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Additive-Free Decarboxylative Coupling of Cinnamic Acid Derivatives in Water: Synthesis of Allyl Amines

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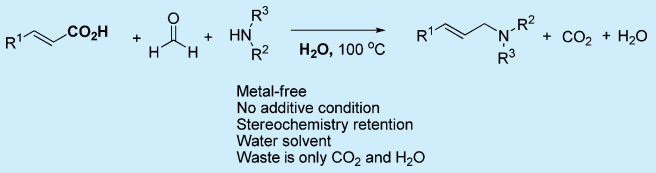
Supporting Information

ABSTRACT: The first example of an additive-free decarboxylative coupling of cinnamic acid derivatives with formaldehyde and amines to afford the corresponding allyl amines is reported. This reaction is highly environmentally friendly because it was conducted in H_2O and without any additives, releasing only CO_2 and H_2O as byproducts. This reaction showed a broad substrate scope including cyclic and acyclic amines and high functional group tolerance. Moreover, phenyl dienoic acid participated in this type of decarboxylative coupling reaction.



Development of an environmentally friendly synthetic method has received much attention in the pharmaceutical and chemical industries because it is ultimately cost-effective.[1] Although a number of green processes have been developed, the disposal of solvent and contaminated water derived from workup processes is still of significant concern.[2] One ideal solution involves developing a reaction that conducts in water-based solvent and releases nontoxic waste.[3] Water is the most inexpensive, nonflammable, and nontoxic solvent.[4] To reduce waste, no additive reaction conditions are required.[5] To meet this demand, we report an extremely green and simple method for the synthesis of allyl amines in water and additive-free conditions.

Allyl amine is one of the most important scaffolds in pharmaceutical and natural products.[6] For example, Naftifine,[7] Cinnarizine,[8] Triprolidine,[9] and Abamine[10] containing this scaffold are used as antifungal, antihistamine, and calcium channel blocker drugs (Figure 1). In addition, it is a preferable

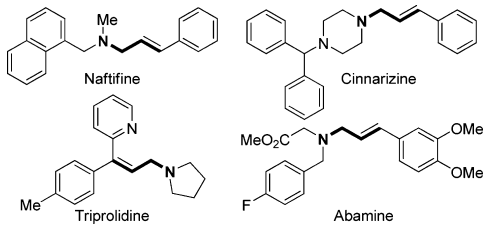


Figure 1. Bioactive compounds having allyl amine structure.

platform for the preparation of nitrogen containing molecules by the isomerization to vinyl amines,[11] intramolecular olefin cross-metathesis to form *N*-heterocyclic compounds,[12] and reduction[13] or oxidation.[14]

A number of preparation methods of allyl amines has been reported. As classical methods, the nucleophilic substitution of allyl alcohol or halides with amines have been widely used (Figure 2a).[6,15] However, they have some drawbacks such as the

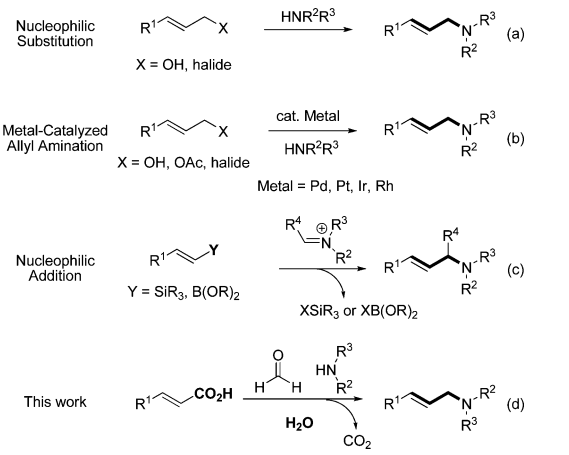


Figure 2. Synthesis of allyl amines.

requirement of harsh conditions and low functional group tolerance. To solve these problems, transition metals such as Pd-, Ir-, Pt-, and Rh-catalyzed allyl aminations have been developed (Figure 2b).[16] Recently, coupling reaction by C−H activation was also employed to construct ally amines.[17] Although these methods afforded an efficient synthetic tool under mild conditions, they all need a metal catalyst. As metal-free conditions, nucleophilic additions of vinyl boronic acid or electrophilic substitution of vinyl silane to imine or iminium were developed (Figure 2c).[18] However, these methods still need expensive vinyl boronic acid or silane as an alkene source. As a part of our ongoing effort in decarboxylative coupling,[5d,19] we found that allyl amines were formed from the reaction with cinnamic acid derivatives, formaldehyde, and amines in the absence of any additives. This finding would address all previous

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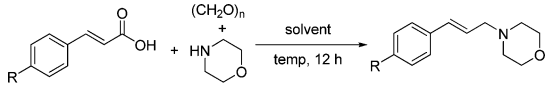
issues. Our reaction method has several advantages. Cinnamic acid derivatives are an abundant and stable source of alkene. In addition, they released only environmentally nontoxic CO_2 after completing reaction.[20] Neither metal catalyst nor any additives are needed. Moreover, this reaction proceeded in H_2O. This is the first report of metal-free decarboxylative coupling of sp^2 carbon to construct carbon−carbon bonds.

To optimize additive-free conditions, cinnamic acid (**1a**) was allowed to react with paraformaldehyde and morpholine (**2a**) under a variety of solvent. As shown in Table 1, most organic

Table 1. Decarboxylative Coupling of 4-Methoxy-cinnamic Acid with Formaldehyde and a Variety of Amines[a]



1 2a 3

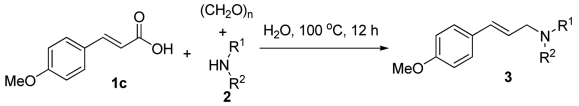
entry	1	R	solvent	temp (°C)	product	yield (%)[b]
1	**1a**	H	MeCN	80	**3aa**	0(96)[c]
2	**1a**	H	DMF	100	**3aa**	0(97)[c]
3	**1a**	H	DMSO	100	**3aa**	0(97)[c]
4	**1a**	H	EtOH	80	**3aa**	0(83)[c](11)[d]
5	**1a**	H	H_2O	100	**3aa**	10(81)[c]
6	**1b**	Me	H_2O	100	**3ba**	35(61)[c]
7	**1c**	OMe	H_2O	100	**3ca**	86(13)[c]
8	**1c**	OMe	H_2O	120[e]	**3ca**	86(13)[c]

[a]Reaction conditions: **1** (0.36 mmol), $(CH_2O)_n$ (0.36 mmol), and **2a** (0.3 mmol) were reacted in solvent (1.0 mL) at 100 °C for 12 h. [b]GC yields. [c]Yields of the cinnamic acid derivatives recovered after reaction complete. [d]Yield of ethyl cinnamate. [e]The reaction at the sealed tube reactor.

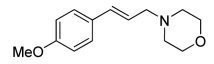
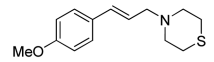
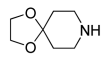
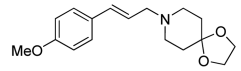
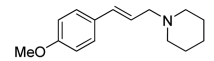
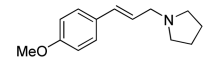
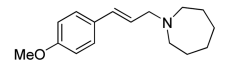
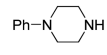
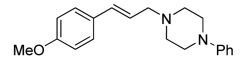
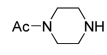
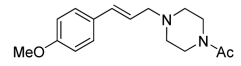
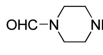
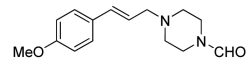
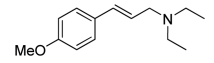
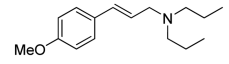
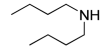
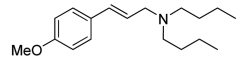
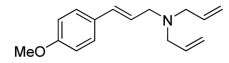
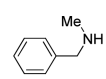
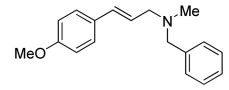
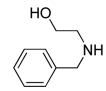
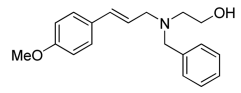
solvents did not give the desired product (entries 1−4). Under EtOH solvent, ethyl cinnamate was formed with 11% yield without any formation of allyl amine **3aa** (entry 4). Replace of water as solvent afforded the allyl amine product **3aa** with 10% yield (entry 5). Reaction with 4-methylcinnamic acid (**1b**) provided the corresponding product **3ba** with 35% yield (entry 6). Surprisingly, 4-methoxycinnamic acid (**1c**) afforded the corresponding allyl amine **3ca** with 86% yield (entry 7). When the reaction was carried out at 120 °C, the yield was 86% (entry 8)

To evaluate this metal-free coupling reaction in water, the coupling reactions of **1c** and formaldehyde with diverse amines were investigated (Table 2). Cyclic amines such as morpholine (**2a**), thiomorpholine (**2b**), 1,4-dioxa-8-azaspiro[4.5]decane (**2c**), piperidine (**2d**), pyrrolidine (**2e**), and azepane (**2f**) afforded the corresponding allyl amines in 53−86% yields (entries 1−6). The reaction with 1-phenylpiperazine (**2g**) afforded the corresponding product in poor yield (entry 7). However, 1-acetylpiperazine (**2h**) and 1-formylpiperazine (**2i**) resulted in good yields (entries 8 and 9). The reactions of acyclic diamines such as *N*,*N*-diethyl and *N*,*N*-dipropyl amines also afforded the corresponding products in 63% and 64% yields, respectively (entries 10 and 11). However, *N*,*N*-dibutyl and *N*,*N*-allyl amines resulted in slightly low yields (entries 12 and 13). When **2l** was reacted in the presence of phase transfer catalyst, the yield was increased to 53% (entry 12). The reactions of *N*-benzylmethylamine (**2n**) and 2-benzylaminoethanol (**2o**) afforded the corresponding products in good yields (entries 14 and 15). In particular, **2o** with an aliphatic hydroxyl group gave

Table 2. Decarboxylative Coupling of 4-Methoxycinnamic Acid with Formaldehyde and a Variety of Amines[a]



1c 2 3

entry	amines		product		yield(%)[b]
1		**2a**		**3ca**	86
2		**2b**		**3cb**	82
3		**2c**		**3cc**	61
4		**2d**		**3cd**	63
5		**2e**		**3ce**	60
6		**2f**		**3cf**	53
7		**2g**		**3cg**	31
8		**2h**		**3ch**	74
9		**2i**		**3ci**	79
10		**2j**		**3cj**	63
11		**2k**		**3ck**	64
12		**2l**		**3cl**	31(53)[c]
13		**2m**		**3cm**	46
14		**2n**		**3cn**	81
15		**2o**		**3co**	79

[a]Reaction conditions: **1c** (3.6 mmol), $(CH_2O)_n$ (3.6 mmol), and amines (3.0 mmol) were reacted in H_2O (10.0 mL) at 100 °C for 12 h. [b]Isolated yield. [c]GC yield of the reaction using octadecyl trimethylammonium chloride (0.3 wt % of H_2O) as a PTC.

the desired product in good yield. No desired products were formed when primary amines such as cyclohexylamine or aniline were employed.

To expand the substrate scope of the reaction, diverse cinnamic acid derivatives with electron-donating substituents were employed in the coupling reaction with formaldehyde and amines (Figure 3). The coupling reactions of trimethoxy-substituted cinnamic acids **1e** and **1f** with formaldehyde and

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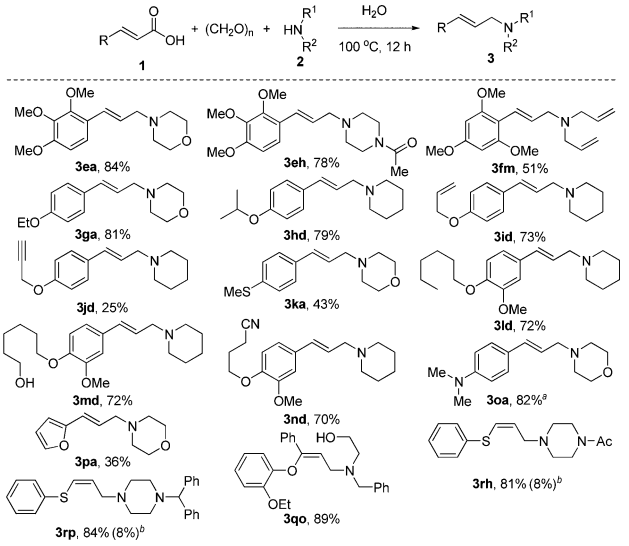

Figure 3. Decarboxylative coupling of substituted cinnamic acids with formaldehyde and amines. Reaction conditions: **1** (3.6 mmol), $(CH_2O)_n$ (3.6 mmol), and **2** (3.0 mmol) were reacted in H_2O (10.0 mL) at 100 °C for 12 h. (a) Reaction time is 3 h. (b) Yield of (*E*)-isomer.

amines such as **2a**, **2h**, and **2m** afforded the corresponding allyl amines **3ea**, **3eh**, and **3fm** in 84%, 78%, and 51% yields, respectively. Cinnamic acids with ethoxy, isopropoxy, and allyloxy groups in the para position afforded the corresponding products in good yields; however, propynyloxy and thiomethoxy groups resulted in slightly lower yields. Caffeic acid derivatives with alkoxy, alcohol, and cyano groups afforded the corresponding allyl amines **3ld**, **3md**, and **3nd** in 72%, 72%, and 70% yields, respectively. The reaction of 4-dimethylamino cinnamic acid (**1o**) for 3 h afforded the corresponding product in 82% yield. However, 3-(2-furan-2-yl)acrylic acid resulted in 36% yield. In contrast, 3,3-disubstituted acrylic acid **1q** afforded the corresponding allyl amine in 89% yield. The stereochemistry of cinnamic acids was retained in the reactions. (*E*)-Cinnamic acids afforded the corresponding (*E*)-allyl amines without the formation of (*Z*)-isomers. The coupling of (*Z*)-phenylthioacrylic acid with formaldehyde and amines such as **2h** and **2p** afforded the corresponding stereo-retention products **3rh** and **3rp**, respectively, as the major products with small amounts of (*E*)-isomers.

To investigate the stereochemistry of this coupling reaction, (*Z*)-cinnamic acid derivatives such as **1c** and **1d** were selected as the coupling substrates and reacted with formaldehyde and amines. As shown in Figure 4, the major stereochemistry of the product was (*Z*) with high ratios (*Z*/*E* = 6.7:1−16.7:1). The coupling reactions with (*Z*)-4-methoxycinnamic acid and amines such as **2a**, **2h**, and **2n** resulted in higher yields than those with (*Z*)-2-methoxycinnamic acid, which is sterically demanding. However, (*Z*)-2-methoxycinnamic acid afforded higher stereoselectivity.

Interestingly, phenyl dienoic acid **4**, which has an additional double bond in the cinnamic acid unit, participated in the decarboxylative coupling reaction with formaldehyde and amines, even though it does not have any substituent at the phenyl group (Figure 5). The coupling reactions of **4** with morpholine, thiomorpholine, and *N*-methyl-*N*-benzylamine afforded the corresponding products in 63%, 55%, and 48% yield, respectively. The coupling reactions with piperidine and

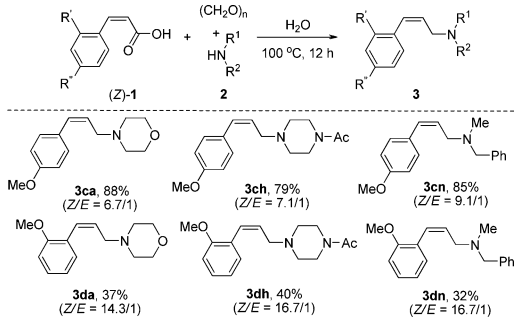

Figure 4. Stereochemistry of the decarboxylative coupling of (*Z*)-cinnamic acid derivatives. Reaction conditions: (*Z*)-**1** (3.6 mmol), $(CH_2O)_n$ (3.6 mmol), and **2** (3.0 mmol) were reacted in H_2O (10.0 mL) at 100 °C for 12 h. The ratio of (*Z*)-**3**/(*E*)-**3** was determined by ^1H NMR.

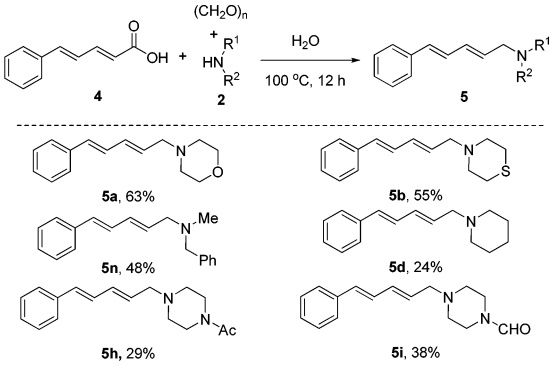

Figure 5. Decarboxylative coupling of phenyl dienoic acid with formaldehyde and amines. Reaction conditions: **4** (3.6 mmol), $(CH_2O)_n$ (3.6 mmol), and **2** (3.0 mmol) were reacted in H_2O (10.0 mL) at 100 °C for 12 h.

piperazines resulted in slightly lower yields. Notably, all the products contained 2−3% of stereoisomeric products.

The effect of electronic substituents on reaction intermediates was evaluated using the Hammett equation (see Supporting Information).[21] The initial rate constants of the reaction with different sets of para-substituted cinnamic acids were correlated using the σp+ values of each substituent, *p*-NMe_2, *p*-OEt, *p*-OMe, *p*-SMe, and *p*-Me, in cinnamic acid. A linear relationship with a negative slope of 1.64 was observed by plotting the rate constants of each reaction, indicating that the rate-determining transition state is more stabilized by electron-donating substituents.

On the basis of the results of the Hammett equation and the retention of stereochemistry of the double bond, we propose a reaction pathway,[8b,22] as shown in Figure 6. (1) Addition of the iminium ion, which is generated by the condensation of paraformaldehyde and amines, to the C−C double bond of cinnamate affords a benzyl carbocation. (2) The carboxylic carbon lies in the same plane as the adjacent vacant p-orbital. (3) The subsequent facile decarboxylation leads to C−C double bond formation and affords the allyl amine as the expected stereospecific product. However, we do not rule out the possibility of forming a lactone as an intermediate in the proposed mechanism.[23]

In summary, a new and simple method for the synthesis of allyl amines was developed by the decarboxylative three-component reaction of cinnamic acids, formaldehyde, and amines. Most importantly, this method is environmentally friendly. This decarboxylative coupling reaction proceeds in water without

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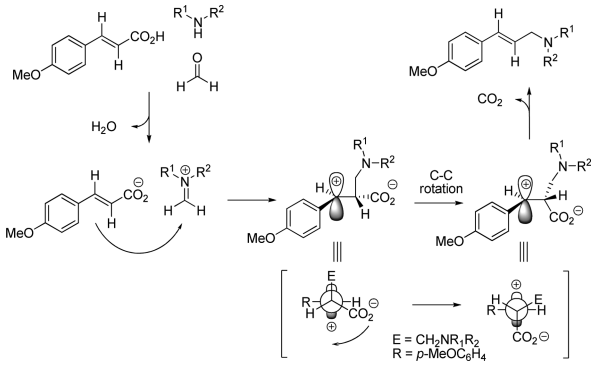

Figure 6. Proposed mechanism.

any transition-metal catalysts or additives and generates nonhazardous wastes such as CO_2 and H_2O. Therefore, the proposed method is cost-effective. Cinnamic acid derivatives are good sources of alkenes because they are abundant and chemically stable. The coupling reaction has a broad substrate scope, including cyclic and acyclic amines, and shows good tolerance to diverse functional groups such as alcohol, ether, thioether, ketone, cyano, allyl, and alkyne. The stereoretention products predominated in the reaction with (*Z*)-cinnamic acid derivatives. Moreover, phenyl dienoic acid participated in this decarboxylative coupling reaction.

■ ASSOCIATED CONTENT

Supporting Information

Hammett correlation; general methods and experimental procedures; and NMR spectra. 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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