Saturated N-Heterocyclic Carbene Oxime and Amine Palladacycle Catalysis of the Mizoroki–Heck and the Suzuki Reactions¹

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Abstract: *ortho*-Palladated aryl oxime and amines with a N-heterocyclic carbene ligand show increased thermal stability and catalyze the Mizoroki–Heck and Suzuki reaction with high yields, and moderate TON (2,000–92,000) and TOF (200–4,300 h⁻¹). Homo coupling of the aryl halides gave low yields of the biaryls in the presence of these catalysts.

Key words: saturated N-heterocyclic carbene, oxime and amine palladacycle, Mizoroki–Heck reaction, Suzuki reaction, biaryl

Non phosphine based complexes for the Mizoroki–Heck and other reactions are of importance due to the oxidative degradation and side reactions observed with phosphines and the need for more efficient ligands and catalysts. We have initiated a study of N-ligands as alternatives to phosphines for these reactions. Phosphine palladacycles and imidazole based N-heterocyclic carbene ligands have been reported to give very high yields and TON's for the Mizoroki–Heck reaction and Suzuki reaction^{2,3} and show very high thermal stability and insensitivity towards air and moisture. Saturated N-heterocyclic carbenes are more basic compared to unsaturated analogues, showing increased activity of the catalysts.⁴ Aryl oxime and amine palladacycles offer scope for electronic tuning by varying the substituents on the aromatic ring.^{5,6} Salen, DMG, DAB, oxine and diamine ligands have been used for the activation of aryl bromides and chlorides in the Mizoroki– Heck, Suzuki and aryl amination reactions giving high yields and turn over numbers.⁷ Phosphorous based ligands have been shown to increase the activity of ferrocenyl oxime palladacycles.⁸

Saturated N-heterocyclic carbenes coordinated to the palladacycles were expected to increase the stability and reactivity compared to the P-ligands and the effect of these ligands in the Mizoroki–Heck and Suzuki reaction was therefore investigated (Scheme 1). N-Heterocyclic carbene orthopalladated oxime and amine catalysts were prepared in moderate yield by the treatment of the corresponding dimeric palladacycles with the N-heterocyclic carbene dimers in *m*-xylene as previously reported.⁹



Scheme 1 Preparation of saturated N-heterocyclic carbene palladacycles.

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Complexes 2 and 3 showed excellent activity for the reaction of aryl bromides with ethyl acrylate and styrene to give 43.5–93.2% yield of the substitution products (TON's 2, 777–791, 950). A high TON of 91, 950 was obtained for the coupling of 1-bromonaphthalene with styrene in the presence of acetophenone oxime carbene complex 1 (Scheme 2).

For comparison, monomeric phosphine and phosphite analogues **4–5** were also prepared by the reaction of the dimeric oxime complex **A** with PPh₃ and $P(OC_2H_5)_3$. For the reaction of 1-bromonaphthalene with ethyl acrylate, catalyst **2** gave the highest yield of 93.2% with a TON of 65, 019 and TOF of 9, 288 h⁻¹ compared to the catalyst **4** (yield 65.7%, TON 49, 773 and TOF 2, 074 h⁻¹) and catalyst **5** (yield 76.4%, TON 48, 000 and TOF 2, 274 h⁻¹). For the reaction with styrene, catalyst **3** gave the highest yield of 86.8%, TON of 59, 500 and TOF of 8, 500 h⁻¹ compared to catalyst **4** (yield 89.3%, TON 67, 575 and TOF 2, 941 h⁻¹) and catalyst **5** (yield 82.5%, TON 51, 725 and TOF 2, 343 h⁻¹). The carbene complexes gave better yield, higher TON's and TOF compared to the phosphine and phosphite complexes. The results of the Heck reactions with these catalysts are shown in Table 1.



Scheme 2 Vinylation of aryl bromides and chlorides with palladacycles 1–5.

Entry	Aryl halide (mmol)	Olefin (mmol)	Catalyst (mmol)	Time (h)	Yield (TON) (%)
1	C ₆ H ₅ Br	CH ₂ =CHCOOC ₂ H ₅	1 (0.0004)	24	70.2 (43, 750)
	(25 mmol)	(50 mmol)	2 (0.00036)	24	54.7 (38, 055)
			3 (0.0004)	24	43.5 (27, 514)
2	C ₆ H ₅ Br	C ₆ H ₅ CH=CH ₂	1 (0.0004)	24	71.6 (41, 500)
	(25 mmol)	(30 mmol)	2 (0.0004)	24	71.2 (44, 500)
			3 (0.0004)	24	80.1 (50, 000)
3	$1-C_{10}H_7Br$	CH ₂ =CHCOOC ₂ H ₅	1 (0.0004)	21	88.4 (55, 420)
	(25 mmole)	(50 mmol)	2 (0.00036)	7	93.2 (65, 019)
			3 (0.0004)	9	86.3 (53, 925)
			4 (0.00033)	24	65.7 (49, 773)
			5 (0.0004)	21	76.4 (48, 000)
4	$1-C_{10}H_7Br$	C ₆ H ₅ CH=CH ₂	1 (0.0002)	36	73.2 (91, 950)
	(25 mmole)	(30 mmole)	1 (0.0004)	36	92.6 (61, 950)
			2 (0.00036)	36	77.9 (54, 166)
			3 (0.0004)	7	86.8 (59, 500)
			4 (0.00033)	23	89.3 (67, 575)
			5 (0.0004)	22	82.5 (51, 725)
5	4-CH ₃ OC ₆ H ₄ Br	CH ₂ =CHCOOC ₂ H ₅	1 (0.0016)	10	86.5 (5, 461)
	(10 mmol)	(20 mmol)	2 (0.0014)	7	67.8 (4, 923)
			3 (0.0018)	24	50.0 (2, 777)
6	4-CH ₃ COC ₆ H ₄ Cl ^b	CH ₂ =CH.COOC ₂ H ₅	1 (0.0018)	24	38.5 (2, 140)
	(10 mmol)	(20 mmol)	2 (0.0018)	24	50.0 (2, 777)
7	4-CH ₃ COC ₆ H ₄ Cl ^b	C ₆ H ₅ CH=CH ₂	1 (0.0018)	24	54.9 (3, 103)
	(10 mmol)	(16 mmol)	2 (0.0023)	24	75.7 (3, 347)
	× ,	. ,	3 (0.001)	24	61.4 (3, 070)
8	4-CNC _c H ₄ Cl ^b	C _c H ₅ CH=CH ₂	1 (0.0018)	24	73.4 (4, 111)
	(10 mmol)	(16 mmol)	2 (0.0017)	24	70 (3, 902)
	· · · ·	. ,	3 (0.002)	24	34.1 (1, 705)

 Table 1
 Mizoroki–Heck Reaction Catalyzed by Saturated N-Heterocyclic Carbene Palladacycles^a

^a Temperature: 130-150 °C.

^b NBu₄Br (1 mmol); Base: NaOAc (1.2 equiv); Solvent: NMP.

4-Chloroacetophenone and 4-chlorobenzonitrile reacted with styrene and ethyl acrylate to give the corresponding *E*-4-acetyl/nitrile stilbene (75.7%, 70% yield respectively) and *E*-4-acetyl ethyl cinnamate (50%) under similar conditions (Bu₄NBr was used as co-catalyst). The TON's obtained for the aryl chlorides were lower (2500–4100) compared to the bromides.

The results of the Suzuki reaction catalyzed by catalyst **2** (Scheme 3) is given in Table 2. Both aryl iodides and bromides gave excellent yields of the biaryl products (73–99%). Activated chlorides, 4-chloronitrobenzene and 4-chlorobenzonitrile gave 78% and 49% yields of biaryls (TON: 871 and 717) while chlorobenzene was also activated but gave a low, 25% yield (TON: 185) of the biphenyl.

Similarly, in a single experiment, the catalyst- 2 was also used for the amination of bromobenzene with morpholine to give *N*-phenyl morpholine in low yield. The attempted Sonogashira coupling of 4-nitroiodobenzene, 4-methoxyiodobenzene and 1-bromonaphthalene with phenyl acetylene was unsuccessful with both catalysts 1 and 2.



R: 4-NO2, 4-OCH3, 4-CH3 X: I, Br, Cl

Scheme 3 Suzuki reaction catalyzed by N-heterocyclic carbene palladacycle **2**.

Surprisingly, homo coupling of aryl iodides and bromides catalyzed by the complex **2** gave low yields of the biaryls (Table 3). Reaction of 4-nitroiodobenzene (1.0 mmol) in presence of zinc dust (1 mmol) catalyzed by **2** (0.0009 mmol) in DMF at 110 °C gave the 4,4'-dinitrobiphenyl in 12% yield. Bromobenzene did not react under these conditions, while 2-bromopyridine gave 16% yield of 2,2'-bipyridyl (NMP, 140 °C, 0.0015 mmol of catalyst **2**). Higher quantities of Zn did not affect the reaction.

In summary, orthometallated oxime and amine palladacycle complexes with a saturated N-heterocyclic carbene ligand catalyze the Mizoroki–Heck and Suzuki reactions of aryl bromides and activated aryl chlorides with high

Table 2Suzuki Reaction Catalyzed by N-Heterocyclic Carbene Palladacycle $2^{a,10}$

Entry	Aryl Halide (mmol)	Time (h)	Catalyst 2 (mmol)	Yield (%)	TON
1	$C_6H_5I(2)$	24	(0.0007)	43.5	1, 243
2	$4\text{-}CH_{3}OC_{6}H_{4}I\left(1\right)$	24	(0.0012)	88.0	733.6
3	4-NO ₂ C ₆ H ₄ I (0.5 mmol)	24	(0.0018)	80.4	224
4	C ₆ H ₅ Br (2 mmol)	24	(0.0007)	73.8	2,096
5	4-CH ₃ OC ₆ H ₄ Br (1 mmol)	24	(0.001)	66.7	684
6	1-BrNp (2 mmol)	14	(0.0009)	99.0	2, 313
7	$4-CH_3C_6H_4Br$	7	(0.001)	77.0	771
8	4-CH ₃ OOCC ₆ H ₄ Br	6	(0.0018)	85.7	471
9	$4-NO_2C_6H_4Cl$	19	(0.001)	78.0	871
10	4-CNC ₆ H ₄ Cl	4	(0.0007)	49.0	717
11	C ₆ H ₅ Cl	24	(0.0014)	25.0	185

^a Base: K₃PO₄ (2 equiv); Solvent: DMF; Temperature: 120 °C; C₆H₅B(OH)₂: 1.5 equiv.

Table 3 Biaryl Coupling Catalyzed by N-Heterocyclic Carbene Palladacycle 2 and Zn/K₂CO₃

Entry	Aryl Halide (mmol)	Time (h)	Catalyst 2 (mmol)	Yield (%)	Coupling Agent
1	4-NO ₂ C ₆ H ₄ I (1.0 mmol)	40	(0.0009)	12.1	Zn
2	4-CH ₃ OC ₆ H ₄ I (0.5 mmol)	24	(0.00045)	4	Zn
3	C ₆ H ₅ Br (1 mmol)	24	(0.0009)	NR	Zn
4	2-BrPy (1 mmol)	24	(0.003)	16	K ₂ CO ₃

^a Reaction conditions : $4-NO_2C_6H_5I$: 1 mmol, Catalyst **2**: 0.0009 mmol, Zn dust: 5 mmol, DMF: 5 mL, 110 °C, 40 h; Yield : 0.142 g, 12.1%.

TON and TOF. The activity of these complexes are similar to previously reported oxime and amine palladacycle complexes and the stability and reactivity is increased by the N-heterocyclic carbenes compared to the phosphine ligands.

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(a) Mizoroki-Heck reaction with benzophenone oxime carbene palladacycle (Cat 3): To 5.175 g (25 mmol) of 1bromonaphthalene, styrene (3.03 g, 30 mmol) and 25 mL Nmethylpyrrolidinone were added to, followed by 2.49 g (30 mmol) of NaOAc and 0.00022 g (0.0004 mmol) of the (Cat 3) benzophenone oxime palladacycle carbene catalyst. The reaction mixture was heated to 140-150 °C in an oil bath until the bromonaphthalene was completely consumed (36 h). HCl (10%, 100 mL) was added to the reaction mixture and extracted with ethyl acetate (3×100 mL). Washing the organic extracts with brine, drying over anhydrous Na₂SO₄, concentration on a rotary evaporator and purification by column chromatography (silica gel: 100-200 mesh) gave 5.32 g (92.6%, TON 61, 956) of E-1-naphthylstilbene. (b) Suzuki coupling of bromobenzene with phenyl boronic acid catalyzed by carbene palladacycle (Cat -2): Bromobenzene (0.314 g, 2 mmol), phenyl boronic acid (0.367 g, 3 mmol), catalyst (3, 0.0004 g, 0.0007 mmol) and K₃PO₄ (0.920 g, 4.34 mmol) were dissolved in DMF (5 mL) and the reaction mixture heated to 120 °C for 24 h. The biphenyl product was isolated by addition of HCl (10%, 25 mL) and extracted with ethyl acetate followed by purification by column chromatography (silica gel: 100-200 mesh) in 73.3% (0.226 g, TON 2, 096) yield. (c) Biaryl coupling catalyzed by carbene palladacycle (Cat-2) and K₂CO₃. 2-Bromopyridine (0.158 g, 1.0 mmol), K₂CO₃ (0.165 g, 1.2 mmol), catalyst (2, 0.0017 g, 0.003 mmol) were dissolved in DMF (5 mL) and heated to 140 °C for 24 h. The bipyridyl was isolated by the usual extractive procedure with water and ethyl acetate. Purification by column chromatography (silica gel: 100-200 mesh) gave 0.025 g (16%) yield of the 2,2'-bipyridyl. ¹H NMR (δ , 200 MHz, CDCl₃) 8.69-8.71 (d, 2 H), 8.39-8.43 (d, 8 Hz, 2 H), 7.80–7.88 (m, 2 H), 7.27–7.36 (m, 2H).