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Synthesis of 1,5-disubstituted tetrazoles via Suzuki–Miyaura cross-coupling of 5-chloro-1-phenyltetrazole

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ABSTRACT

Suzuki–Miyaura coupling reactions of 5-chloro-1-phenyl-tetrazole with various functionalized arylboronic acids were investigated. In the presence of catalytic amounts of SPhos/$Pd(OAc)_2$ or RuPhos/$Pd(OAc)_2$, the reaction proceeded smoothly to afford 1,5-diaryltetrazoles in good to excellent yields.

The Suzuki–Miyaura cross-coupling reaction is a powerful method for carbon–carbon bond formation in organic synthesis[1] and has been widely used to synthesize biologically active molecules because of the commercial availability, functional group compatibility, and low toxicity of boronic acids, as well as the facile removal of the side products.

While tremendous progress has been made in the development of catalytic systems for coupling aryl chlorides and hindered arylboronic acids,[2] the cross-coupling reaction of heteroaryl halides, particularly five- or six-membered heteroaryl chlorides, remains problematic.[3] The Suzuki–Miyaura cross-coupling of chlorotetrazoles is particularly difficult; despite the utility of 1,5-disubstituted tetrazoles as anti-inflammatory and anti-hypertensive agents,[4] their synthesis via the Suzuki–Miyaura cross-coupling of 5-chlorotetrazole is exceedingly rare.[5] Furthermore, 1-aryl-5-chlorotetrazoles are poorer coupling partners, because of their electron-rich nature as well as their potential to bind Pd catalysts. Therefore, our goal was to identify robust Suzuki–Miyaura reaction conditions to couple 5-chloro-1-phenyl-tetrazoles with a variety of boronic acids and esters. These reaction conditions may then have the potential to be expanded to Suzuki–Miyaura cross-coupling of other heteroaryl chlorides.

Our study began with the optimization of reaction conditions for the cross-coupling of 5-chloro-1-phenyl-tetrazole with 2-methoxyphenylboronic acid (Scheme 1).

Reaction conditions were screened using common Pd catalysts (5 mol %), with or without a variety of ligands (10 mol %, Fig. 1). Results are summarized in Table 1. The commonly used catalysts $Pd(PPh_3)_4$ and $PdCl_2(dppf)$ proved ineffective in the coupling of our unactivated chlorotetrazole. The catalyst $Pd[P(tBu)_3]_2$, which had been successfully used for the room temperature cross-coupling reaction of aryl chlorides,[6] was effective in catalyzing the cross-coupling of 5-chloro-1-phenyl-tetrazole, which proceeded at room temperature to afford the desired product in 40% yield (Table 1, entry 3). Increasing the reaction temperature did not improve the reaction yield. The catalysts $PdCl_2[PtBu_2(PhNMe_2)]_2$[7] and $Pd(OAc)_2$/BuPAd$_2$ (di-(1-adamantyl)-*n*-butylphosphine)[8] afforded poor yields of desired product. We also examined the *N*-heterocyclic carbene, 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene (IMes), as ligand[9] in combination with Pd_2dba_3, but this proved to be an ineffective catalytic system for our substrate (Table 1, entry 6). Pentaphenylferrocenyl di-*t*-butylphosphine (QPhos)[10] was similarly disappointing, yielding only complex reaction mixtures under similar conditions. However, the use of $Pd(OAc)_2$ with 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (XPhos) or 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl (SPhos)[11] was promising (Table 1, entries 9 and 10), affording 47 and 55%, respectively, the desired product. The encouraging results obtained with SPhos and XPhos were partially attributed to these ligands' increased steric bulk and, in the case of SPhos, the presence of two methoxy groups with potential to interact with palladium.[5a] Indeed, Martin and Buchwald reported that the use of electron-rich and bulky phosphine ligands enhanced the rate of the oxidative addition and reductive elimination processes in Suzuki catalytic

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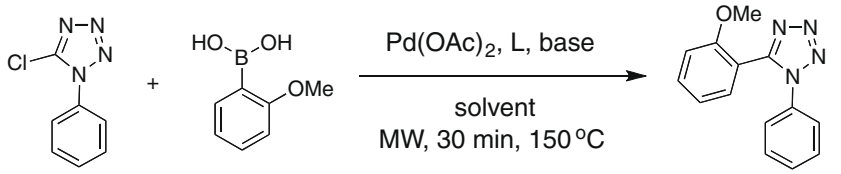


Scheme 1.

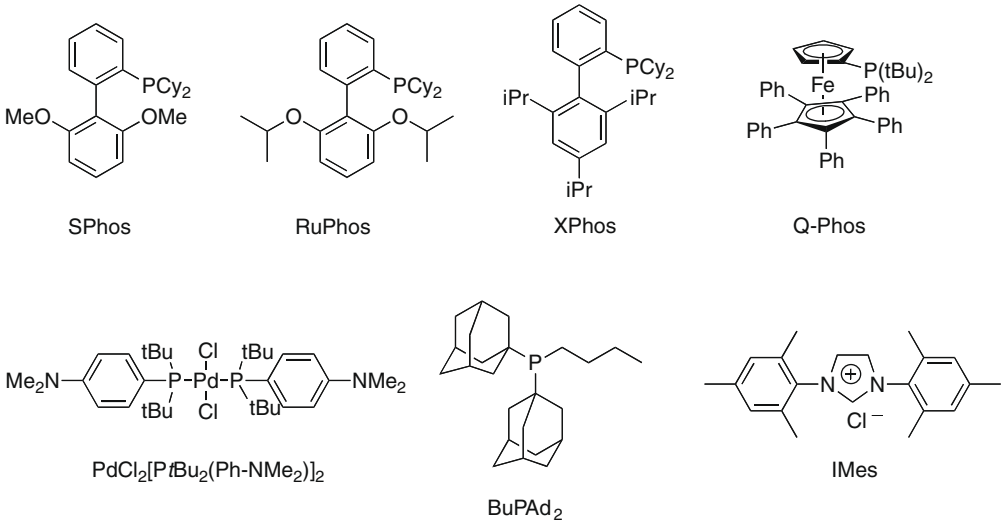
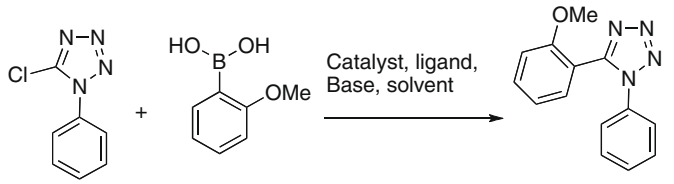


Figure 1. Ligands or Pd catalyst used in the Suzuki reaction.

Table 1
Screening conditions for the coupling of 2-methoxyphenyl boronic acid with 1-phenyl-5-chlorotetrazole[a]



Entry	Catalyst/ligand	Base	Solvent	Yield[b] (%)
1	$Pd(PPh_3)_4$	K_3PO_4	*n*-BuOH	Trace
2	$PdCl_2$(dppf)	K_3PO_4	*n*-BuOH	Trace
3[c]	$Pd[P(tBu)_3]_2$	K_3PO_4	Dioxane	40
4	$PdCl_2[PtBu_2(Ph\text{-}NMe_2)]_2$	K_3CO_3	Toluene/H_2O[d]	Trace
5	$Pd(OAc)_2$/BuPAd$_2$	K_3PO_4	*n*-BuOH	20
6	$Pd_2(dba)_3$/IMes	$CsCO_3$	Dioxane	Trace
7	$Pd(OAc)_2$/QPhos	K_2CO_3	Dioxane	Trace
8	$Pd_2(dba)_3$/PCy_3	K_3PO_4	Dioxane/H_2O[d]	10
9	$Pd(OAc)_2$/XPhos	K_3PO_4	*n*-BuOH/H_2O[d]	47
10	$Pd(OAc)_2$/SPhos	K_3PO_4	*n*-BuOH/H_2O[d]	55
11	$Pd(OAc)_2$/RuPhos	$CsCO_3$	Toluene/H_2O[d]	51
12	$Pd(OAc)_2$/RuPhos	$CsCO_3$	*n*-BuOH/H_2O[d]	63
13	$Pd(OAc)_2$/RuPhos	K_3PO_4	*n*-BuOH/H_2O[d]	71

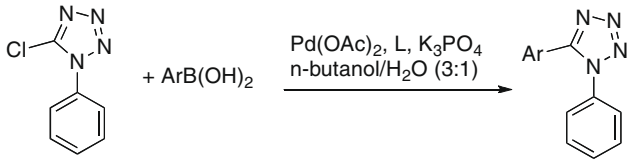
[a] Reaction conditions: ArCl (1 equiv), 2-methoxyphenylboronic acid (1.1 equiv), Pd catalyst (5%), ligand (10%), solvents (2 mL), base (3 equiv), MW 30 min at 150 °C.
[b] Isolated yield after silica gel chromatography.
[c] Room temperature, 24 h.
[d] 3:1 ratio.

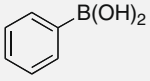
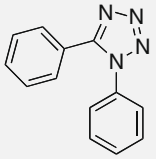
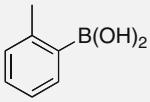
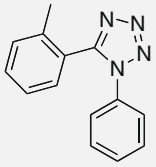
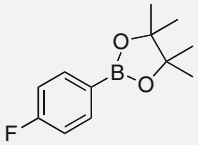
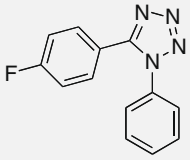
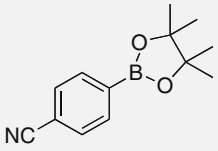
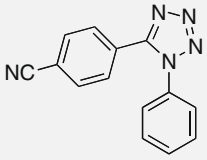
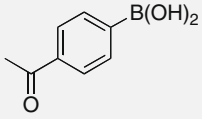
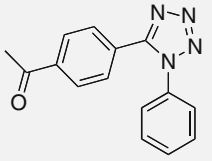
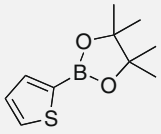
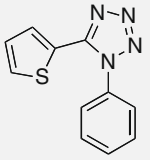
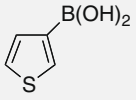
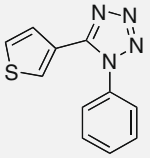
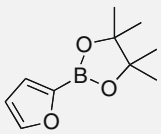
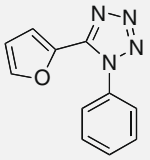
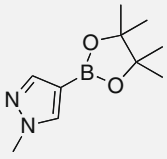
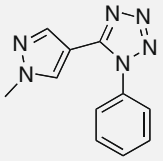
cycle.[2b] Therefore, it seemed possible that the RuPhos ligand, with its increased steric bulk and electron-rich character, would be a superior ligand for our substrate. This hypothesis proved to be correct, and the use of RuPhos yielded increased isolated yields of desired product, as shown in Table 1 (entries 11–13). We ultimately settled on $Pd(OAc)_2$ with RuPhos with either K_3PO_4 or $CsCO_3$ in 3:1 *n*-butanol/water under microwave conditions as our preferred method.[12]

Having established practical and good-yielding reaction conditions, we investigated next the substrate scope of this method. Table 2 shows the reaction of 5-chloro-1-phenyl-tetrazole with various aryl- and heteroaryl-boronic acids and pinacol esters. 5-chloro-1-phenyl-tetrazole coupled to phenylboronic acids in excellent yields under our optimized conditions (Table 2, entries 1–5). Slightly lower yields were achieved with electron-deficient phenylboronic acids (entries 3–5). We also found that $Pd(OAc)_2$ in combination with RuPhos, SPhos, or XPhos were all effective catalyst systems for the coupling of heteroaryl-boronic acids with 5-chloro-1-phenyl-tetrazole. Thiopheneboronic acids were coupled in excellent yields using $Pd(OAc)_2$ with SPhos and RuPhos (entries 6 and 7). Furan-2-boronic acid (entry 8) was coupled to 5-chloro-1-phenyl-tetrazole in moderate yield using SPhos. This lower yield is presumably due to the slow oxidative addition of the aryl chloride, as well as the instability of furan boronic acids. Reaction of 1-methylpyrazole-4-boronic acid using XPhos also afforded the desired biaryl compounds in moderate yield. Finally, coupling of an alkenyl boronate also proceeded in respectable yield (entry 10) using XPhos.

In summary, we have identified highly active catalytic systems comprising $Pd(OAc)_2$ and the dialkylbiphenylphosphino ligands SPhos, XPhos, or RuPhos for the Suzuki–Miyaura cross-coupling of 5-chloro-1-phenyl-tetrazoles with a variety of aryl- and heteroaryl-boronic acids.

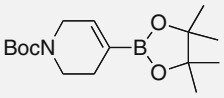
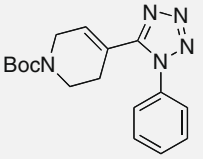
Table 2
Coupling of 1-phenyl-5-chlorotetrazole with various boronic acids and esters[a]



Entry	Ar-B(OH)$_2$	Ligand	Products	Yield
1		RuPhos		82[c]
2		SPhos		93[b]
3		RuPhos		63[c]
4		RuPhos		45[b]
5		SPhos		68[b]
6		SPhos		75[b]
7		RuPhos		71[c]
8		SPhos		38[b]
9		XPhos		44[b]

(*continued on next page*)

Table 2 (*continued*)

Entry	Ar-B(OH)$_2$	Ligand	Products	Yield
10		XPhos		56

[a] Reaction conditions: 1-phenyl-5-chlorotetrazole (1.0 equiv), boronic acid/ester (1.1 equiv), base (3 equiv), *n*-butanol/H_2O (3:1) (2 mL/mmol of halide), 5% ($Pd(OAc)_2$, 10% ligand, 150 °C, 30 min. microwave.
[b] K_3PO_4 was used.
[c] Cs_2CO_3 was used.

Acknowledgments

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12. *Experimental procedure*: A mixture of 1-phenyl-5-chlorotetrazole (180 mg, 1 mmol), boronic acid (168 mg, 1.1 mmol), $Pd(OAc)_2$ (11 mg, 0.05 mmol), SPhos (41 mg, 0.1 mmol), and K_3PO_4 (636 mg, 3 mmol) in *n*-butanol (1.5 mL) and water (0.5 mL) was purged with N_2 for 10 min and was heated to 150 °C by microwave for 10–30 minutes. The reaction mixture was diluted in EtOAc, washed with H_2O and brine, dried over sodium sulfate, filtered, and concentrated in vacuo. The crude mixture was purified by flash chromatography to afford the desired product. ^{1}H NMR (500 MHz, $CDCl_3$) 7.7 (dd, 1H), 7.55 (t, 1H), 7.49–7.50 (m, 3H), 7.32–7.43 (m, 2H), 7.15 (t, 1H), 6.88 (d, 1H). ^{13}C NMR (500 MHz, $CDCl_3$) 156.61, 152.11, 135.51, 133.14, 131.42, 129.91, 123.43, 123.11, 122.71, 121.13, 115.44, 113.32, 111.52, 54.84. FIA MS: m/z = 253.11 as [M+1] peak.