

Activation of Alcohols with Carbon Dioxide: Intermolecular Allylation of Weakly Acidic Pronucleophiles

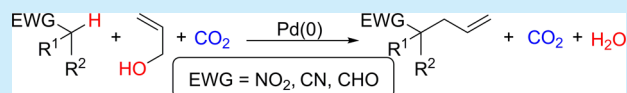
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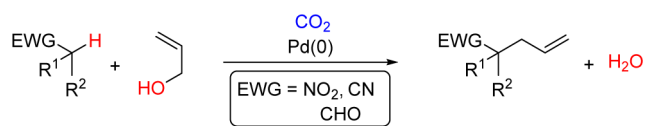
Supporting Information

ABSTRACT: The direct coupling of allyl alcohols with nitroalkanes, nitriles, and aldehydes using catalytic Pd(PPh₃)₄ has been accomplished via activation of C–OH bonds with CO₂. The *in situ* formation of carbonates from alcohols and CO₂ facilitates oxidative addition to Pd to form reactive π -allylpalladium intermediates. In addition, the formation of a strong base activates nucleophiles toward the reaction with the π -allylpalladium electrophile. Overall, this atom economical reaction provides a new C–C bond without the use of an external base and generates water as the only byproduct.



Allylic alcohols are intriguing surrogates to traditional activated electrophiles used in transition-metal-catalyzed allylation reactions due to their wide availability, facile synthesis, and low toxicity. The condensation of an alcohol with a C–H bond to eliminate water and form a new C–C bond is topologically obvious in addition to being step and atom economical.¹ However, alcohols often possess low reactivity because the C–O bond is strong and hydroxide is a poor leaving group.² This challenge has resulted in the development of methods utilizing Lewis^{3,4} or Brønsted acids⁵ to activate allylic alcohols toward coupling with a variety of substrates. We sought to find a straightforward method using relatively benign reagents to activate allyl alcohols directly toward the allylation of weakly acidic pronucleophiles.⁶ Herein we report an *in situ* activation of allylic alcohols with CO₂ that simultaneously generates active electrophiles and a requisite base to activate pronucleophiles (Scheme 1).

Scheme 1. CO₂-Catalyzed Allylation

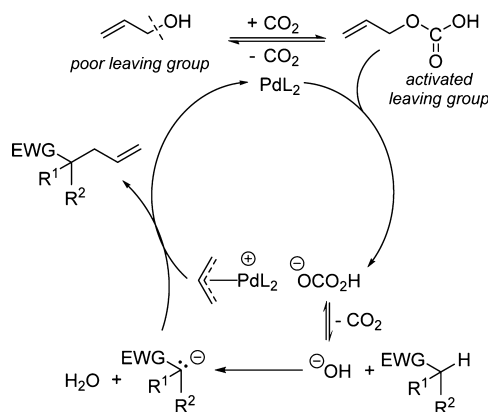


Since it is known that alcohols react reversibly with carbon dioxide to form carbonic acids and carbonates *in situ*,⁷ CO₂ should activate alcohols toward transition-metal-catalyzed allylic alkylation reactions. Importantly, Yamamoto has demonstrated that CO₂ can activate allyl alcohols toward substitution; however, the C–C bond formation was limited to highly stabilized malonate-like enolates (pK_a ~11–14 in DMSO).^{8,9} Using these initial results as inspiration, we sought to develop a synthetically useful method for the intermolecular

allylation of weakly acidic nucleophiles such as nitroalkanes, nitriles, and aldehydes.

Based on Yamamoto's findings we imagined that nucleophilic attack of the allyl alcohol on CO₂ would form an allyl carbonate that is activated toward oxidative addition (Scheme 2).

Scheme 2. Proposed CO₂-Catalyzed C–O Bond Activation



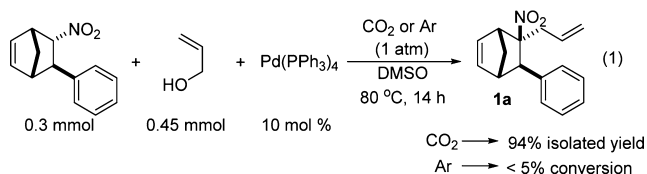
Decarboxylation of the resulting bicarbonate to generate CO₂ and hydroxide might allow deprotonation of even weakly acidic C–H bonds to activate pronucleophiles.¹⁰ Subsequent nucleophilic attack on the palladium π -allyl complex is expected to form a new C–C bond and regenerate the active catalyst while producing water as the only byproduct.

An initial screen of reaction conditions revealed that the use of a polar aprotic solvent, Pd(PPh₃)₄, and 1 atm of CO₂ heated in a sealed vial overnight afforded **1a** in good yield (eq 1).

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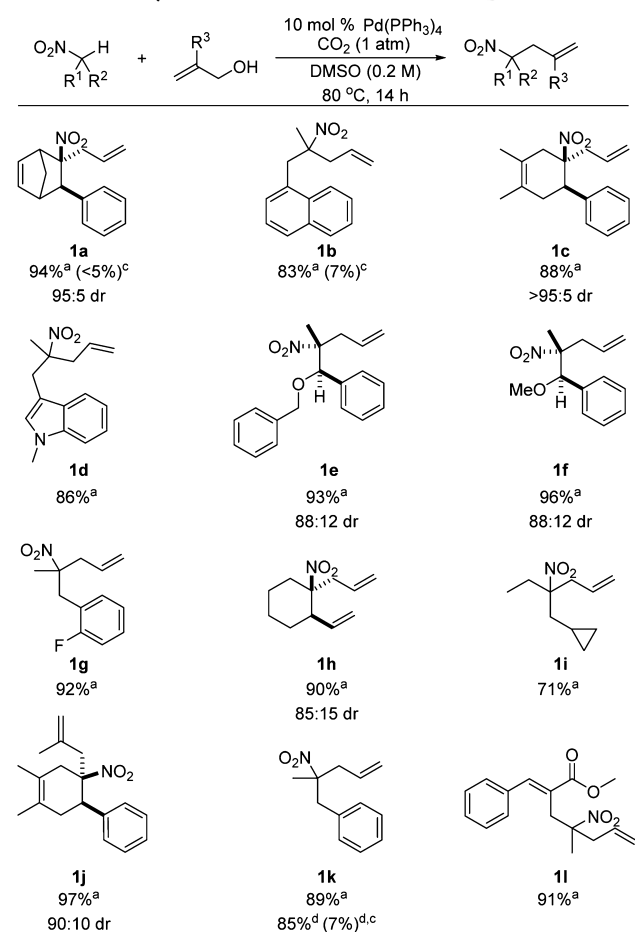
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When the CO₂ was replaced with argon no appreciable amount of **1a** was detected by ¹H NMR spectroscopy of the crude reaction mixture.



To investigate the substrate scope, the aforementioned reaction conditions were applied to the reactions of other nitroalkanes (Scheme 3). Under these conditions, a variety of substrates that were readily derived from Diels–Alder,¹¹ Baylis–Hillman,¹² and Henry¹³ reactions were allylated in good to excellent yields.

Scheme 3. Allylation of Nitroalkanes via CO₂ Activation^{a,b}



^aNitroalkane (0.3 mmol) and allyl alcohol (0.45 mmol) in 1.75 mL of DMSO under 1 atm of CO₂. ^b Isolated yields. ^c Ar replaced CO₂ (% conversion via crude ¹H NMR). ^d Allyl alcohol (0.9 mmol), 160 °C, 20 min in a microwave reactor.

Both cyclic and acyclic nitroalkanes were activated by the standard reaction conditions. A variety of functional groups including olefins (**1a,c,h**), an α,β -unsaturated ester (**1l**), ethers (**1e,f**), and indole (**1d**) were compatible with the reaction conditions. Good to excellent diastereoselectivities were observed with cyclic nitroalkanes (**1a,c,h,j**). In addition, 1,2-stereocontrol was good even with acyclic nitroalkanes bearing

β -ethers (**1e,f**). Allylation also occurred in high yield directly from β -methallyl alcohol (**1j**).

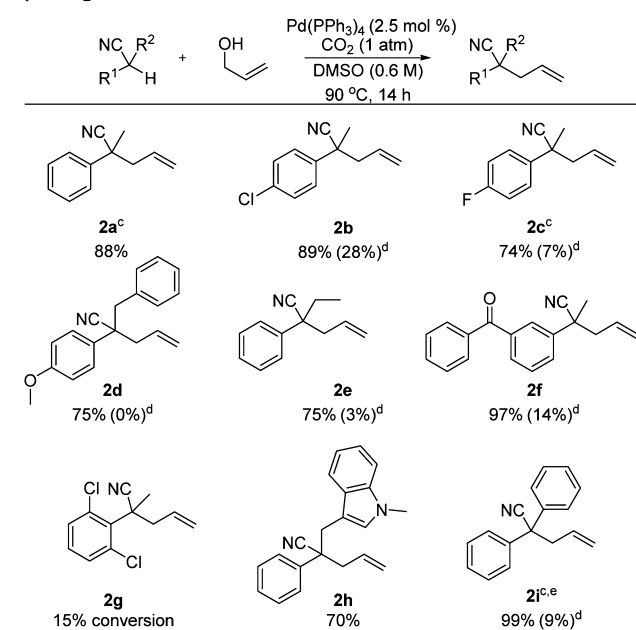
Unfortunately, allyl alcohols such as prenyl and crotyl alcohol which bear alkyl substituents were not compatible with the standard reaction conditions.

Lastly, the allylation could be performed in just 20 min under microwave irradiation, although additional equivalents of alcohol were required (**1k**). Again, replacing CO₂ with Ar under microwave conditions did not produce significant quantities of the desired product.

While it was exciting that nitroalkanes could be allylated in high yield under conditions of CO₂ activation, nitroalkanes are relatively acidic (pK_a ~17 in DMSO).¹⁴ To probe the strength of the base generated *in situ* under our reaction conditions, we turned our attention toward the allylation of tertiary nitriles (pK_a ~23–25 in DMSO).¹⁵

To begin, the reaction scope was explored utilizing commercially available nitriles as well as those synthesized via methylation, benzylation, or Knoevenagel condensation (Scheme 4). As with the nitroalkanes, CO₂ activation allowed

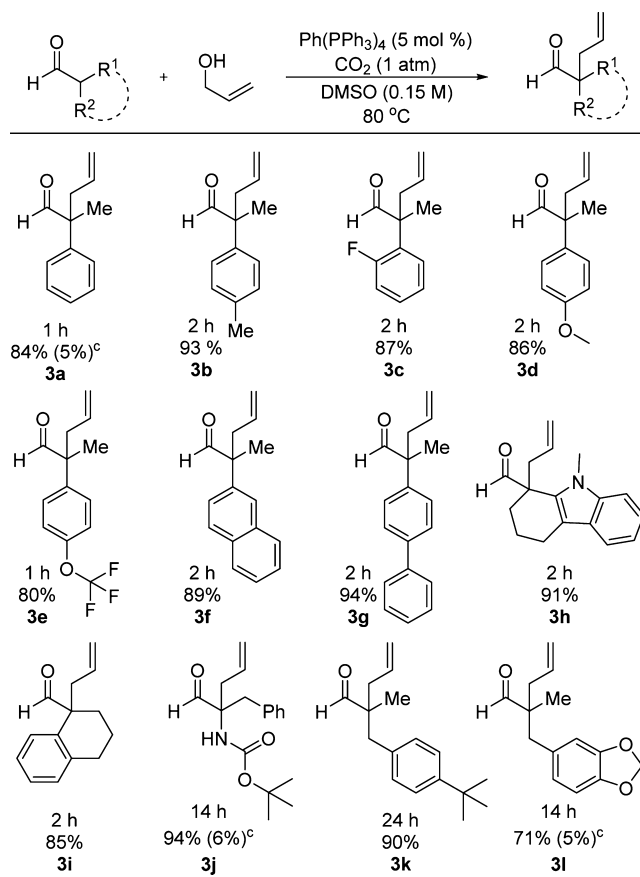
Scheme 4. Allylation of Nitriles with Allyl Alcohol Activated by CO₂^{a,b}



^aNitrile (0.3 mmol) and allyl alcohol (0.6 mmol) in 0.5 mL of DMSO under 1 atm of CO₂. ^b Isolated yields. ^c 2 mL of DMSO used. ^d Ar replaced CO₂ (% conversion via GC/MS). ^e Reaction at 80 °C.

the allylation of a variety of nitriles in high yield. The method was found to tolerate halogens (**2b,c**), aryl ether (**2d**), ketone (**2f**), and indole substituents (**2h**). However, allylation of a sterically congested ortho-disubstituted nitrile was unsuccessful under the given reaction conditions (**2g**). Further, a more acidic diarylalkyl nitrile substrate was successfully allylated at a lower reaction temperature (80 °C) and resulted in a higher isolated yield (**2i**). Lastly, when argon replaced the CO₂ atmosphere, a significant decrease in yield was observed (0%–28%, entries **2b–2f** and **2i**) thus supporting the requirement of CO₂ as an *in situ* activator of allyl alcohol for nucleophilic allylation.

Aldehydes, which are prone to aldol dimerization, were also allylated in high yield utilizing similar conditions (Scheme 5).¹⁶

Scheme 5. Allylation of Aldehydes^{a,b}

^aAldehyde (0.30 mmol) and alcohol (0.45 mmol) in 2.0 mL of DMSO under 1 atm of CO₂. ^b Isolated yields. ^c Ar replaced CO₂ (% conversion via GC/MS).

Acyclic (3a–3g) and cyclic (3h, 3i) α -aryl aldehydes bearing various electron-donating (*p*-Me, *p*-OMe) and -withdrawing (*o*-F, *p*-OCHF₃) groups reacted quickly (1–2 h) and gave high yields of allylated products. Substrates with α -benzyl substituents (3k, 3l), including a protected amino aldehyde (3j), required longer reaction times but still provided good yields of product. Control reactions again revealed that a CO₂ atmosphere was required for good reactivity.

Next, the scope of the reaction of nitriles and aldehydes with substituted allylic alcohols was examined. Gratifyingly, except for the prenyl alcohol (4i), isolated reaction yields with substituted allylic alcohols were found to be comparable to those utilizing the unsubstituted allyl alcohol (Table 1). Both alkyl and aryl substituted allylic alcohols provided the allylated products in good to excellent yields with generally good selectivity for formation of the linear allyl regioisomer.¹⁷ One exception is crotyl alcohol, which showed only slight selectivity for the linear *trans* product (4c);¹⁸ this selectivity was significantly enhanced upon increasing the substituent size to ethyl or propyl (4d, 4e). The linear selectivity of the CO₂-activated intermolecular variant is thought to arise from an outer-sphere C-allylation mechanism, and the observed increase in *trans* selectivity with substituent size may be attributed to a higher bias for the *syn*-palladium π -allyl intermediate.¹⁹

In conclusion, we have shown that CO₂ can activate allyl alcohols toward oxidative addition of palladium. In addition to activating the alcohol, the conditions provide a base strong

Table 1. Scope of Allyl Alcohols^{a,b}

Substrate	Alcohol	Product	Yield	I:b
Ph-CH ₂ -CN	CH ₂ =CH-CH ₂ -OH	4a ^b	94%	--
Ph-CH ₂ -CN	Ph-CH=CH-OH	4b ^b	79%	--
Ph-CH ₂ -CN	CH ₂ =CH-CH(OH)-Me	4c ^{b,c}	73%	2:1
Ph-CH ₂ -CN	CH ₂ =CH-CH(OH)-Et	4d	99%	10.5:1
Ph-CH ₂ -CN	CH ₂ =CH-CH(OH)-Pr	4e ^d	99%	11.2:1
Ph-CH ₂ -CN	CH ₂ =CH-CH(OH)-Ph	4f	94%	>95:5
Ph-CH ₂ -CN	Ph-CH=CH-OH	4g	79%	>95:5
Ph-CH ₂ -CN	CH ₂ =CH-CH(OH)-Me	4h ^e	99%	1.4:1
Ph-CH ₂ -CN	CH ₂ =CH-CH(OH)-Me	4i ^f	0%	--
H-CH ₂ -CN	CH ₂ =CH-CH ₂ -OH	4j	77%	--
H-CH ₂ -CN	CH ₂ =CH-CH(OH)-Et	4k	79%	93:7
H-CH ₂ -CN	CH ₂ =CH-CH(OH)-Ph	4l	79%	86:14
H-CH ₂ -CN	BnO-CH ₂ -CH=CH-OH	4m ^g	73%	>95:5
H-CH ₂ -CN	Ph-CH=CH-OH	4n ^h	70%	>95:5
H-CH ₂ -CN	pCF ₃ -Ph-CH=CH-OH	4o ⁱ	79%	>95:5

^aNitrile (0.3 mmol) and allylic alcohol (0.6 mmol) in 2 mL of DMSO under 1 atm of CO₂. ^bReaction at 90 °C in 0.5 mL of DMSO. ^c1:2.5 (cis/trans). ^d1:14.3 (cis/trans). ^e1:4.6 (cis/trans). ^fReaction time 4 h. ^gReaction time 19 h. 1:5.3 (cis/trans). ^hReaction time 8 h; a 23% conversion in the control reaction was observed. ⁱReaction time 7 h.

enough to activate weakly acidic pronucleophiles with a pK_a up to ~25. Thus, CO₂ participates in both the activation of the electrophile and the nucleophile toward C–C bond formation.

Ultimately, the combination of palladium catalysis with CO₂ activation allows the substitution of allylic alcohols by nitroalkanes, nitriles, and aldehydes and produces water as the only byproduct.

■ ASSOCIATED CONTENT

■ Supporting Information

Experimental procedures, ¹H, ¹³C, ¹⁹F NMR spectra, and characterization data of all novel products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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