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Alkaline-Earth Metal Catalyzed Dehydrative Allylic Alkylation

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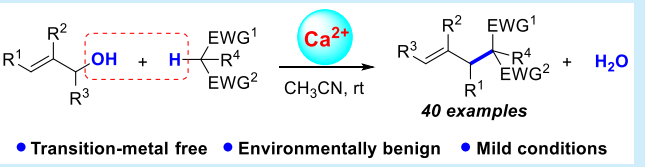
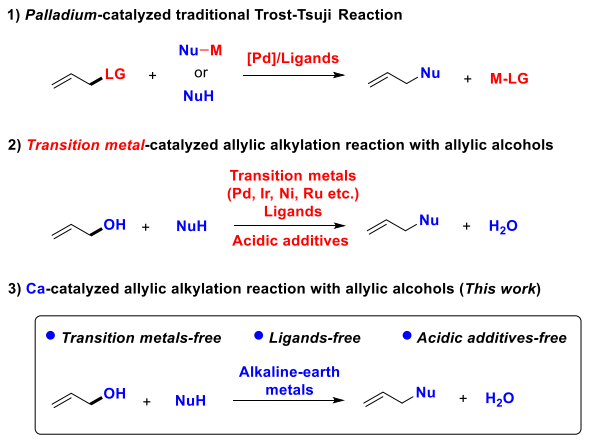
Supporting Information

ABSTRACT: An alkaline-earth metal catalytic system for environmentally benign allylic alkylation was developed. Allylic alcohols can be utilized directly at room temperature in this transition-metal-free process, producing water as the only byproduct. A variety of allylic compounds, including the ones containing all-carbonyl quaternary centers, can be obtained with high yields.



The development of organic transformations that utilize inexpensive, innocuous, transition-metal-free, and readily available feedstock to reduce the economic and environmental impact continues to be one of the major goals in organic synthesis.[1] In recent decades, the palladium-catalyzed allylic alkylation of carbon nucleophiles with allylic halides or their equivalents[2] (Scheme 1, 1) has been widely used by the synthetic community.[3] Taking waste minimization and sustainability into account, the direct substitution of allylic alcohols via dehydrative cross-coupling is highly sought-after and represents a much greener, atom- and step-economical approach (Scheme 1, 2).[4] However, it is challenging to break the inherently strong C−O bond of C−OH by using palladium.[4,5] Until now, transition metals (Pd,[6] Au,[7] Ir,[8] Ru,[9] Ni,[10] etc.[11]), external activators, such as Brønsted or Lewis acids, and even high temperature were required to promote the allylation of specific substrates. Despite these important advances, the dehydrative cross-coupling reaction still needs to be optimized to overcome the dependence on transition metals and limited nucleophile/allylic alcohol copartners.

Scheme 1. Metal-Promoted Allylic Alkylation



In light of our interest in the development of greener and more practical organic transformations,[12] we turned our attention to the dehydrative cross-coupling of allylic alcohols with 1,3-dicarbonyl compounds under transition-metal-free conditions. The alkaline-earth metals exhibited robust catalytic activity[13,14] for hydrogenation,[14a] hydroamination,[14b] and Friedel−Crafts-related cationic cycloaddition[15] and proved to be promising reagents for the C−OH bond activation. We envisioned that the interaction between calcium salts and allylic alcohols might enable the C−OH bond dissociation supplying calcium hydroxide, which might then function as a base, promoting the cross-coupling process. This approach would be one of the most efficient and environmentally friendly ways to achieve allylic alkylation of nucleophiles by using allylic alcohols (Scheme 1, 3).

Initially, the allylic alcohol **1a** (methyl 2-(hydroxy(phenyl)-methyl)acrylate) and the 1,3-dicarbonyl compound **2a** (ethyl 2-oxocyclopentane-1-carboxylate) were selected as the model substrates to investigate the dehydrative cross-coupling process in the presence of alkaline-earth metal catalysts (Table 1). The calcium salt $Ca(NTf_2)_2$ alone was inefficient at promoting this transformation at room temperature (Table 1, entry 1). A trace amount of (or no) desired product **3a** (ethyl (*E*)-1-(2-(methoxycarbonyl)-3-phenylallyl)-2-oxocyclopentane-1-carboxylate) was detected when the Lewis acidity of calcium was increased by introducing additives such as KPF_6, Et_4NPF_6, Et_4NBF_4, and Bu_4NPF_6 (Table 1, entries 2−5). To our delight, the desired product **3a** was isolated in 75% yield when $Ca(NTf_2)_2$ and PPh_3 were combined (Table 1, entry 6).

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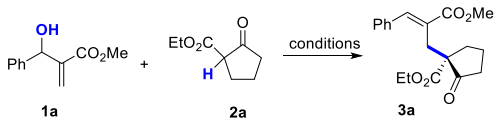
Table 1. Screening Reaction Conditions[a]



1a 2a 3a

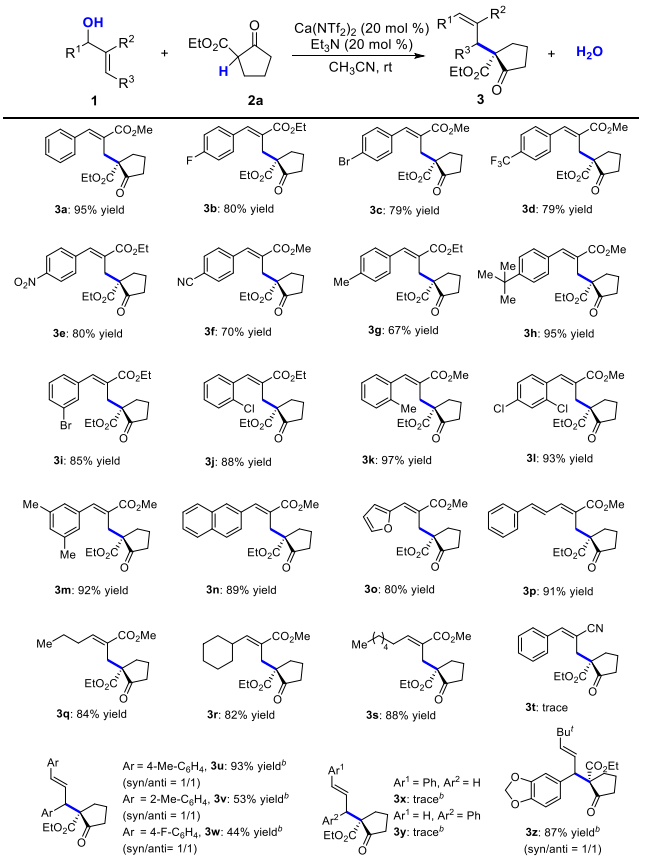
entry	cat.	add.(mol %)	solvent	yield of 3a[d] (%)
1	$Ca(NTf_2)_2$		CH_3CN	0
2	$Ca(NTf_2)_2$	KPF_6 (30)	CH_3CN	9
3	$Ca(NTf_2)_2$	Bu_4NPF_6 (30)	CH_3CN	0
4	$Ca(NTf_2)_2$	Et_4NPF_6 (30)	CH_3CN	0
5	$Ca(NTf_2)_2$	Et_4NBF_4 (30)	CH_3CN	0
6	$Ca(NTf_2)_2$	PPh_3 (30)	CH_3CN	75
7	$Ca(NTf_2)_2$	DABCO (30)	CH_3CN	80
8	$Ca(NTf_2)_2$	DMAP (30)	CH_3CN	74
9	$Ca(NTf_2)_2$	NEt_3 (30)	CH_3CN	90
10	$Ca(NTf_2)_2$	Na_2CO_3 (30)	CH_3CN	trace
11	$Ca(NTf_2)_2$	K_2CO_3 (30)	CH_3CN	38
12	$Ca(OTf)_2$	NEt_3 (30)	CH_3CN	81
13	$CaCl_2$	NEt_3 (30)	CH_3CN	38
14	$Ba(NTf_2)_2$	NEt_3 (30)	CH_3CN	70
15	$Cu(OTf)_2$	NEt_3 (30)	CH_3CN	complex
16[b]	$Ca(NTf_2)_2$	NEt_3 (20)	CH_3CN	95
17[b]	$Ca(NTf_2)_2$	NEt_3 (20)	toluene	81
18[b]	$Ca(NTf_2)_2$	NEt_3 (20)	EtOH	trace
19[b]	$Ca(NTf_2)_2$	NEt_3 (20)	H_2O	trace
20[b]	$Ca(NTf_2)_2$	NEt_3 (20)	DMA[e]	0
21[b]	$Ca(NTf_2)_2$	NEt_3 (20)	DCE	64
22[b]	$Ca(NTf_2)_2$	NEt_3 (20)	dioxane	20
23[b]	$Ca(NTf_2)_2$	NEt_3 (10)	CH_3CN	88
24[c]	$Ca(NTf_2)_2$	NEt_3 (20)	CH_3CN	82
25[c]	$Ca(NTf_2)_2$	NEt_3 (10)	CH_3CN	81
26[b]	$Ca(NTf_2)_2$	NEt_3 (20)	CH_3CN	88
27[b]	$Ca(NTf_2)_2$	NEt_3 (10)	CH_3CN	82
28		NEt_3 (20)	CH_3CN	0
29	TsOH		CH_3CN	0
30	TfOH		CH_3CN	0
31	$HNTf_2$		CH_3CN	0

[a]Allyl alcohols **1** (0.3 mmol) and **2** (0.36 mmol) were dissolved in solvent (2.0 mL) in a Schlenk tube (10 mL); catalyst (30 mol %) and additive were then added subsequently. The reaction was stirred at 30 °C for 48 h. [b]Catalyst (20 mol %) was used. [c]Catalyst (10 mol %) was used. [d]Isolated yields. [e]DMA = $MeCONMe_2$.

Screening other cocatalysts revealed that NEt_3 was better than DABCO or DMAP (Table 1, entries 7–9). Interestingly, a much lower yield was obtained when NEt_3 was replaced by an inorganic base, such as Na_2CO_3 or K_2CO_3 (Table 1, entries 10 and 11). In addition to $Ca(NTf_2)_2$, other alkaline-earth metal catalysts, such as $CaCl_2$, $Ca(OTf)_2$, and $Ba(NTf_2)_2$, can promote this transformation, albeit with a lower yield (Table 1, entries 12–14). However, the traditional strong Lewis acid $Cu(OTf)_2$ was not a suitable catalyst for this reaction under identical conditions (Table 1, entry 15). The reaction was solvent-sensitive, disfavoring protic solvents such as alcohols or water (Table 1, entries 16–18). Other solvents, such as toluene or DCE, promoted the formation of **3a** in moderate to high yield (Table 1, entries 19 and 20). The desired product was obtained in a notably low yield when 1,4-dioxane or DMSO was used (Table 1, entries 21 and 22). Decreasing the catalyst load to 10 mol % had a limited effect on this transformation (Table 1, entries 16, 23–27). In the control experiments, neither calcium nor Et_3N alone could promote this reaction effectively (Table 1, entries 1, 28). In the tested case, the Brønsted acid such as TsOH, TfOH or $HNTf_2$ was also inefficient (Table 1, entries 29–31).

Next, the scope of this transformation was investigated under the optimized conditions. As shown in Scheme 2,

Scheme 2. Dehydrative Cross-Coupling of Allylic Alcohols[a]



[a]Experimental conditions: **1** (0.30 mmol), **2** (1.2 equiv, 0.36 mmol), $Ca(NTf_2)_2$ (20 mol %, 0.06 mmol), and Et_3N (20 mol %, 0.06 mmol) were dissolved in CH_3CN (2.0 mL) and then stirred at 30 °C for 27–72 h. Isolated yields. [b]**2** (1.5 equiv, 0.45 mmol) was used at 80 °C for 24 h.

various Morita–Baylis–Hillman (MBH) alcohols were compatible with these reaction conditions and delivered the corresponding allylic compounds in good to excellent yield. The electronic properties of the phenyl ring on the allylic alcohols were also studied. Both electron-withdrawing (**3a**–**3f**) and electron-donating groups (**3g**, **3h**) on the phenyl ring were tolerated. For instance, even the trifluoromethyl (**3d**), nitro (**3e**), and cyano (**3f**) groups were amenable to this protocol. The sterically demanding MBH alcohols also afforded **3h** in excellent yield. The substituent position (*ortho*, *para* or *meta*) had limited effect on the yield. The multisubstituted compounds were also able to undergo this transformation. MBH alcohols with a fused-aromatic ring (**3n**), and a furan-2-yl group (**3o**) reacted with **2a** to deliver the corresponding products in high yields. In addition, a 1,3-diene skeleton (**3p**) could be easily obtained by selecting ethyl (*E*)-3-hydroxy-2-methylene-5-phenylpent-4-enoate as the starting material. In addition to the aromatic substituted compounds, both cyclic and straight-chain alkyl-substituted MBH alcohols were suitable substrates, affording **3q**–**3s** in high yields. Allylic

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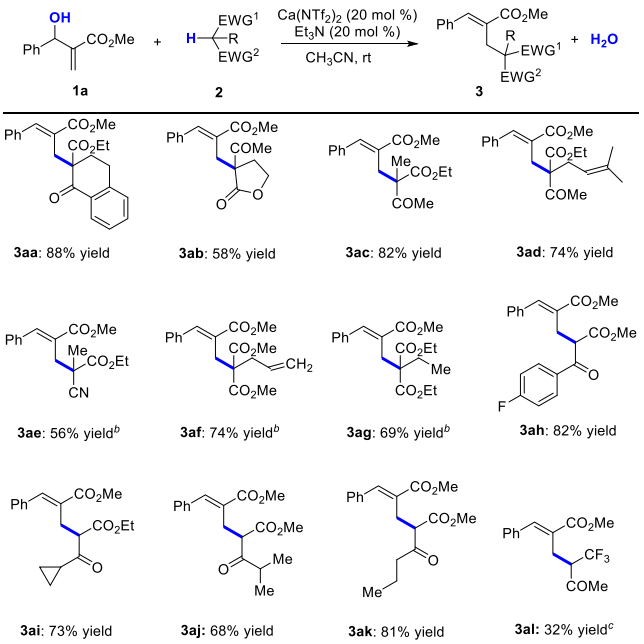
alcohols with β-cyano substituents did not work well, which indicated that the ester group on the MBH alcohol skeleton was important for this process (**3t**). In addition to the MBH alcohols, other allylic alcohols, such as (*E*)-1,3-diarylprop-2-en-1-ol, with either electron-withdrawing or electron-donating aryl substituents, were screened (**3u**–**3w**); these compounds were also able to undergo this transformation, although higher temperature was required. In this case, the reaction was sensitive to steric hindrance (**3u** and **3v**) and electronic properties of the aryl group (**3u** and **3w**). For **3u**–**3w**, mixtures of two diastereomers (the ratio of *syn*/*anti* isomers is about 1/1) were generated. Under the identity conditions, 1,1-diphenylprop-2-en-1-ol and (E)-3-phenylprop-2-en-1-ol only can delivered a trace amount of the desired product (**3x** and **3y**). Remarkably, the anticonvulsant drug stiripentol (diacomit; ME-2080) could also be easily modified using this method (**3z**). In all of the tested case, the final products **3a**–**3w**, **3z** were detected only with *E*-configuration.

Further experiments were conducted to explore the nature of the nucleophiles that can be used under the optimized conditions (Scheme 3). A large variety of cyclic and acyclic β-ketoesters were found to be suitable substrates for this protocol (**3aa**–**3ad**). Thus, all-carbon quaternary centers with various substituents could be constructed effectively. The reaction with ethyl 2-cyanopropanoate also proceeded smoothly to deliver the corresponding product (**3ae**) in moderate yield. These results revealed that the carbonyl group of **2** was not crucial for this transformation. Notably, malonate ester derivatives were also excellent substrates for this transformation (**3af**, **3ag**). In addition to ethyl 2-oxocyclopentane-1-carboxylate **2a**, a variety of β-ketoesters, bearing both aryl (**3ah**) and alkyl (**3ai**–**3ak**) substituents, were proved to be valuable substrates for this allylic alkylation process. It should be noted that the trifluoromethyl group could also be incorporated into the corresponding product by selecting 4,4,4-trifluorobutan-2-one as the nucleophile source, although **3al** was isolated in lower yield.

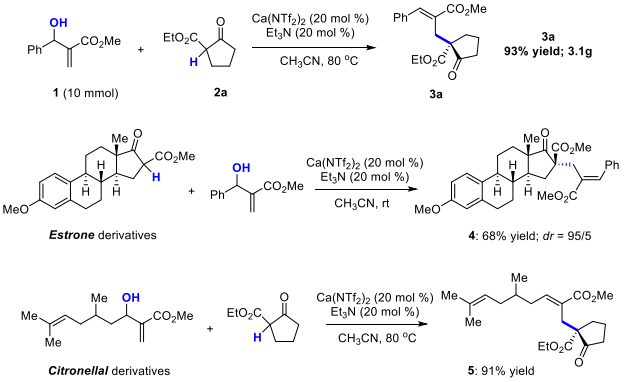
Scheme 3. Dehydrative Cross-Coupling with Carbonic Nucleophiles (NuH)[a]



[a]Experimental conditions: **1** (0.30 mmol), **2** (1.2 equiv, 0.36 mmol), $Ca(NTf_2)_2$ (20 mol %, 0.06 mmol), and Et_3N (20 mol %, 0.06 mmol) were dissolved in CH_3CN (2.0 mL) and then stirred at 30 °C for 24–48 h. Isolated yields. [b]At 80 °C. [c]At 60 °C.

Calcium-catalyzed allylic alkylation could be performed on a 10 mmol scale and deliver the desired product **3a** in 93% yield (3.1 g). Remarkably, *estrone* derivatives could readily react with allylic alcohols (**4**). For allylic alcohols with adjacent C–H bonds, the competitive self-dehydration process that delivered 1,3-dienes presented a very challenging organic synthesis task. A *citronellal* derivative could also react with **2a** to afford the corresponding product **5** in good yield. Our results revealed that this novel dehydrative allylic alkylation methodology can enhance organic transformations and pharmaceutical molecule modifications (Scheme 4).

Scheme 4. Gram-Scale Reaction and Preliminary Protocol Applications[a]



The detailed reaction mechanism still remained unclear. Based on the solvent effect observations (Table 1, entries 16–22), we preliminarily came to the conclusion that hydrogen bonding and coordination might be important for this transformation. Based on the essential role of the cooperative catalytic system, we propose the following mechanism (Figure 1). The reaction may proceed via a dual activation model, in which both the 1,3-dicarbonyl compound and allylic alcohol form coordination complexes with calcium and generate intermediates **A** and **B**, respectively. In intermediate **A**, the participation of both calcium and the amine could help stabilize formation of the enol tautomer of the nucleophiles. In the presence of a protic solvent, the hydrogen bond that forms between the protic solvent hydrogen and the amine prevents the generation of **A**. On the other hand, the sluggish C–OH bond of allylic alcohol is activated by calcium through coordination (intermediate **B**), which facilitates the subsequent allylic nucleophilic substitution, affording the final

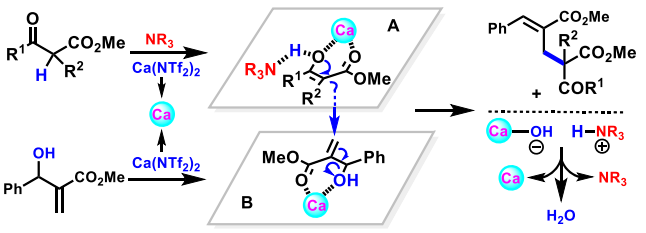


Figure 1. Proposed allylic alkylation mechanism.

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product **3a** with water as the only byproduct. In contrast, the oxygen atom of the solvent (1,4-dioxane or DMSO) fully coordinates to calcium and might result in catalyst deactivation. In addition, the carbocation process, especially for the 1,3-diaryl alcohols, can not be completely ruled out. For instance, the regioselectivity is poor and four isomers (α,γ-selectivity and syn/anti isomers) can be detected by ^{1}H NMR when (*E*)-3-(4-fluorophenyl)-1-phenylprop-2-en-1-ol was selected as the substrate.

In summary, we have developed a dehydrative cross-coupling transition-metal- and halogen-free allylic alkylation protocol. The developed calcium catalytic system can directly and reliably incorporate allylic alcohols at room temperature, thus enabling this reaction to proceed in an environmentally benign manner while producing only water as a byproduct. The all-carbon quaternary centers with different allylic substituents can be isolated in good to excellent yields, and a wide-spectrum of functional groups is tolerated. This investigation also sheds light on alkaline-earth metal catalysis with respect to the dehydrative cross-coupling process, although at this stage, only the MBH alcohols and some activated versions can be used.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b03730.

Experimental procedures, screening reaction conditions, analytical data for all new compounds, and NMR spectra of products (PDF)

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Notes

The authors declare no competing financial interest.

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