol-%) at room temperature, and the mixture was stirred until conversion of the alcohol was complete (monitored by TLC and/or GC). For isolation of the product, sat. $NaHCO_3$ solution (5 mL) was added, the aqueous phase was extracted with dichloromethane (2×). The combined organic extracts were dried with Na_2SO_4 and concentrated in vacuo, and the crude product was purified by column chromatography.

Supporting Information (see footnote on the first page of this article): Experimental procedures and copies of the ^1H NMR spectra of all products.

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