

COMMUNICATION

Cu-catalyzed three-component coupling reactions using nitriles, 1,3-dienes and silylboranes

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This paper reports novel Cu-catalyzed three-component coupling reactions using nitriles, 1,3-dienes and silylboranes. The desired reactions proceed at room temperature and yield β,γ -unsaturated ketones with a (dimethylphenylsilyl)methyl moiety at the α -position. Diverse nitriles participate in the reaction and the corresponding products were obtained in good to high yields with high regioselectivity.

The catalytic generation of functionalized nucleophiles followed by trapping with carbon electrophiles is a capable methodology for preparing complex molecules via a carbon-carbon (C-C) bond forming reaction. Conjugated dienes such as 1,2-dienes¹ and 1,3-dienes² are valuable reaction platforms owing to their diverse array of products. Silyl functionalities are highly useful in organic synthesis and achieve a variety of efficient transformations.³ Recently, Cu-catalyzed silylative transformation of 1,2-dienes has been investigated.⁴ We⁵ and other groups^{6,7} found the Cu-catalyzed silylative allylation of carbon electrophiles such as carbon dioxide (CO₂),^{5a} formates,^{5b} aldehydes,^{5c} ketones,^{5c,6} and imines⁷ (Scheme 1a). A key to the transformation is the regioselective addition of silyl copper species⁸ to 1,2-dienes, yielding β -silyl allyl copper intermediates. Addition of copper species to 1,3-dienes is also a method, generating functionalized allyl copper intermediates. Actually, Cu-catalyzed functionalization of 1,3-dienes have been recently reported.^{9–11} However, the control of regioselectivity remains challenging task when simple monosubstituted 1,3-dienes such as isoprene are used as substrates.^{10c,e,f}

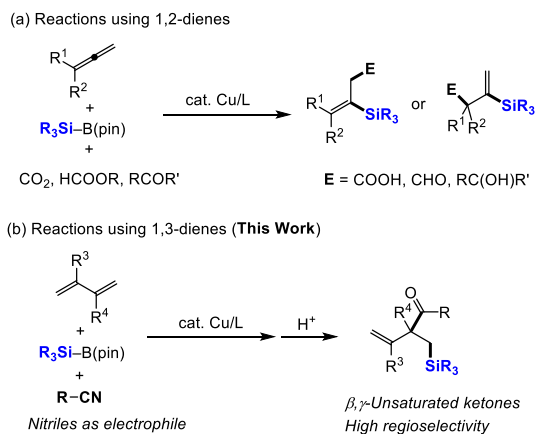
Nitrile is a fundamental organic molecule in organic synthesis.¹² The alkylation of aliphatic nitriles at the α -position is an important methodology for constructing a new C-C bond.¹³ In addition, nucleophilic addition at the carbon atom in CN group is also known as a protocol that yields functionalized imines and ketones via a C-C bond formation.¹⁴ However, in general, the stoichiometric amount of

strong nucleophiles such as Grignard reagents are necessary owing to their stability.¹⁴ Although catalytic acylation using nitriles has been reported,¹⁵ there are several limitations such as intramolecular reactions,^{15b,d} or harsh reaction conditions.^{15c,e} Therefore, the catalytic addition of functionalized nucleophiles to nitriles that yields functionalized imines and ketones remains challenging. In this context, very recently, Hoveyda group has reported Cu-catalyzed enantioselective coupling reactions using 1,2-diene, diborane, and nitriles.¹⁶

Herein we report on catalytic three-component coupling reactions using nitriles, 1,3-dienes, and silylboranes in the presence of copper catalysts (Scheme 1b). The desired reactions proceed at room temperature, and β,γ -unsaturated ketones with a (dimethylphenylsilyl)methyl moiety at the α -position are obtained in good to high yields with high regioselectivity after acidic work-up.

First, the reaction of benzonitrile (**1a**), 2,3-dimethyl-1,3-butadiene (**2a**), and PhMe₂Si-B(pin) was conducted by employing 4.0 mol % of CuOAc and 10 mol % of a ligand in toluene at room temperature (Table 1).¹⁷ Employing PPh₃, the reaction proceeded and β,γ -unsaturated ketones with a (dimethylphenylsilyl)methyl moiety at the α -position (**3a**) was obtained in 88% yield after acidic work-up (entry 1).

Scheme 1 Three-component coupling reactions using conjugated dienes, silylboranes and electrophiles.



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Table 1 Ligand effect on the Cu-catalyzed three-component coupling using benzonitrile (**1a**), 2,3-dimethyl-1,3-butadiene (**2a**) and a silylborane^a

entry	ligand	yield of 3a (%) ^b
1	PPh ₃	88
2	P(3,5-Xy) ₃	99 (83) ^c
3	P(DTBM) ₃	74
4	P(<i>o</i> -Tol) ₃	0
5	PCy ₃	86
6 ^d	xantphos	0
7 ^d	dppbz	0
8 ^e	P(3,5-Xy) ₃	50
9 ^f	P(3,5-Xy) ₃	3
10 ^g	P(3,5-Xy) ₃	4

^a Reaction conditions: benzonitrile (**1a**, 0.40 mmol), 2,3-dimethyl-1,3-butadiene (**2a**, 0.52 mmol, 1.3 equiv), PhMe₂Si-B(pin) (0.52 mmol, 1.3 equiv), CuOAc (4.0 mol %), ligand (10 mol %) in toluene (1.0 mL) at room temperature for 19 h, then HCl aq. was added. ^b Determined by GC and GC-MS analysis. ^c Isolated yield of **3a**. ^d 5.0 mmol of ligand was used. ^e PhCOF was used in place of **1a**. ^f (PhCO)₂O was used in place of **1a**. ^g PhCO₂Me was used in place of **1a**.

Under the reaction conditions, no isomer was detected by analyzing crude reaction mixture using GC-MS and NMR measurements. Tri(3,5-xylyl)phosphine (P(3,5-Xy)₃) resulted in the highest yield, giving **3a** in 99% GC yield (entry 2). From the reaction mixture, pure **3a** was successfully isolated in 83% yield. The use of more bulky tris(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphine (P(DTBM)₃) slightly decreased the yield of **3a** (entry 3). The reaction using a sterically hindered P(*o*-Tol)₃ did not afford **3a** at all (entry 4). Employing PCy₃, **3a** was also obtained in high yield (entry 5). On the other hand, bidentate phosphine ligands such as xantphos and dppbz were not efficient (entries 6 and 7). These phosphines would prevent the coordination of 1,3-diene to Cu center. For catalytic acylation reactions, Riant¹⁸ and our group¹⁹ used acid fluorides and acid anhydrides, respectively, in the Cu-catalyzed bora-acylation of 1,2-dienes. When these reagents were tested instead of **1a**, **3a** was obtained in 50% and 3% yields, respectively (entries 8 and 9). In the latter case, an acylsilane that was formed by the reaction of silylcopper with benzoic anhydride was detected. Esters such as methyl benzoate were not suitable acylation reagents (entry 10). The present procedure using P(3,5-Xy)₃ as the ligand was amenable to a gram-scale reaction. Thus, starting from 0.83 g (6.0 mmol) of **1a**, 1.66 g of **3a** was obtained in 86% isolated yield.

Using **2a**, various nitriles were employed as substrates under the optimal reaction conditions (Table 2). Aromatic nitriles bearing an electron-donating (**1b** and **1c**) or an electron-withdrawing (**1d**, **1e** and **1f**) group were converted to the corresponding products in good to high yields with perfect

Table 2 Scope of substrates^a

entry	nitrile	1,3-diene	Isolated yield of 3
1			 3b : 99%
2		2a	 3c : 66%
3		2a	 3d : 94%
4		2a	 3e : 90%
5		2a	 3f : 58%
6		2a	 3g : 63%
7		2a	 3h : 71%
8		2a	 3i : 70%
9 ^c		2a	 3j : 30% ^b
10	1a		 3k : 23% ^c

^a Reaction conditions: **1** (0.40 mmol), **2** (0.80 mmol, 2.0 equiv), PhMe₂Si-B(pin) (0.60 mmol, 1.5 equiv), CuOAc (4.0 mol %), P(3,5-Xy)₃ (10 mol %) in toluene (1.0 mL) at room temperature for 19 h, then HCl aq. was added. Isolated yields of **3** were shown. ^b PCy₃ (10 mol %) was used as the ligand. ^c Determined by GC and GC-MS analysis.

Table 3 Ligand effect on the Cu-catalyzed three-component coupling of **1a**, isoprene (**2c**) and a silylborane^a

entry	ligand	GC yield (%) and selectivity (4a/4a' + others) ^b
1	PPh ₃	82 (89/11)
2	P(3,5-Xy) ₃	86 (86/14)
3	P(DTBM) ₃	85 (94/6)
4	P(<i>o</i> -Tol) ₃	0
5	PCy ₃	90 (86/14)
6 ^c	xantphos	3 (99/1)
7 ^c	dppbz	29 (99/1)

^a Reaction conditions: benzonitrile (**1a**, 0.40 mmol), 2,3-dimethyl-1,3-butadiene (**2a**, 0.52 mmol, 1.3 equiv), PhMe₂Si-B(pin) (0.52 mmol, 1.3 equiv), CuOAc (4.0 mol %), ligand (10 mol %) in toluene (1.0 mL) at room temperature for 19 h, then HCl aq. was added. ^b Determined by GC and GC-MS analysis. ^c 5.0 mmol of ligand was used.

regioselectivity (entries 1–5). Several functional groups such as Br-C(sp²) (**1e**), ester (**1g**), and B(pin) (**1h**) moieties were tolerated in the reaction (entries 4, 6 and 7). When the reaction of *o*-tolunitrile (**1i**) with **2a** was carried out, an unexpectedly stable iminium salt (**3i**) was precipitated during the acidification of the reaction mixture (entry 8). Acetonitrile (**1j**) could participate in the reaction and the corresponding product **3j** was obtained using PCy₃ as the ligand (entry 9). However, other aliphatic nitriles such as valeronitrile afforded the corresponding products in low yields. Regarding other 2,3-disubstituted 1,3-butadienes, 2,3-dibutyl-1,3-butadiene was not a suitable substrate and the corresponding product (**3k**) was obtained in low yield (entry 10).

Next, the reaction of **1a**, isoprene (**2c**), and PhMe₂Si-B(pin) was conducted by employing 4.0 mol % of CuOAc and 10 mol % of a ligand in toluene at room temperature (Table 3).¹⁷ Using PPh₃, a mixture of regioisomers was obtained in 82% total yield with good selectivity (**4a/4a'** and others = 89/11), after acidic work-up (entry 1). In the reaction, a product (**4a**) functionalized at the less hindered carbon-carbon double bond in **2c** was obtained as a major isomer. P(3,5-Xy)₃ showed a similar efficiency compared to PPh₃ (entry 2). In contrast, P(DTBM)₃ resulted in the highest selectivity (85% yield, 94/6) (entry 3), while P(*o*-Tol)₃ did not produce **4a** at all (entry 4). The use of PCy₃ gave **4a** in high yield, but selectivity was not enough (entry 5). As the case using **2a**, bidentate phosphines were not good ligands in the reaction (entries 6 and 7).

Using P(DTBM)₃ as the ligand, various aromatic nitriles provided β,γ-unsaturated ketones with a (dimethylphenylsilyl)methyl moiety at the α-position in good to high isolated yields with high regioselectivity (Table 4, entries 1–6). Several functional groups such as Cl-C(sp²) (**4d**), Br-C(sp²) (**4e**), ester (**4g**), and B(pin) (**4h**) groups were tolerated in the reaction. For 1,3-dienes, myrcene (**2d**) was subjected to the reaction and the corresponding product (**4i**) was

Table 4 Scope of Substrates^a

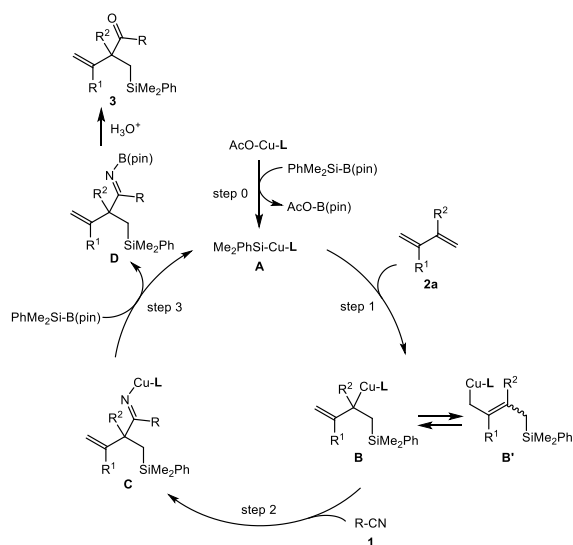
entry	nitrile	1,3-diene	Isolated yield (4/4')
1			 4a : 82% (94/6)
2			 4d : 92% (92/8)
3			 4e : 70% (94/6)
4			 4f : 58% (91/9)
5			 4g : 80% (94/6)
6			 4h : 63% (92/8)
7			 4i : 67% (96/4)
8 ^c			 4m : 61% (98/2)

^a Reaction conditions: nitrile (**1**, 0.40 mmol), 1,3-dienes (**2**, 0.80 mmol, 2.0 equiv), PhMe₂Si-B(pin) (0.60 mmol, 1.5 equiv), CuOAc (4.0 mol %), ligand (10 mol %) in toluene (1.0 mL) at room temperature for 19 h, then HCl aq. was added. ^b Determined by GC and GC-MS. ^c Et₃Si-B(pin) in place of PhMe₂Si-B(pin) was used.

obtained in good yield (entry 6). Regarding 2-substituted 1,3-butadienes, 2-phenyl-1,3-butadiene did not afford the corresponding product at all. The reaction using Et₃Si-B(pin) instead of PhMe₂Si-B(pin) afforded a triethylsilyl-substituted product (**4m**) in moderate yield (entry 8).

Scheme 2 shows a plausible reaction mechanism. It is known that silyl copper species (**A**) is generated upon the reaction of $\text{PhMe}_2\text{Si-B(pin)}$ with copper complexes.⁸ Thus, **A** is the key catalyst species involved in the catalytic cycles (step 0). Then, **A** is subsequently added across a sterically less hindered C-C double bond of 1,3-diene (**2**), yielding an allylcopper intermediates **B** or **B'** (step 1). Next, **B'** would react with a nitrile (**1**) at the γ -position to provide **C** via 6-membered ring transition state (step 2), as proposed in the allylation of nitriles.¹⁴ Donating ability of monodentate phosphines facilitates the nucleophilic attack step. Finally, the σ -bond metathesis of **C** with $\text{PhMe}_2\text{Si-B(pin)}$ produces an imine (**D**) and regenerates the active catalyst species **A** (step 4). Acidic work-up provides the corresponding ketone (**3**).

Scheme 2 Possible Catalytic Cycle



In conclusion, three-component coupling reactions using nitriles, 1,3-dienes, and silylboranes were reported for the first time. The desired reactions proceeded smoothly in the presence of copper catalysts. The corresponding β,γ -unsaturated ketones with a (dimethylphenylsilyl)methyl moiety at the α -position were obtained in good to high yields with high regioselectivity. Further studies to clarify reaction mechanism and application to enantioselective reactions are now in progress.

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Conflicts of interest

There are no conflicts to declare.

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