A Cyclobutene-1,2-Bis(imidazolium) Salt as Efficient Precursor of Palladium-Catalyzed Room-Temperature Suzuki–Miyaura Reactions

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Abstract: 3,3'-[3,4-Bis(dichloromethylene)cyclobut-1-ene-1,2diyl]bis(1-methyl-1*H*-imidazolium) bis(tetrafluoroborate), palladium(II)acetate, and sodium *tert*-butoxide in toluene catalyze effectively Suzuki–Miyaura cross-coupling reactions of aryl bromides, chlorides, and iodides with arylboronic acids at room temperature.

Key words: biphenyls, cross-coupling, Suzuki–Miyaura cross-coupling reactions

As C-C bond formations are often key steps in a broad variety of organic processes, transition-metal-catalyzed cross-coupling reactions represent a valuable tool in organic synthesis.¹ Among these, the Suzuki–Miyaura reaction has emerged as a favorite, as numerous organoboron nucleophiles can be coupled with aryl iodides, bromides, chlorides, and aryl and vinyl sulfonates (triflates, nonaflates, tosylates) as electrophiles.² Ligand structure proved to be crucial in successfully achieving metal-catalyzed cross-coupling, and, as a consequence, a plethora of different ligands have been investigated. The most important goals of catalyst design has been the ability to couple a broad substrate scope, to establish methods for the synthesis of sterically hindered biaryls, the possibility to work at room temperature, and the development of reaction conditions which allow a low catalyst loading. Remarkable success has been achieved during the last decade.1-3

We report here Suzuki–Miyaura reactions using a cyclobutene-1,2-bis(imidazolium) bis(tetrafluoroborate) as catalyst precursor which proceed at room temperature starting from a variety of substrates.

The catalyst is readily available from 1,2-dichloro-3,4bis(dichloromethylene)cyclobut-1-ene (1) on treatment with 1-methylimidazole (NMI) which results in the formation of (cyclobut-1-ene-1,2-diyl)bis(1-methylimidazolium) bischloride. In a one-pot procedure anion exchange gave 3,3'-(3,4-bis(dichloromethylene)cyclobut-1-ene-1,2-diyl)bis(1-methyl-1*H*-imidazolium) bis(tetrafluoroborate) (2) in 73% yield (Scheme 1).⁴

The Suzuki–Miyaura reaction of 4-bromotoluene and phenylboronic acid was used to optimize the reaction conditions with respect to catalyst loading, temperature, and time (Scheme 2). Thus, the reaction of 1.0 mmol of 4-bromo-

SYNLETT 2010, No. 9, pp 1327–1330 Advanced online publication: 13.04.2010 DOI: 10.1055/s-0029-1219824; Art ID: G06810ST © Georg Thieme Verlag Stuttgart · New York toluene, 1.2 mmol of phenylboronic acid, and 1.7 mmol of NaO*t*-Bu in 5.0 mL of toluene at room temperature gave 96% of 4-phenyltoluene within 30 minutes, when 2.0 or 1.0 mol% of Pd(OAc)₂ and bis(imidazolium) salt **2** were employed, respectively (Table 1). Smaller amounts of palladium salt and imidazolium salt **2** required longer reaction times and/or elevated temperatures to give slightly decreased yields of the product. To examine the scope of the reaction, we used the conditions of entry 2 (Table 1).



Scheme 1 Synthesis of the precursor



1 equiv

Scheme 2 Conditions of Suzuki–Miyaura reactions using precursor 2

 Table 1
 Optimizing Reaction Conditions

| Entry | Pd(OAc) ₂ /2 (mol%) | Temp (°C) | Time (h) | Yield (%) |
|-------|--------------------------------|-----------|----------|-----------|
| 1 | 2 1 | r.t. | 0.5 | 96 |
| 2 | 1 1 | r.t. | 0.5 | 96 |
| 3 | 0.5 | r.t. | 2.5 | 91 |
| 4 | 0.2 | r.t. | 5 | 91 |
| 5 | 0.2 | 50 | 3 | 94 |
| 6 | 0.1 | 50 | 5 | 92 |

Table 2 Suzuki–Miyaura Reactions at Room Temperature

| Entry | Aryl halide | Boronic acid | Product | Time (min) | Yields (%) ^a |
|-------|----------------------|-------------------------------------|-------------------|---------------|----------------------------|
| 1 | Br | (HO) ₂ B | | 25 | 94 |
| 2 | Br | (HO) ₂ B | | 60 | 87 |
| 3 | Br | (HO) ₂ B | | 70 | 96 |
| 4 | F ₃ C- | (HO) ₂ B | F ₃ C | 60 | 99 |
| 5 | F ₃ C-Br | (HO) ₂ B | F ₃ C | 60 | 94 |
| 6 | F ₃ C-Br | (HO) ₂ B | F ₃ C | 45 | 99 |
| 7 | OMe Br | (HO) ₂ B | OMe | 100 | 91 |
| 8 | Me ₂ N-Br | (HO) ₂ B | Me ₂ N | 150 | 86 |
| 9 | F ₃ C- | (HO) ₂ B | F ₃ C | 75 | 94 |
| 10 | OH Br | (HO) ₂ B | OH | 120 | 94 |
| 11 | Br | (HO) ₂ B | Ph | 90 | 91 |
| 12 | | (HO) ₂ B-CF ₃ | | 70 | 93 |
| 13 | | (HO) ₂ B | | 55 | 96 |
| 14 | OMe I | (HO) ₂ B | OMe | 100 | 94 |
| 15 | | (HO) ₂ B | | 65 | 97 |
| 16 | — CI | (HO) ₂ B | | 55 | 93 |
| 17 | F ₃ C-CI | (HO) ₂ B | F ₃ C | 70 | 95 |
| 18 | F ₃ C-CI | (HO) ₂ B | F ₃ C | 70 | 96 |

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| Entry | Aryl halide | Boronic acid | Product | TimeYields(min)(%) ^a |
|-------|-------------|---------------------|---------|---------------------------------|
| 19 | CI | (HO) ₂ B | | 75 91 |
| 20 | NCI | (HO) ₂ B | | 80 93 |

 Table 2
 Suzuki–Miyaura Reactions at Room Temperature (continued)

^a Yields refer to isolated products characterized by spectroscopic data [¹H NMR, ¹³C NMR, MS (EI), IR, CHN analyses].

As illustrated in Table 2, our catalytic system enables the cross-coupling of electron-rich as well as electron-deficient aryl bromides (entries 1-11) in very good to excellent yields at room temperature. Thus our method to prepare terphenyl (entry 2) competes with recent Suzuki-Miyaura reactions under microwave irradiation in water (7 h, 83%),⁵ or a procedure starting from boronic esters in aqueous EtOH or *i*-PrOH (6–18 h, 90–95%).⁶ Alternatively, this coupling can be carried out in the presence of an encapsulated Pd catalyst under microwave irradiation (15 min, >98%)⁷ or using hydrazones as catalyst precursors (3) h, 88%).⁸ The synthesis of 4-trifluoromethylbiphenyl (entry 4) proceeds in quantitative yield within only 1 hour applying our catalyst system. As a comparison, a recent literature procedure using cyclometallated cis-chelated bidentate benzimidazolylidene palladium complexes gave 91% yield within 24 hours at room temperature.⁹ Essentially, the same yield of 4-methyl-4'-(trifluoromethyl)biphenyl (Table 2, entry 5) was obtained either starting from cyclic triol borates and JohnPhos as ligand of Pd(OAc)₂ in DMF-water within a period of 5 hours,¹⁰ or according to our procedure within 60 minutes. Noteworthy are the reactions of the very electron-rich 4-bromo-N,N-dimethylaniline (entry 8) and 2-bromophenol (entry 10) which gave 86% and 94% yield of the corresponding biaryls at room temperature, respectively, in considerably shorter reaction times than reported for other catalyst systems (24 h,¹¹ 18 h¹²). Aryl iodides usually are the most reactive halides in Suzuki-Miyaura reactions. All iodides tested here reacted in excellent yields (entries 12-15). The 1,4-diiodobenzene (entry 15) was reacted with two equivalents of phenyl boronic acids to give terphenyl in almost quantitative yield at room temperature. A literature survey revealed that our cross-coupling requires the mildest reaction conditions (entries 12, 13,¹³ and 14¹⁴), or the shortest reaction time at room temperature (entry 15^{15}). The use of chlorides as coupling partners has been a challenge over a longer period of time, as they proved to be less reactive under standard Suzuki-Miyaura conditions; nevertheless efforts have been devoted to this class of compounds due to its attractive cost and readily available diversity.¹⁶ We tested 4-chlorotoluene, 1-chloro-4-trifluoromethylbenzene, 1-acetyl-2-chlorobenzene, and 4-chloropyridine as coupling partners which all reacted at room temperature in 91% to 95% yield (entries 16–18). The preparation of 4-(trifluoromethyl)biphenyl (entry 17) as presented here is by far the mildest method, except for the usage of in situ generated nanoparticles in PEG-400 under aerobic conditions.¹⁷ To the best of our knowledge, no room-temperature Suzuki–Miyaura reactions of the chlorides presented in entries 18–20 have been published to date. Noteworthy is the formation of the sterically hindered 1-(trimethylbiphenyl-2-yl)ethanone (entry 19) which is a tri-*ortho*-substituted biaryl.

In summary we present a very efficient catalyst system for Suzuki–Miyaura reactions which allows for roomtemperature cross-couplings.¹⁸

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- (18) Typical Procedure for the Synthesis of 3-Methylterphenyl (Entry 3)A flame-dried two-necked flask was charged with 4-bromo-

biphenyl (1 mmol, 233 mg), 3-methylphenylboronic acid

(1.2 mmol, 163.2 mg), salt 2 (1 mol%, 0.01 mmol, 5.6 mg), Pd(OAc)₂ (1 mol%, 0.01 mmol, 2.5 mg), and NaOt-Bu (1.7 mmol, 163.5 mg), capped with a rubber septum, evacuated, and refilled with nitrogen. Evaporation and refilling was repeated three times. Then toluene (5 mL) was added via a syringe. The reaction mixture was stirred at r.t. for 70 min, then diluted with of n-hexane (10 mL), and filtered through a small amount of silica gel. The solvent was then evaporated, and the residue was purified by column chromatography (silica gel). The compound was obtained as colorless solid in 96% yield (234 mg), mp 123-124 °C. ¹H NMR (200 MHz, CDCl₃): $\delta = 7.65$ (s, 5 H), 7.62–7.60 (m, 1 H), 7.48–7.29 (m, 6 H), 7.18–7.17 (m, 1 H), 2.41 (s, 3 H) ppm. ¹³C NMR (50 MHz, CDCl₃): δ = 140.8, 140.7, 140.3, 140.0, 138.4, 128.8, 128.7, 128.4, 128.1, 127.9, 127.5, 127.4, 127.3, 127.1, 124.2, 21.6 ppm. IR (KBr): 3033, 2974, 2845, 1626, 1585, 1210, 973, 827 cm⁻¹. MS: *m/z* (%) = 244 (100%) [M⁺]. Anal. Calcd for $C_{19}H_{16}$: C, 93.40; H, 6.60. Found: C, 93.48; H, 6.49.

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