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Practical Heck−Mizoroki Coupling Protocol for Challenging Substrates Mediated by an N-Heterocyclic Carbene-Ligated Palladacycle

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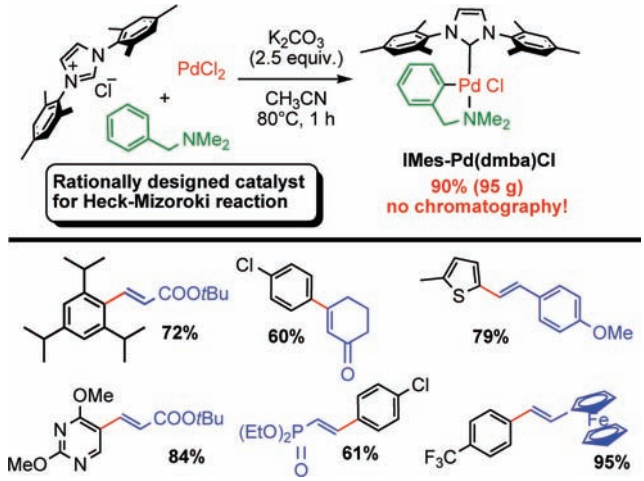
ABSTRACT



A highly active, N-heterocyclic carbene-palladacycle precatalyst for the Heck−Mizoroki reaction was rationally designed. The complex can be synthesized on a large scale in excellent yield by a novel, one-pot, three-component reaction and is tolerant to air, moisture, and long-term storage. A wide range of challenging substrates is successfully coupled under a simple and user-friendly reaction protocol.

The development of novel catalysts with improved performance for Pd-mediated cross-coupling reactions underpins the broad range of applications of cross-coupling reactions in organic synthesis.[1] The Heck−Mizoroki reaction[2] has become one of the most widely employed within this family of transformations for the assembly of complex molecules.[3] While coupling of simple aryl iodides or bromides can be achieved in high yields with virtually any Pd source,[4] cross-coupling of functionalized aryl and heteroaryl substrates such as those found in drug molecules poses significant challenges[5] and requires the addition of a spectator ligand that modifies the steric and electronic properties of the Pd center. In recent years, two families of highly active, broadly applicable classes of ligands have emerged: phosphanes[1,6] and N-heterocyclic carbenes (NHCs).[7] Wide adoption of catalytic protocols is facilitated when availability, cost,

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(2) (a) Bräse, S.; De Meijere, A. *Metal-catalyzed cross-coupling reactions*, 2nd ed.; De Meijere, A., Diederich, F., Eds.; Weinheim, 2004; Vol. 1, p 217. (b) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009.

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(4) Review: Farina, V. *Adv. Synth. Catal.* **2004**, *346*, 1553.

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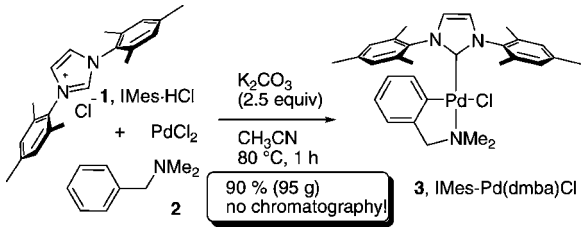
stability, tolerance to impurities, oxygen and moisture, avoidance of highly toxic and difficult to remove reagents, as well as ease of usage are taken into consideration, in addition to the intrinsic activity of the catalyst. Herein, we present such a totally designed Heck−Mizoroki protocol for the coupling of challenging aryl bromides and iodides based on a novel NHC-ligated palladacycle.

Under cross-coupling conditions, palladacycles are shown to decompose with the liberation of catalytically active, ligandless palladium.[8] Even though Pd complexes of a bulky carbene, 1,3-dimesitylimidazolyl-2-ylidene (IMes), have been shown to catalyze Heck-type coupling of simple aryl bromides or aryl diazonium salts with acrylates or styrene,[9] more complex, functionalized substrates have received little attention. Therefore, we reasoned that the hitherto unknown[10] complex (**3**, Scheme 1, Figure 1) of IMes and *o*-palladated

Scheme 1. Optimized, One-Pot, Three-Component Synthesis of a NHC-Palladacycle



N,*N*-dimethylbenzylamine (dmba)[11] would possess expanded substrate scope, while maintaining high activity as a

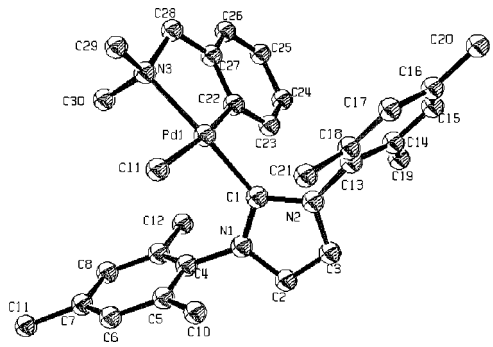
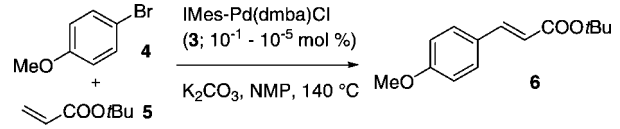


Figure 1. ORTEP representation of the solid-state molecular structure of complex **3**. The thermal ellipsoids are shown at 30% probability, and the hydrogen atoms are omitted for clarity.

Heck−Mizoroki precatalyst. However, the current methods for NHC-palladacycle preparation require purified dimeric palladacycles. The carbene ligands are then introduced via μ-chloride displacement with isolated, highly moisture- and air-sensitive NHCs.[12] On the other hand, methods that use moisture- and air-tolerant carbene surrogates have limited scope and proceed only in low to moderate yields.[13] To address these shortcomings, we sought a practical, high-yielding NHC-palladacycle synthesis that would employ stable NHC precursors (imidazolium salts) and in situ prepared palladacycles without the need for anhydrous techniques or a glovebox. Heating $PdCl_2$ and the commercially available, inexpensive amine **2** in HPLC-grade acetonitrile in air in the presence of excess K_2CO_3 followed by the addition of commercial NHC precursor IMes·HCl (**1**) led to near quantitative yield of complex **3**. Under optimized conditions, a large quantity of **3** (95 g; 90% yield) was obtained after simple crystallization. The initial assessment of the catalytic activity of **3** (Table 1) was conducted at

Table 1. Initial Assessment of the Catalytic Activity of **3**[a]



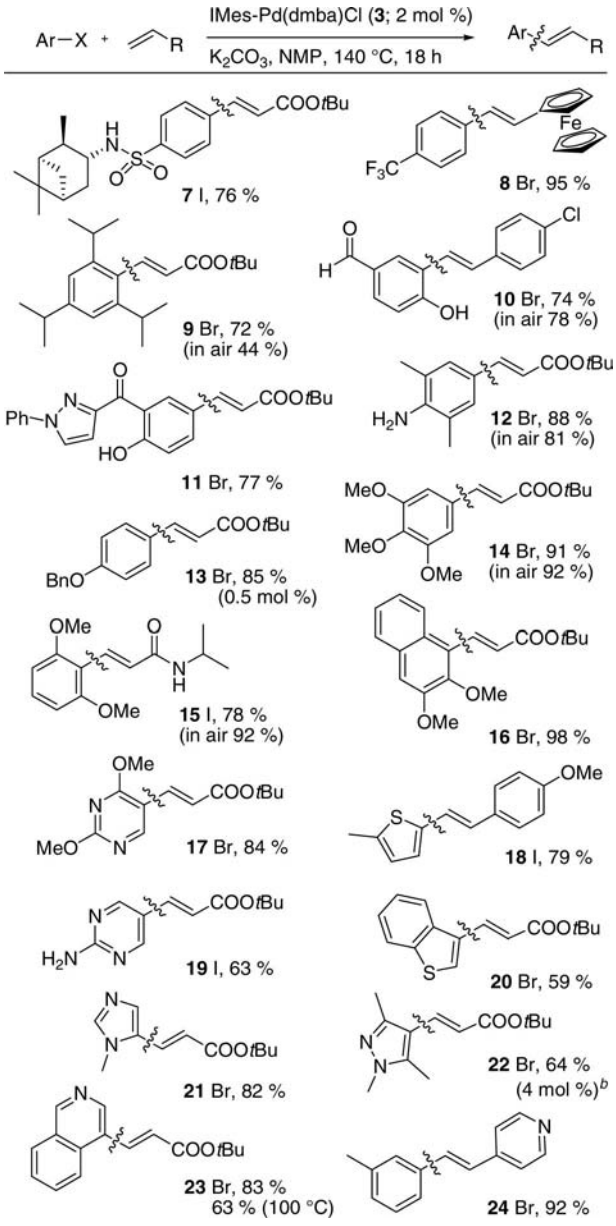
entry	3 (mol %)	time (h)	6/4 (%)	TON[b]
1	2.0	18	100/0[c]	–
2	0.10	24	86/6.2	–
3	0.010	72	59/32	–
4	1.0×10^{-3}	72	54/40	–
5	1.0×10^{-4}	168	11/81	1.14×10^5
6	1.0×10^{-5}	168	5.2/74	5.22×10^5

[a] The reactions (1.0 M of *p*-bromoanisole (**4**), 2.0 M of *tert*-butyl acrylate (**5**)) were performed in duplicate. The average product yield and starting material recovery (±4%) were determined by quantitative ^{1}H NMR spectroscopy (internal standard: *N*,*N*-dimethylformamide (DMF)). [b] TON = mmol **6**/mmol **3**. [c] Isolated yield.

catalyst loadings of $0.1-10^{-5}$ mol % with *tert*-butyl acrylate (**5**) and a deactivated arylbromide, *p*-bromoanisole (**4**). Notably, 54% of **6** was formed at 10 ppm of Pd, comparable with the FDA-approved limit for Pd content in pharmaceuticals. The catalyst attained a maximum turnover number (TON) of 5.22×10^5 at a loading of 1.0×10^{-5} mol %.

More challenging aryl halides, such as those containing two *o*-substituents (**9**, **15**, **16**; Scheme 2), free anilines (**12**, **19**) or phenols (**10**, **11**), and multiple methoxy groups (**19**−**22**) coupled well over 2 mol % of **3**. The protocol was compatible with aryl chlorides (**10**) and benzyl-protected phenols (**13**). The coupling of the heterocycle was sensitive to the nature of the heterocyclic ring. Pyrimidine (**17**, **19**), pyridine (**23**, **24**), or thiophene derivatives (**18**, **20**) coupled in good to excellent yields. Whereas the imidazole derivative **21** was obtained in 82% isolated yield, the challenging bromopyrazole containing two *o*-methyl groups only coupled in 32% yield (**22**)[14] (4 mol % of **3**; 49% of the starting bromide was recovered). However, the presence of heterocyclic rings further away from the reaction site was well tolerated (**16**, **29**). Among Heck acceptors, vinylferrocene (**8**) and 4-vinylpyridine (**24**) were coupled for the first time under NHC-Pd catalysis. Moreover, the catalyst could be used in air without significant loss of activity in most cases. Notably, by careful choice of base, we have achieved the first Heck−Mizoroki couplings (Table 2) of diethyl vi-

Scheme 2. Heck−Mizoroki Couplings of Functionalized Aryl and Heteroaryl Bromides and Iodides Mediated by Complex **3**, Showing Isolated Yields of Chromatographically Homogeneous Materials, Average of Two Runs (NMP = 2-Methyl-1-pyrrolidone)[a]

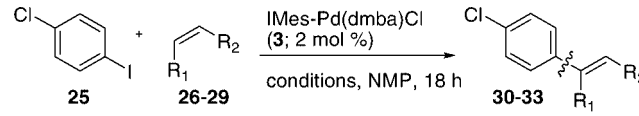


[a]The reactions were not optimized with respect to time. [b]The yield of **22** is based on the recovered starting bromide (49%).

nylphosphonate (**27**), phenyl vinyl sulfone (**28**), and cyclohexenone (**29**) mediated by NHC-Pd catalysts (products **31**, 61%; **32**, 37%; and **33**, 60%, respectively).

A comparison of the catalytic activity of complex **3** and a total of 14 Heck−Mizoroki precatalysts[15] revealed some interesting observations. (i) The catalysts were tested against a panel of three "challenges" — "steric" (**34**), "electronic" (**35**), and "catalyst poison" (**36**). The bulky bromide **34** was the most discriminating, whereas the imidazole-derived

Table 2. Heck−Mizoroki Couplings of Less Common Alkenes Mediated by Complex **3**[a]



entry	conditions	alkene	R_1	R_2	yield (%)
1	K_2CO_3, 100 °C	**26**	H	CN	88 (**30**)[b]
2	iPr$_2$NEt, 120 °C[c]	**27**	H	$PO(OEt)_2$	61 (**31**)
3	NaOAc, 120 °C[c]	**28**	H	SO_2Ph	37 (**32**)
4	$NaHCO_3$, 120 °C	**29**	$-(CH_2)_3-C(=O)-$		60 (**33**)

[a] Isolated yields of chromatographically homogeneous materials, average of two runs. The reactions were not optimized with respect to time. [b] *E*:*Z* = 6:1 (^{1}H NMR). [c] In the presence of finely ground 4 Å molecular sieves.

bromide **36** showed almost identical yields.[16] Even though there was no single catalyst that was the best for all three substrates, some ligands such as IMes, Cy$_3$P (Cy = cyclohexyl), and P*t*Bu$_3$ allowed good yields to be attained for the

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(6) Reviews: (a) Mauger, C. C.; Mignani, G. A. *Aldrichimica Acta* **2006**, *39*, 17. (b) Zapf, A.; Beller, M. *Chem. Commun.* **2005**, 431.

(7) Reviews and books: (a) *N-Heterocyclic Carbenes in Transition Metal Catalysis*; Glorius, F., Ed.; Springer-Verlag: Berlin Heildergerg, 2007. (b) Kantchev, E. A. B.; O'Brien, C. J.; Organ, M. G. *Angew. Chem., Int. Ed.* **2007**, *46*, 2768. (c) *N-Heterocyclic Carbenes in Synthesis*; Nolan, S. P., Ed.; Wiley-VCH: Weinheim, 2006. (d) Herrmann, W. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1290.

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(10) While this work was in progress, a similar complex was reported independently: Cao, X.-H.; Zheng, Y.; Yu, H.-W.; Shi, J.-C. *J. Coord. Chem.* **2007**, *60*, 207.

(11) Pfeffer, M. *Inorg. Synth.* **1989**, *26*, 211.

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three substrates ("privileged" or "universal" ligands).[17] (ii) Generally, the ligand activity increased in the order: ligandless < phosphane < NHC at a ligand:Pd molar ratio of 1:1. However, phosphane catalysts with more than one phosphane per Pd tended to have better overall performance (Table 3, entries 11 and 12). In contrast, *trans*-$(IMes)_2PdCl_2$ was completely inactive.[9a] (iii) The composition of the Pd source was as important as the ligand — the palladacycles showed overall best performance in the Heck−Mizoroki reaction regardless of the nature of the ligand. (iv) Among the Pd precursors investigated, preformed, well-defined, single-component precatalysts generally outperformed in situ prepared "brews" from (pro)ligands and simple Pd salts. The fact that two of the very active and versatile biarylphosphane ligands developed by Buchwald's group (**43**, **44**) led to very low yields under our protocol (entries 9 and 10, Table 3) was a case in point.[18]

In conclusion, we have developed a novel NHC-palladacycle as a rationally designed precatalyst (**3**) for the Heck−Mizoroki reaction of challenging substrates with respect to both catalytic performance and practicality. The preparation of other NHC-palladacycles and their use as catalysts in Pd-mediated transformations are underway.

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Supporting Information Available: Synthetic procedures and characterization data for compounds **3**, **6**, **7**−**24**, **30**−**33**, **40**, and **41** and crystallographic information file (.cif) for complex **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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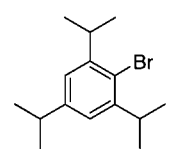
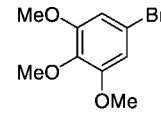
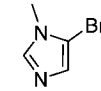
Table 3. Comparison of the Catalytic Activity of Complex **3** with Other Precatalysts (1 mol % Pd) in the Heck−Mizoroki Couplings of Challenging Aryl Bromides **34**−**36** with *tert*-Butyl Acrylate (**5**)[a]



34



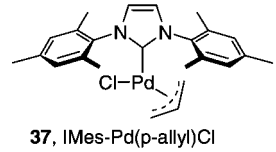
35



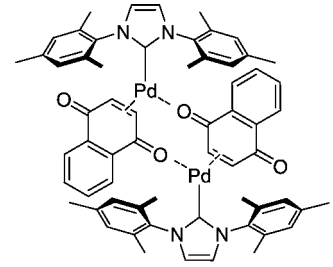
36

entry	Pd catalyst (1 mol %)	9/34 (%)	14/35 (%)	21/36 (%)
1	IMes-Pd(dmba)Cl (**3**)	77/23	92/0.0	63/17
2	IMes-Pd(π-allyl)Cl (**37**)	30/66	85/1.2	60/31
3	[IMes-Pd(NQ)]$_2$ (**38**)	27/73	65/12	65/25
4	Pd-PEPPSI-IMes (**39**)	32/69	65/17	32/58
5	IMes·HCl (**1**)/Pd(OAc)$_2$	3.0/98	34/42	46/41
6	Cy_3P−Pd(dmba)Cl (**40**)[b]	70/19	71/2.7	50/33
7	Complex **42**	29/57	91/0.0	69/7.8
8	[Pd(PtBu$_3$)$_2$]	80/19	75/0.0	63/27
9	DavePhos (**43**)/Pd(OAc)$_2$	0.9/89	52/22	62/79
10	XPhos (**44**)/Pd(OAc)$_2$	0.0/100	0.0/100	73/7.3
11	Ph_3P−Pd(dmba)Cl (**41**)[b]	21/64	62/13	74/0.5
12	[Pd(PPh_3)$_4$]	93/2.2	43/25	61/8.8
13	[Pd(dmba)Cl]$_2$	5.7/87	78/4.6	62/18
14	Pd(OAc)$_2$ as PdEnCat 30	7.5/93	52/33	55/8.8
15	Pd/C (10 wt %)	0.5/89	35/60	18/78

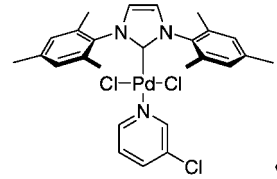
[a] Conditions: K_2CO_3 (2 equiv), NMP, 140 °C, 18 h. The catalysts were handled in air and added as freshly prepared, argon-degassed 0.05 M solution in NMP unless insoluble or >5 mg was needed. [b] Prepared according to the NHC-palladacycle synthesis protocol with slight modifications (Scheme 1). **40**: 78% yield. **41**: 98% yield.



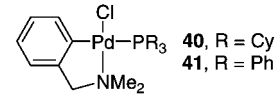
37, IMes-Pd(p-allyl)Cl



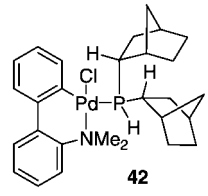
38, [IMes-Pd(NQ)]$_2$



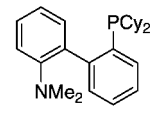
39, Pd-PEPPSI-IMes



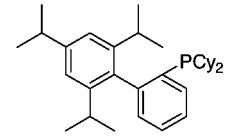
40, R = Cy
41, R = Ph



42



43, Dave-Phos



44, X-Phos

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