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Tri(*o*-tolyl)phosphine for Highly Efficient Suzuki Coupling of Propargylic Carbonates with Boronic Acids

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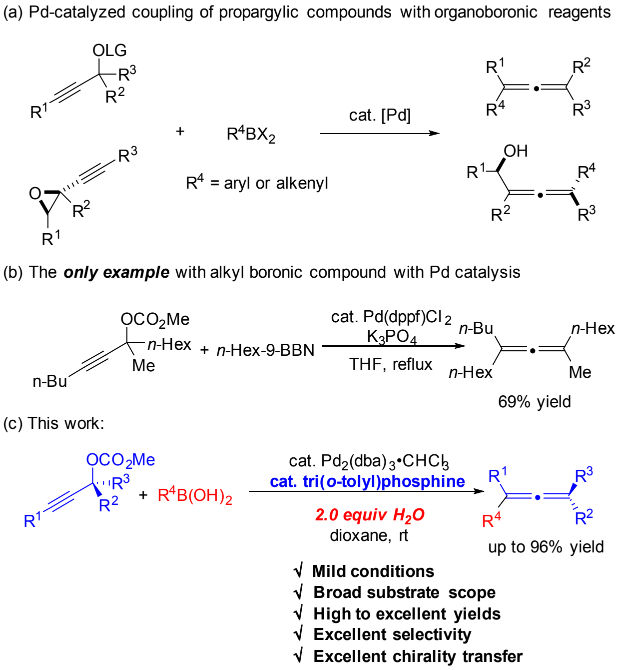
A highly efficient catalytic system consisting of $Pd_2(dba)_3{\cdot}CHCl_3$ and tri(*o*-tolyl)phosphine has been identifed for the coupling of propargylic carbonates with different types of organo boronic acids at room temperature. Excellent central-to-axial chirality transfer was also demonstrated.

Due to the importance and increasing interest of allenes,[1,2] chemists have been focusing on developing efficient methods for the synthesis of different types of allenes.[3] One of the most straightforward methods would be the palladium-catalyzed coupling of propargylic derivatives with organometallic reagents.[4] Although the commercially available organoboronic compounds have also been applied to couple with propargylic compounds (Scheme 1a),[5] however, there still remain some challenges such as limitation for rather sluggish alkyl boronic compounds (Scheme 1b),[5a] efficiency for chirality transfer,[5f,5g,5i] and high temperature (mostly above 60 °C). Regiocontrol is another issue in such reactions since such coupling at *γ* or *α* position would give allenes[5a,5d-i] or alkynes[6] and in some cases, the allene-alkyne mixture.[5b,c] Here we wish to report a highly active catalytic system with a commercially available robust ligand for such coupling reactions at room temperature covering a very broad scope affording allenes efficiently (Scheme 1c).



Scheme 1. Pd-catalyzed coupling of propargylic compounds with organoboronic reagents

We began the study with propargylic carbonate **1a** and phenylboronic acid **2a** as the model substrates to identify the ligands for the reaction at ambient temperature, thus, the temperature for the coupling reaction was set at 30 °C. *o*-(Diphenylphosphino)benzaldehyde (**L1**) was initially employed as the ligand[5i] and the desired allene product **3aa** was formed in only 58 % yield. Triphenylphosphine (**L2**) resulted in 3% yield of **3aa** with 97% recovery of **1a**. Tuning the electronic property of the phenyl group by using *para*-methyl-substituted triphenyl phosphine (**L4**) improved the yield to 38%. Tris(4-methoxy)-phenyl)phosphine (**L5**) failed to further improve the yield. Interestingly, we found that bis(ortho-methoxy)phenyl phenyl phosphine (**L6**) could give **3aa** in 41% yield. Excitingly, tri(o-tolyl)phosphine (**L7**) provided 83% yield of **3aa** with only 4% recovery of **1a**. Zheda-Phos (**L8**)[7] failed to give the allene product.

Other palladium catalysts did not improve the yield (Table 2, entries 1-4). No better result was obtained in MTBE, toluene, THF, Et_2O, or MeCN (Table 2, entries 5-9). The yield could be slightly improved to 87% with a higher loading of palladium catalyst and the ligand (Table 2, entry 10). To our surprise, the addition of 2 equiv of water further accelerated the coupling reaction, which completed in 30 min with almost quantitative yield even at room temperature (Table 2, entry 11).

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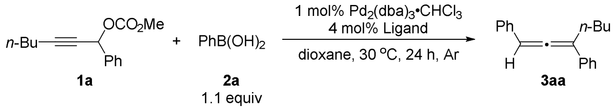
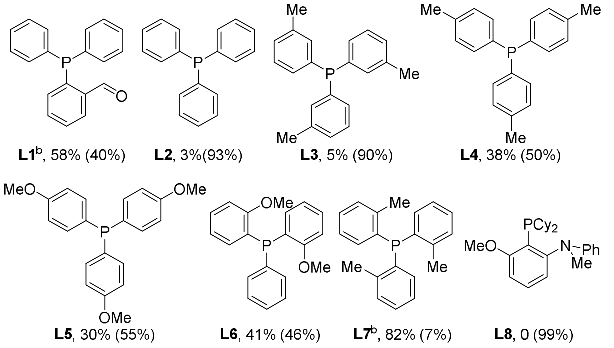
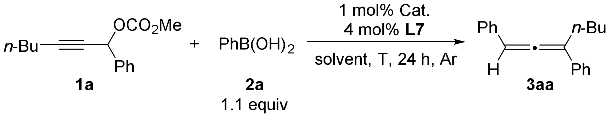
Table 1. Ligand Screening[a]





[a] The reaction was conducted with 0.5 mmol of **1a**, 0.55 mmol of **2a**, 1 mol% of $Pd_2(dba)_3$ •$CHCl_3$, and 4 mol% ligand in 1 mL of distilled dioxane at 30 °C for 24 h under Ar atmosphere. The yield and recovery were determined by ^{1}H NMR analysis, and the recovery of **1a** is shown in the parentheses. [b] 1.0 mmol of **1a** and 2 mL of distilled dioxane were used.

Table 2. Further optimization of reaction parameters

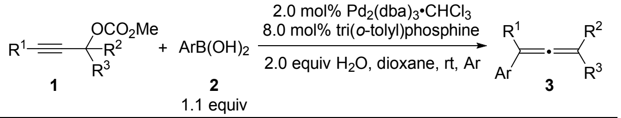


Entry	Cat.	Solvent	T (°C)	Yield of **3aa** (%)	Recovery of **1a** (%)
1	$[Pd(allyl)Cl]_2$	dioxane	30	17	76
2	$Pd_2(dba)_3$	dioxane	30	55	28
3	$Pd(OAc)_2$	dioxane	30	12	81
4	$Pd(PPh_3)_4$	dioxane	30	12	84
5	$Pd_2(dba)_3$•$CHCl_3$	MTBE	30	54	26
6	$Pd_2(dba)_3$•$CHCl_3$	toluene	30	62	18
7	$Pd_2(dba)_3$•$CHCl_3$	THF	30	43	47
8	$Pd_2(dba)_3$•$CHCl_3$	Et_2O	30	70	9
9	$Pd_2(dba)_3$•$CHCl_3$	CH_3CN	30	12	81
10[b]	$Pd_2(dba)_3$•$CHCl_3$	dioxane	30	86	/
11[b,c]	***$Pd_2(dba)_3$•$CHCl_3$***	***dioxane***	***rt***	***100***	/

[a] The reaction was conducted with 0.5 mmol of **1a**, 0.55 mmol of **2a**, 1 mol% of Cat., and 4 mol% of ligand in 1 mL of distilled dioxane at 30 °C for 24 h under Ar atmosphere. The yield and recovery were determined by ^{1}H NMR analysis. [b] 2 mol% of Cat. and 8 mol% of **L7** were used. [c] The reaction was conducted with 1.0 mmol of **1a** and 2.0 equiv of H_2O at rt in 2 mL of distilled dioxane for 0.6 h.

With the optimized conditions in hand, we next examined the reaction scope. A wide range of propargylic carbonates with different substituents at different positions all reacted smoothly with aryl boronic acid **1a** or **1b** forming the corresponding allene products with good to excellent efficiency (Table 3). The reaction is amenable to both electron-withdrawing and electron-donating aryl groups (R^2). Various functional groups, including halides (**3ba**, **3ca**, **3da**, and **3ia**), ester (**3ea**), nitro (**3fa**), cyano (**3ga**), and vinyl (**3ka** and **3la**) are well tolerated in the 2-alkynylic carbonates. Not only secondary propargylic carbonates, terminal tertiary propargylic carbonate **1j** was also working affording the corresponding tri-substituted allene **3jb** (entry 10). 1,3-Disubstituted allene **3na** (entry 13) and tetrasubstituted allene **3oa** (entry 14) could also be obtained via this Pd-catalyzed transformation.

Table 3. Scope of propargylic carbonates[a]



Entry	**1**			**2**	t (h)	Yield (%)
	R^1	R^2	R^3	Ar		
1	*n*-Bu	Ph	H (**1a**)	Ph (**2a**)	1.1	94 (**3aa**)
2	*n*-Bu	4-FC_6H_4	H (**1b**)	Ph (**2a**)	2.3	91 (**3ba**)
3	*n*-Bu	4-ClC_6H_4	H (**1c**)	Ph (**2a**)	2.2	94 (**3ca**)
4	*n*-Bu	4-BrC_6H_4	H (**1d**)	Ph (**2a**)	4.1	93 (**3da**)
5	*n*-Bu	4-$MeO_2CC_6H_4$	H (**1e**)	Ph (**2a**)	2.2	92 (**3ea**)
6	*n*-Bu	4-$O_2NC_6H_4$	H (**1f**)	Ph (**2a**)	1.1	92 (**3fa**)
7	*n*-Bu	4-NCC_6H_4	H (**1g**)	Ph (**2a**)	1.1	95 (**3ga**)
8	*n*-Bu	3-$MeOC_6H_4$	H (**1h**)	Ph (**2a**)	1.1	96 (**3ha**)
9	$Cl(CH_2)_4$	4-ClC_6H_4	H (**1i**)	Ph (**2a**)	2.1	94 (**3ia**)
10	H	Me	Me (**1j**)	4-PhC_6H_4 (**2b**)	1.1	84 (**3jb**)
11	Allyl	4-ClC_6H_4	H (**1k**)	Ph (**2a**)	2.1	92 (**3ka**)
12	Allyl	Ph	H (**1l**)	Ph (**2a**)	3.1	92 (**3la**)
13[b]	H	*n*-C_5H_{11}	H (**1n**)	Ph (**2a**)	24	36 (**3na**)
14[b]	*n*-Bu	Me	*n*-Pr (**1o**)	Ph (**2a**)	24	87 (**3oa**)

[a] The reaction was conducted with 1.0 mmol of **1**, 1.1 mmol of **2**, 2.0 mol% of $Pd_2(dba)_3$•$CHCl_3$, 8.0 mol% of tri(*o*-tolyl)phosphine, and 2.0 equiv of H_2O in 2 mL of dioxane at rt under Ar atmosphere. [b] The reaction was carried out at 40 °C.

The substrate scope of boronic acids with propargylic carbonate **1a** or **1m** is shown in Table 4. The reaction efficiency is not affected by the electronic nature of the aryl boronic acid. Both electron-rich and electron-deficient arylboronic acids gave the products in high to excellent yields. Heterocycles such as thiophene and furan may also be incorporated in the products **3a** and **3ak**. It is worth to mention that alkylboronic acids, which have never been applied in such reactions, also work under the optimized conditions (**3ml**, **3mm**, **3al**, **3am,** and **3an**). The practicality was demonstrated by applying 6.0 mmol of **1a**, affording **3ah** in 93% yield under the standard conditions (Table 4, entry 15).

Enantioenriched allenes are of high interest not only because of their wide occurrence in natural products and biologically active compounds but also due to their importance in organic synthesis as chiral building blocks. We then turned our attention to central-to-axial chirality transfer for the synthesis of rather sensitive 1,3-diarylallenes, which were easy to racemize in the presence of palladium catalysts.[5f] After further optimization on reaction temperature (for details, see Table S1 supporting information), we found the reaction may proceed even at a lower temperature in a mixed solvent of dioxane and diethyl ether affording the desired products with a high efficiency of chirality transfer (Table 5).[8] However, such

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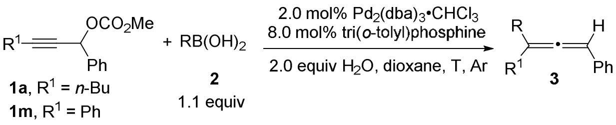
chirality transfer failed since the reaction of (*S*)-**1m** with cyclopropyl boronic acid is very sow (6% by NMR for 10 h). We are still working on it.

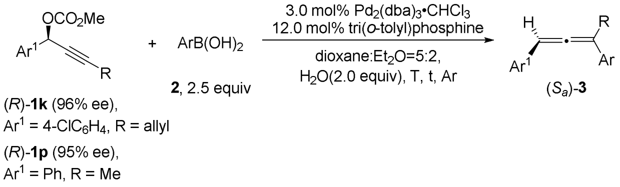
Table 4. Scope of boronic acids with 1a or 1m[a]



Entry	1	2 R	T (°C)	t (h)	Yield (%)
1	**1a**	2-MeC_6H_4 (**2c**)	rt	1.1	93 (**3ac**)
2	**1a**	3-MeC_6H_4 (**2d**)	rt	2.1	93 (**3ad**)
3	**1a**	4-MeC_6H_4 (**2e**)	rt	24	92 (**3ae**)
4	**1a**	4-*t*-BuC_6H_4 (**2f**)	rt	2.1	93 (**3af**)
5[b]	**1a**	4-AcC_6H_4 (**2g**)	60	1.5	95 (**3ag**)
6[b]	**1a**	4-ClC_6H_4 (**2h**)	40	1.1	96 (**3ah**)
7[b]	**1a**	2-naphthyl (**2i**)	40	1.1	91 (**3ai**)
8[b]	**1a**	2-thienyl (**2j**)	40	1.1	86 (**3aj**)
9[b]	**1a**	3-furyl (**2k**)	40	1.1	89 (**3ak**)
10[b]	**1m**	Me (**2l**)	40	2.1	91 (**3ml**)
11[b]	**1m**	cyclopropyl (**2m**)	40	2.1	91 (**3mm**)
12[b]	**1a**	Me (**2l**)	40	8.1	73 (**3al**)
13[b]	**1a**	cyclopropyl (**2m**)	40	12.1	58 (**3am**)
14[b]	**1a**	*n*-Bu (**2n**)	40	24	42 (**3an**)
15[c]	**1a**	4-ClC_6H_4 (**2h**)	40	1.1	93 (**3ah**)

[a] The reaction was conducted with 1.0 mmol of **1**, 1.1 mmol of **2**, 2.0 mol% of $Pd_2(dba)_3$•$CHCl_3$, 8.0 mol% of tri(*o*-tolyl)phosphine, and 2.0 equiv of H_2O in 2 mL of dioxane under Ar atmosphere. [b] 1.5 equiv of **2** was used. [c] The reaction was conducted with 6.0 mmol of **1a**, 9.0 mmol of **2h** to afford 1.5717 g **3ah**.

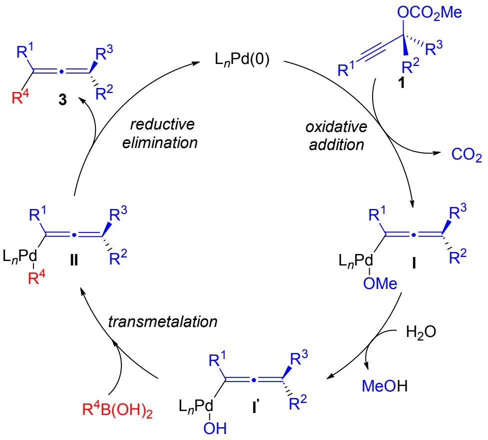
Table 5. Substrate scope of chiral propargylic carbonates[a]



Entry	(*R*)-**1**	**2** Ar	T (°C)	t (h)	(*S*)-**3** yield (%)	 ee (%)
1	(*R*)-**1k**	Ph (**2a**)	0	12	96	96 ((*S_a*)-**3ka**)
2	(*R*)-**1k**	4-$MeOC_6H_4$ (**2o**)	0	18	82	93 ((*S_a*)-**3ko**)
3[b]	(*R*)-**1p**	Ph (**2a**)	-5	1	86	91 ((*S_a*)-**3pa**)
4[b,c]	(*R*)-**1p**	2-MeC_6H_4 (**2c**)	-5	0.5	62	93 ((*S_a*)-**3pc**)

[a] The reactions were conducted with 0.5 mmol of (*R*)-**1**, 1.25 mmol of **2**, 3.0 mol% of $Pd_2(dba)_3$•$CHCl_3$, 12.0 mol% of tri(*o*-tolyl)phosphine, and 2.0 equiv of H_2O in 1.4 mL of mixture of dioxane:Et_2O = 5:2 under Ar atmosphere. Isolated yield and ee was determined by chiral HPLC analysis. [b] The reactions were conducted on a 0.2 mmol scale. [c] 37% recovery of (*R*)-**1p** as determined by 1H NMR analysis of the crude product using CH_2Br_2 as internal standard.

A mechanism is proposed as shown in Scheme 2. Pd(0) would undergo S_N2'-type oxidative addition with propargylic carbonates **1** in an *anti*-stereospecific manner to give the allenylic palladium intermediate **I**. The methoxy anion was protonated with water to generate intermediate **I'**.[9] Subsequently, intermediate **I'** would undergo transmetalation with the boronic acid to form the intermediate **II**. We reasoned that the electron-rich and steric bulky nature of tri(*o*-tolyl)phosphine ligand accelerates the oxidative addition as well as reductive elimination[10,11] to give the coupling product **3** and regenerates the catalytically active Pd(0) complex.



Scheme 2. The proposed mechanism

In summary, we have developed a general and highly efficient catalytic system for the coupling of propargylic carbonates with commercially available aryl or alkyl boronic acids with the commercially available tri(*o*-tolyl)phosphine as ligand. The mild reaction enjoys a wide substrate scope and functional group compatibility. In addition, excellent chirality transfer was observed. A catalytic asymmetric protocol is in progress in our laboratory.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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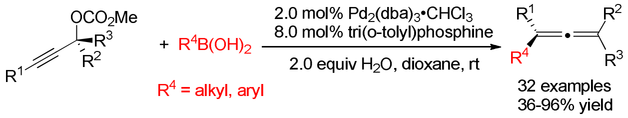
Graphic abstract



√ Mild conditions √ Broad substrate scope √ High to excellent yields
√ Excellent regioselectivity and chirality transfer

Tri(*o*-tolyl)phosphine has been identified as the highly efficient ligand for Pd-catalyzed coupling of propargylic carbonates with different types of organo boronic acids at room temperature.