A versatile catalyst system for Suzuki–Miyaura syntheses of sterically hindered biaryls employing a cyclobutene-1,2-bis(imidazolium) salt[†]

Andreas Schmidt* and Alireza Rahimi

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The catalyst system consisting of 3,3'-(3,4-bis(dichloro-methylene)-cyclobut-1-ene-1,2-diyl)bis(1-methyl-1*H*-imidazolium) bis(tetra-fluoroborate), Pd(OAc)₂ and NaOtBu in toluene proved to be very effective for a broad variety of Suzuki–Miyaura reactions at room temperature. It is also suited for the synthesis of sterically hindered compounds including 2,6-di-*tert*-butyl-2'-substituted biaryls at elevated temperatures.

The Suzuki-Miyaura reaction has become an extremely versatile and successful synthetic tool for carbon-carbon bond formation.^{1,2} A broad substrate scope, methods to prepare sterically hindered biaryls, the ability to operate at low levels of catalyst for a range of substrates, and the ability to work at room temperature have been the most important goals of rational catalyst design,^{3,4} and remarkable success has been achieved in the last years.¹⁻⁴ As the Suzuki-Miyaura reaction is inter alia influenced by parameters such as palladium source, ligand, additive, solvent, stoichiometry, and temperature, a plethora of protocols for accomplishing this transformation has been published. With respect to this, poly(N-heterocyclic carbene)s have attracted considerable attention as ligands because they allow the preparation of organometallic compounds with a broad variety of geometries.5 In continuation of our interest in N-heterocyclic carbenes⁶ we report here a new cyclobutene-1,2-bis(imidazolium) salt as very efficient catalyst precursor for a broad variety of Suzuki-Miyaura reactions at room temperature. The system can also successfully be employed for the synthesis of sterically hindered tri- and tetra-ortho-substituted biaryls.

The bis(imidazolium) salt was prepared starting from perchloropropene 1 which formed 1,2-dichloro-3,4-bis-(dichloro-methylene)cyclobut-1-ene 2 on treatment with Al/Hg.⁷ Reaction of cyclobutene 2 with 1-methylimidazole (NMI) resulted in the formation of (cyclobut-1-ene-1,2-diyl)bis-(1-methylimidazolium) chloride which was subjected to anion exchange in a one-pot procedure. Thus, tetrafluoroborate 3 was formed in 73% yield from 2. The salt 3 possesses no water of crystallization and its purification is simple (ESI[†]).

We selected 4-bromotoluene and phenylboronic acid to optimize the conditions of Suzuki–Miyaura reactions (Table 1, entry 1). THF, 2-propanol, and toluene proved to be suitable solvents (ESI[†]), but toluene gave the best results, when sodium *tert*-butylate was used as base. Thus, the reaction of 1.0 mmol of 4-bromotoluene, 1.2 mmol of phenylboronic acid, 1.7 mmol of NaOtBu, 1.0 mol% of Pd(OAc)₂, and 1.0 mol% of the bis(imidazolium) salt **3** conducted in 5.0 mL of toluene at room temperature gave 96% of 4-phenyltoluene.



Table 1 summarizes our results starting from (het)aryl chlorides, iodides, and triflates which all efficiently crosscoupled with arylboronic acids at room temperature in short periods of time. As a comparison, 1-(biphenyl-4-yl)ethanone (entry 2) has been prepared before at rt within 16–40 h in 50-92% yield,⁸ or in a microreactor on a polymer-bound Pd–NHC catalyst in 99% yield.⁹ To the best of our knowledge, the other transformations presented in Table 1 are new.

rt

	(het)aryl—X	$aryl-X + aryl-B(OH)_2 \xrightarrow{Pd(OAc)_2, 3}{NaOtBu}$ (het)aryl-aryl						
Entry	(het)aryl–X	(het)aryl– B(OH) ₂	(het)aryl– (het)aryl	Time/h	Yield (%)			
1	MeBr	(HO) ₂ B	Me-	0.5	96 ^a			
2	Me CI	(HO) ₂ B-		1	92 ^b			
3	}–∕⊂)–ci	(HO) ₂ B-	$\succ \hspace{-1.5cm} \rightarrow \hspace{-1.5cm} \sim \hspace{-1.5cm} \rightarrow $	1	94 ^b			
4		(HO) ₂ B	\sim	3.5	90 ^a			
5	⟨ _s ∖,	(HO) ₂ B	Ne S Me	3.5	91 ^{<i>a</i>}			
6	TfO	(HO) ₂ B	Me	3	93 ^b			
7	MeOTf	(HO) ₂ B-	Me-	1.25	93 ^b			
8	MeOTf	(HO) ₂ B	Me-	2	88 ^b			

^{*a*} 1.0 mol% Pd(OAc)₂, 1.0 mol% **3**, 1.7 eq. NaOtBu. ^{*b*} 2.0 mol% Pd(OAc)₂, 2.0 mol% **3**, 1.7 eq. NaOtBu.

Clausthal University of Technology, Institute of Organic Chemistry, Leibnizstrasse 6, D-38678 Clausthal-Zellerfeld, Germany. E-mail: schmidt@ioc.tu-clausthal.de; Fax: +49-5323-722858; Tel: +49-5323-723861

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The synthesis of sterically extremely hindered tri- and tetra-*ortho* biaryls under mild conditions remains a challenge for Suzuki–Miyaura cross-coupling reactions.^{10,11} We tested our system starting from bromides and chlorides as shown in Table 2.

Tetra-*ortho*-substituted biaryls can successfully be formed from aryl bromides using hindered biarylphosphine ligands and Pd₂(dba)₃ at 100 °C–110 °C,^{4,12} or from aryl chlorides in the presence of IBiox12·HOTf/Pd(OAc)₂ at 110 °C.¹³ In addition, ruthenocenylphosphine R-Phos/Pd(dba)₃ at 50 °C to 100 °C proved to be a suitable catalyst system.¹⁴ To overcome the major drawback of significantly elevated temperatures, Pd-PEPPSI-IPent was employed as catalyst at 65 °C to prepare tetra-*ortho*-substituted biaryls within 24 h.¹⁰ Using our catalytic system, 2,2',4,6,6'-pentamethylbiphenyl is formed starting from 2-bromo-1,3-dimethylbenzene and mesityl boronic acid in 87% yield after only 3.5 h at 60 °C (Table 2, entry 1). Literature procedures for the synthesis of this compound give either considerably lower yields,¹⁴ or require temperatures up to 150 °C,¹⁵ or need 24 h of reaction time at 65 °C.¹⁰ Starting from 2-chloro-1,3,5-trimethylbenzene and 2,6-dimethylphenylboronic acid (entry 2) the same biaryl is formed under comparable conditions as reported.¹⁶ The synthesis of 1-(2,6-dimethylphenyl)-2-methylnaphthalene (entry 3), however, also proceeds in considerably shorter time (4.5 h *vs.* 24 h) in comparison to the usage of Pd-PEPPSI-IPent, although in

Table 2 Suzuki-Miyaura syntheses of tri- and tetra-ortho-substituted biaryls

			toldene			
Entry	Aryl–X	Aryl–B(OH) ₂	Aryl–aryl	Time/h	Temp./°C	Yield (%)
1	Me Br Me	(HO) ₂ B	Me Me Me Me	3.5	60	87 ^{<i>a</i>}
2	Me Me Me	(HO) ₂ B- Me		4	90	79 ^a
3	Br Me	(HO) ₂ B	Me Me	4.5	70	86 ^a
4	Me CI	(HO) ₂ B- Me	Me Me Me	3	50	91 ^b
5	Me Cl	(HO) ₂ B- Me	Me Me Me	3	60	89 ^a
6	C C	(HO) ₂ B Me	Me Me Me	4.5	90	90 ^{<i>a</i>}
7) Br	(HO) ₂ B-		7	90	46 ^b
8	Me	(HO) ₂ B	Me-	10	110	39 ^{<i>a</i>}
9	Me	MeO (HO) ₂ B-	Me	10	110	37 ^a
10	CI	(HO) ₂ B-	Me	10	90	79 ^a

Pd(OAc)₂, **3** NaOtBu

toluono

aryl-aryl

 $aryI-X + aryI-B(OH)_2$

^a 2.0 mol% Pd(OAc)₂, 2.0 mol% 3, 2 eq. NaOtBu. ^b 2.0 mol% Pd(OAc)₂, 2.0 mol% 3, 1.7 eq. of NaOtBu.

almost identical yields.¹⁰ 2'-Isopropoxy-2,4,6-triisopropylbiphenyl (entry 7) was obtained in 46% yield at 90 °C using our catalytic system. This compound has previously been prepared in the presence of the aforementioned biphenylenesubstituted ruthenocenylphosphine in 19% yield at 50 °C.14 The title catalyst system was also able to couple 2.6-di-tertbutyl-6-methylbromobenzene with 2-methylboronic acid and 2-methoxyboronic acid, respectively (Table 2, entries 8 and 9). Although the conversion of the starting materials is 81% and 54%, respectively, the isolated yields of the biaryls are moderate, as CH-activation occurred to give $\alpha.\alpha$ -dimethyl- β -aryl hydrostyrene derivatives as by-products. In a literature-known procedure, the reaction of 2,4,6-tri-tert-butylbromobenzene with 2-methylphenylboronic acid using 2-(2',6'-dimethoxybiphenyl)dicyclohexylphosphine as a ligand yielded an analogous by-product, but no aryl coupling at all was detectable.⁴ Thus, to the best of our knowledge, these reactions presented here are the first Suzuki-Miyaura syntheses of 2'-substituted 2,6-di-tert-butyl-biaryls. The Suzuki-Miyaura synthesis of 9-(2-methylnaphthalen-1-yl)anthracene (entry 10) was finished in 10 h at 90 °C, whereas the usage of 2 mol% of Pd-PEPPSI-IPent required 24 h at 65 °C to give a yield of 88%.¹⁰

In summary we present a new cyclobutene-1,2-bis(imidazolium) salt as component of a versatile catalyst system for Suzuki–Miyaura reactions at rt and for the preparation of sterically hindered biaryls.

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