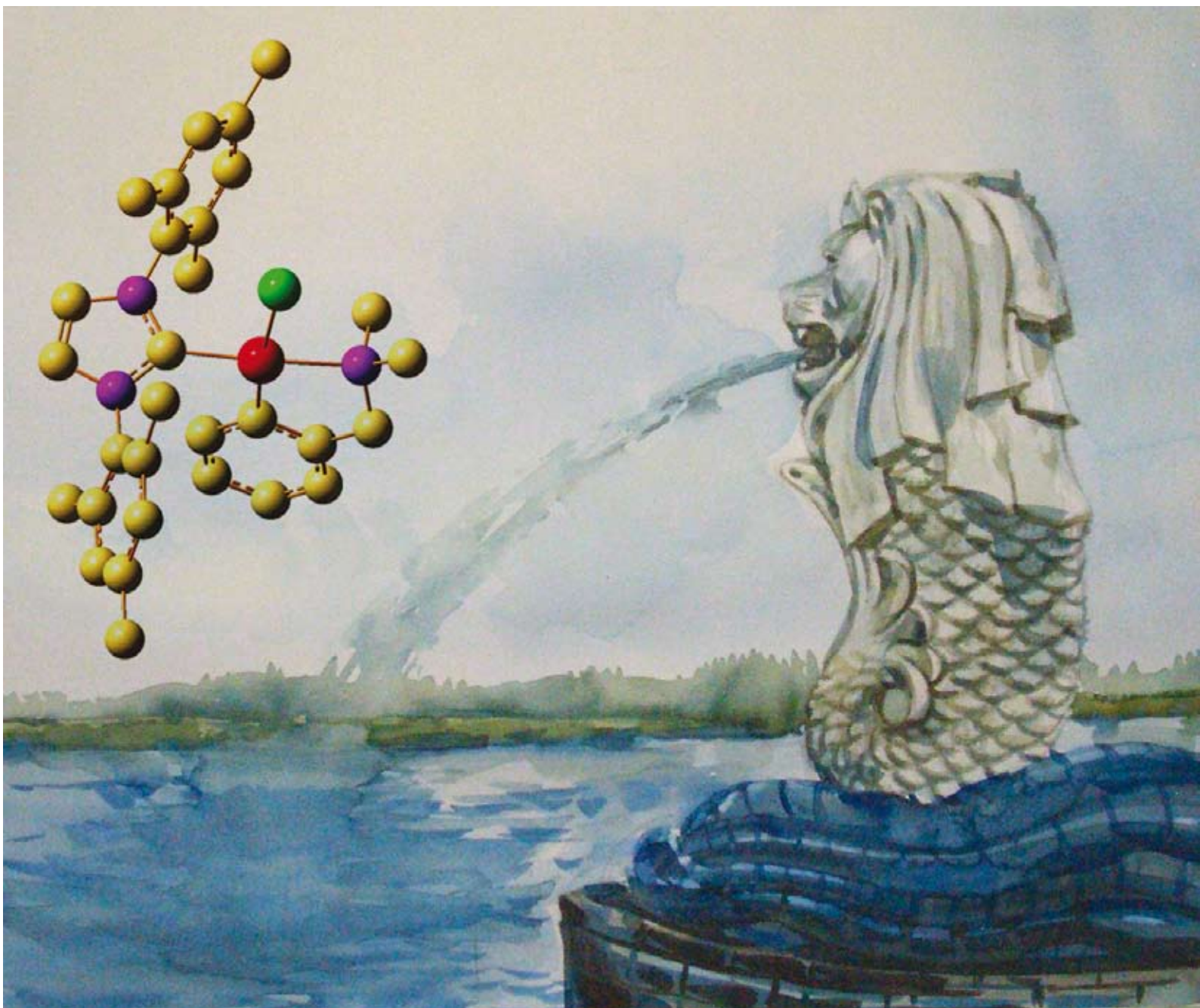


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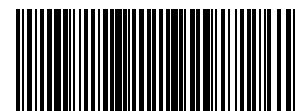
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FULL PAPER

Guang-Rong Peh *et al.*
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Chemical Science

In this issue...



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N-heterocycle carbene (NHC)-ligated cyclopalladated *N,N*-dimethylbenzylamine: a highly active, practical and versatile catalyst for the Heck–Mizoroki reaction†

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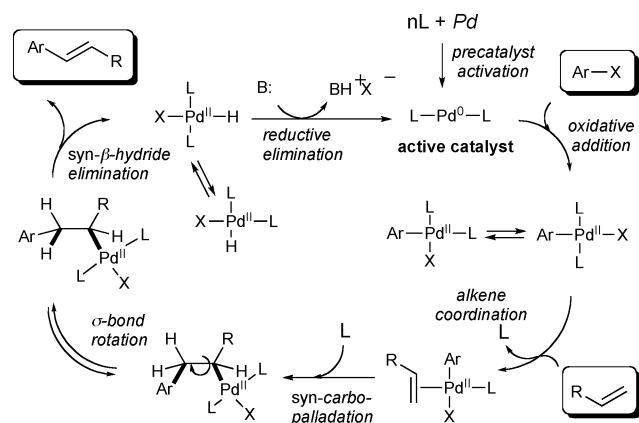
DOI: 10.1039/b821892g

The wide dissemination of catalytic protocols in academic and industrial laboratories is facilitated by the development of catalysts that are not only highly active but also user-friendly, stable to moisture, air and long term storage and easy to prepare on a large scale. Herein we describe a protocol for the Heck–Mizoroki reaction mediated by cyclopalladated *N,N*-dimethylbenzylamine (dmba) ligated with a N-heterocyclic carbene, 1,3-bis(mesityl)imidazol-2-ylidene (IMes), that fulfils these criteria. The precatalyst can be synthesized on ~100 g scale by a tri-component, sequential, one-pot reaction of *N,N*-dimethylbenzylamine, PdCl₂ and IMes·HCl in refluxing acetonitrile in air in the presence of K₂CO₃. This single component catalyst is stable to air, moisture and long term storage and can be conveniently dispensed as a stock solution in NMP. It mediates the Heck–Mizoroki reaction of a range of aryl- and heteroaryl bromides in reagent grade NMP at the 0.1–2 mol% range without the need for rigorous anhydrous techniques or a glovebox, and is active even in air. The catalyst is capable of achieving very high levels of catalytic activity (TON of up to 5.22 × 10⁵) for the coupling of a deactivated arylbromide, *p*-bromoanisole, with *t*Bu acrylate as a benchmark substrate pair. A wide range of aryl bromides, iodides and, for the first time with a NHC-Pd catalyst, a triflate was coupled with diverse acrylate derivatives (nitrile, *tert*-butyl ester and amides) and styrene derivatives. The use of excess (>2 equiv.) of the aryl bromide and *tert*-butyl acrylate leads to mixture of *tert*-butyl β,β-diarylacrylate and *tert*-butyl cinnamate derivatives depending on the substitution pattern of the aryl bromide. Electron rich *m*- and *p*-substituted arylbromides give the diarylated products exclusively, whereas electron-poor aryl bromides give predominantly mono-arylated products. For *o*-substituted aryl bromides, no doubly arylated products could be obtained under any conditions. Overall, the active catalyst (IMes-Pd) shows higher activity with electron-rich aryl halides, a marked difference compared with the more commonly used phosphane-Pd or non-ligated Pd catalysts.

Introduction

It is difficult to imagine organic synthetic chemistry today without cross-coupling reactions, a family of transformations that allow two organic moieties to be joined by a single bond by means of a transition metal catalyst,¹ most often Pd.² Within the family, the Heck–Mizoroki reaction³ has become one of the most prominent. For the pharmaceutical industry in particular, a recent survey of the chemical reactions employed by major pharmaceutical companies for the preparation of drug candidates in process R & D found that among all C–C bond-forming reactions, Pd-catalyzed processes were the single most employed reaction class (22%), with the Suzuki–Miyaura and Heck–Mizoroki reactions claiming the lion's share (11% and 7%, respectively).⁴ In addition,

the Heck–Mizoroki reaction is also a key transformation of strategic importance in natural product synthesis.⁵ The generally accepted mechanism⁶ for the Heck–Mizoroki reaction is shown in Scheme 1. The first step, oxidative addition of the arylhalide into the active Pd(0) catalyst is common for all Pd-mediated



Scheme 1 The generally accepted mechanism of the Heck–Mizoroki reaction.

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cross-coupling reactions. Upon binding of the olefin to the resultant Ar-Pd(II)-X intermediate, *syn*-migratory insertion followed by σ -bond rotation and *syn*- β -hydride elimination ensue, resulting in the formation of the Heck–Mizoroki product and H-Pd(II)-X adduct. Base-promoted reductive elimination of HX completes the cycle and regenerates the catalyst. Ligandless Pd⁷ was the catalyst in the initial reports of this reaction by the groups of Heck⁸ and Mizoroki⁹ and even today it remains one of the top choices owing to low cost and high activity. Pd(OAc)₂ alone^{7,10} or in the presence of tetraalkyl ammonium salts (Jeffery conditions),^{7,11} PdCl₂ and its soluble bis(nitrile) adducts¹² or preformed Pd nanoparticles¹³ have all been explored as readily available ligandless Pd precatalysts. The first use of the cyclopalladated tri(*o*-tolyl)phosphane (Herrmann–Beller palladacycle) a catalyst for the Heck–Mizoroki¹⁴ and Suzuki–Miyaura¹⁵ reactions was published in 1995. As there are a plethora of stable, *o*-palladated aromatic compounds possessing O, N, P or S atoms,¹⁶ this finding caused a surge of enthusiasm with the expectation for asymmetric induction and Pd(II)/Pd(IV) catalytic cycle¹⁷ if the palladacycle framework were retained in the coordination sphere of the Pd atom during catalysis. Subsequent investigation, however, showed that under cross-coupling conditions palladacycles are not stable, but degrade rapidly to give colloidal Pd(0).^{18,19} Today, palladacycles are popular, highly active precatalysts for the ligandless Heck–Mizoroki reaction.²⁰

As a result of numerous studies throughout the years, it has become clear that high-yield couplings of aryl iodides and activated bromides can be achieved with virtually any Pd source.²¹ However, arylhalides derived from more complex, highly substituted aryl and heteroaryl halides usually require the addition of a spectator ligand (L, Scheme 1). The nature of the ligand plays a paramount role for the success of challenging cross-couplings. Triarylphosphanes, for example triphenylphosphane and tri(*o*-tolyl)phosphane are excellent ligands for Heck–Mizoroki couplings of iodo- and, especially, bromoarenes with an extended range of olefins.²² Bulky, electron-rich trialkyl phosphanes such as tri(*tert*-butyl)phosphane and tricyclohexylphosphane are required for coupling the more inert, but cheaper and more widely-available chloroarenes^{23,24} or room temperature Heck–Mizoroki reactions.^{24,25} Finally, *P,C*-palladacycles derived from suitably substituted triarylphosphanes have shown high catalytic activity at comparatively lower catalyst loadings, even towards arylchlorides.¹⁵ When *P,C*-palladacycles are activated, highly active mono-ligated phosphane-Pd(0) complexes are produced.²⁶ However, phosphane ligands suffer from numerous drawbacks. Pd-bound phosphanes are degraded at high temperatures,²⁷ leading to highly colored by-products that could be difficult to remove from the cross-coupling product. In addition, triarylphosphanes readily dissociate from Pd and are usually employed in excess in order to suppress the formation of catalytically inactive Pd-black. On the other hand, trialkylphosphanes, which can be used at 1:1 stoichiometry to Pd, are expensive and air-sensitive, some even pyrophoric. In recent years, N-heterocyclic carbenes (NHCs)^{28,29} have emerged as powerful ligands and catalysts in general,³⁰ and as an alternative to phosphane ligands in Pd-mediated reactions in particular.³¹ NHC-Pd complexes exhibit higher stability³² compared to their phosphane counterparts at the high temperatures often employed during cross-couplings, even at 1:1 Pd/NHC stoichiometry. In addition, the strong

σ -donicity of NHCs facilitates the oxidative addition.³³ Starting with the seminal publication by Herrmann *et al.*,³² the Heck–Mizoroki reaction of simple aryl bromides or iodides with acrylates or styrene has become a favorite benchmark for assessing the catalytic potential of new NHC ligands.^{34,35} Even though these studies have firmly established that NHCs are an excellent choice as ligands for the Heck reaction,^{34,35} less common but more synthetically relevant substrates have not been hitherto explored in a systematic manner. Recently, we communicated our preliminary results on the preparation and use of a well-defined, stable NHC-palladacyclic complex (**1**; Fig. 1) in the Heck–Mizoroki reaction of challenging substrates. Complex **1** showed levels of activity equal to or exceeding other highly active Heck–Mizoroki catalysts.³⁶ Herein we report the full account of the design and development of **1** as a practical, highly active, versatile and user-friendly Heck–Mizoroki catalyst.

Results and discussion

Catalyst design and large scale preparation

Pd-complexes of a bulky carbene, 1,3-bis(mesityl)imidazolyl-2-ylidene (IMes; Fig. 1) mediate the Heck–Mizoroki reaction of simple aryl bromides and diazonium salts with simple acrylates and styrene.^{37–39} An unsymmetrical NHC ligand carrying one *N*-Mes substituent and one chelating phosphane *N*-substituent has also shown high levels of activity.³⁵ Therefore, we focused on IMes as a privileged ligand for the development of a practical, widely applicable NHC-mediated Heck–Mizoroki reaction. However, the nature of the Pd precatalyst responsible for the smooth delivery of Pd from the initial precatalyst into the catalytic cycle also plays an important role in the success of the catalytic process as a whole.^{40,41} As NHCs are highly air- and moisture-sensitive, they are usually generated in-situ⁴² from stable precursors, *e.g.*, imidazolium salts⁴³ and then captured with common Pd sources. This process is difficult to control; hence, the amounts and composition of the active species produced are uncertain.^{37,44,45} The development of stable, well-defined NHC-Pd complexes that can be activated under the reaction conditions can mitigate the above drawbacks. Today, a number of such complexes have been prepared^{38,44,46} and some are now commercially available. Palladacycles decompose in a controlled manner to yield atomic Pd(0) and the corresponding Heck–Mizoroki product at the palladated carbon⁴⁷ (Fig. 1) under the conditions of the reaction.^{18,26} Therefore, palladacycles ligated with a single phosphane^{41,48,49} or carbene ligand^{48,50–52} serve as stable precursors to mono-ligated⁵³ catalytically active bulky phosphane/carbene-Pd(0) species. We reasoned that a complex (**1**, Fig. 1) comprised of IMes and the widely-used *o*-cyclopalladated *N,N*-dimethylbenzylamine (**2**)⁵⁴ had the potential to be an excellent precatalyst for the Heck–Mizoroki reaction of challenging arylhalides by virtue of combining the powerful carbene ligand with palladacycle-controlled active catalyst release. Furthermore, wide adoption of the catalytic protocols is facilitated when a number of practical considerations besides the intrinsic activity of the catalyst—large scale availability, cost, stability, tolerance to impurities, oxygen and moisture, avoidance of highly toxic, difficult to remove reagents and ease-of-use, among others—are met. A survey of the existing methods for preparation of NHC-ligated palladacycles revealed

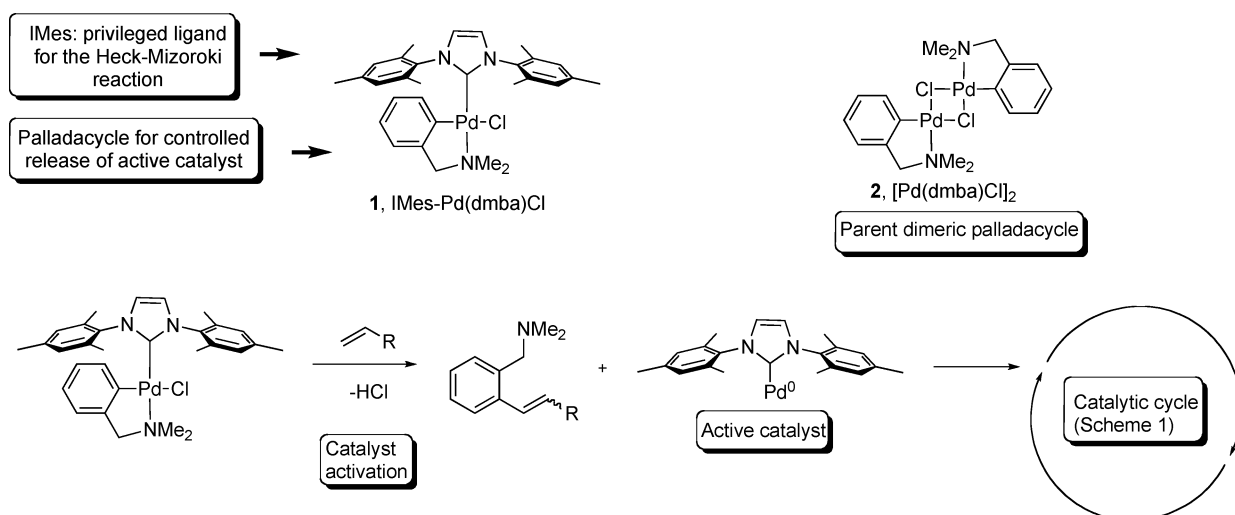


Fig. 1 NHC-Palladacycle **1** as a catalyst for the Heck–Mizoroki reaction: design principles.

that treatment of dimeric palladacycles (*e.g.*, **2**) with isolated carbenes in a glovebox is the most common.^{29,52} On the other hand, alternative methods that employ moisture- and air-tolerant carbene surrogates proceed only in moderate to low yields or are limited in scope.^{50,55} Considering the above, we sought a general, practical, scalable NHC-palladacycle synthesis that would employ stable, easy to handle NHC precursors (imidazolium salts) and in-situ prepared palladacycles without the need for anhydrous techniques or a glove-box.⁵⁶ We discovered that heating PdCl₂ and the amine **4** in HPLC-grade acetonitrile in air in the presence of K₂CO₃ followed by addition of the imidazolium salt IMes·HCl (**3**) led to near quantitative yield of complex **1**. Under optimized conditions, multi-gram quantities of **1** (Scheme 2; 95 g, 90%) were obtained after simple crystallization (CH₃CN). The single crystal X-ray structural analysis†§ confirmed the desired product, revealing a characteristic, slightly distorted square-planar Pd(II) centre with the NHC and the dimethylamino ligands mutually *trans* (Fig. 2; bond angle C(carbene)–Pd–N(NMe₂) = 169.9 °). The Pd–C bond lengths are as expected for single bonds, 1.98 and 2.00 Å for Pd–C(carbene) and Pd–C(*o*-phenyl), respectively. The position of the imidazole ring relative to the puckered palladacycle ring is close to perpendicular (dihedral angle N1(imidazole)–C(carbene)–Pd–C(*o*-phenyl) = –100.8°).

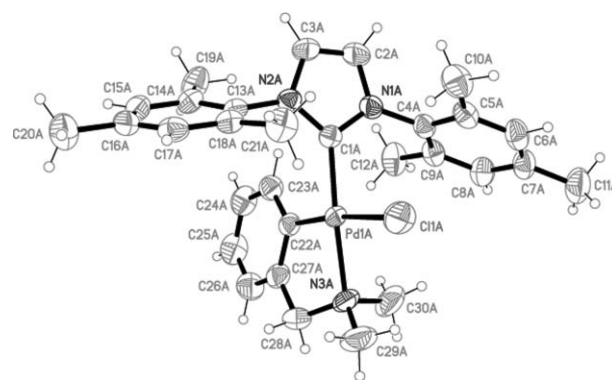
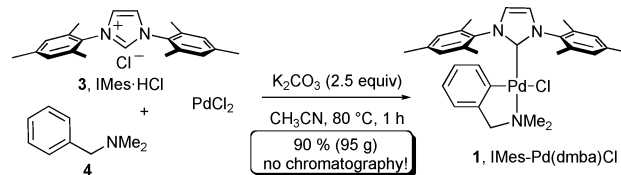


Fig. 2 ORTEP representation of the single crystal X-ray structure of IMes-Pd(dmmba)Cl (**1**). The thermal ellipsoids are shown at 30% probability. The asymmetric unit has two molecules of the Pd complex and a water molecule, which has been assigned 0.5 occupancy. Only one of the Pd complexes is shown. Selected bond distances (Å): N1–C1: 1.360(3); N2–C1: 1.369(3); Pd1–C1: 1.980(2); Pd1–C22: 1.997(2); Pd1–N3: 2.1365(18); Pd1–C11: 2.4025(7). Selected bond angles (°): N1–C1–N2: 104.08(18); C1–Pd1–C22: 91.48(9); C1–Pd1–N3: 169.87(8); C22–Pd1–N3: 82.09(8); C1–Pd1–C11: 94.41(6); C22–Pd1–C11: 173.63(7); N3–Pd1–C11: 91.74(6). Selected dihedral angles (°): N1–C1–C2–N2: –0.04; C1–N1–C4–C9: 88.44; C1–N2–C13–C14: 64.30; N1–C1–Pd–C22: –100.82; C22–C27–C28–N3: –26.28.

§ Crystal data for **1**: Empirical formula: C₃₀H_{36.50}ClN₃O_{0.25}Pd; Formula weight: 584.97; Temperature: 243(2) K; Wavelength: 0.71073 Å; Crystal system: Triclinic; Space group: P-1; Unit cell dimensions: a = 13.5773(6) Å α = 87.2240(10)°, b = 13.5923(6) Å β = 71.8720(10)°, c = 15.9863(7) Å γ = 84.4660(10)°; Volume: 2790.2(2) Å³; Z: 4; Density (calculated): 1.393 Mg/m³; Absorption coefficient: 0.785 mm⁻¹; F(000): 1210; Crystal size: 0.30 × 0.20 × 0.16 mm³; Theta range for data collection: 1.34 to 27.50°; Index ranges: –17 ≤ h ≤ 17, –17 ≤ k ≤ 17, –20 ≤ l ≤ 20; Reflections collected: 35633; Independent reflections: 12801 [R(int) = 0.0277]; Completeness to theta = 27.50°: 99.9%; Absorption correction: Sadabs, (Sheldrick 2001); Max. and min. transmission: 0.8847 and 0.7987; Refinement method: Full-matrix least-squares on F²; Data/restraints/parameters: 12801/3/662; Goodness-of-fit on F²: 1.024; Final R indices [I > 2σ(I)]: R1 = 0.0346, wR2 = 0.0829; R indices (all data): R1 = 0.0427, wR2 = 0.0866; Largest diff. peak and hole: 0.577 and –0.252 e.Å⁻³



Scheme 2 One-pot, three-component synthesis of IMes-Pd(dmmba)Cl (**1**; dmmba = κ²N,C-*N,N*-dimethylbenzylamine).

Initial evaluation of the activity of IMes-Pd(dmmba)Cl in the Heck–Mizoroki reaction and couplings of simple bromoarenes

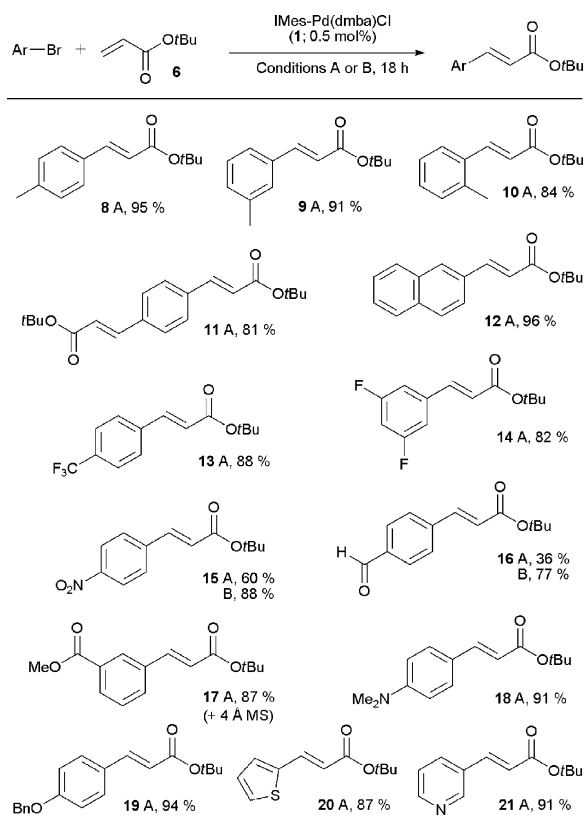
The initial assessment of the catalytic activity of **1** was conducted at catalyst loadings of 0.1–10⁻⁵ mol% on the arylation of *t*Bu acrylate (**6**) with a deactivated arylbromide, *p*-bromoanisole (**5**) (Table 1),

Table 1 Evaluation of complex **1** at low catalyst loadings (0.1–1 × 10⁻⁵ mol%) in the benchmark reactions of a deactivated substrate, *p*-bromoanisole (**5**)

Entry	Mol% 1	Time, h	7/5 , % ^a	TON ^b
1	2.0	18	100 ^c /0	–
2	0.10	24	86/6	–
3	0.010	72	59/32	–
4	0.0010	72	54/40	–
5	1 × 10 ⁻⁴	168	11/81	1.14 × 10 ⁵
6	1 × 10 ⁻⁵	168	5.2/74	5.22 × 10 ⁵

^a The reactions (1.0M **5**, 2.0M **6**, 0.7 mmol scale) were performed in duplicate and averaged product yield and starting material recovery (+/-4%) were determined by quantitative ¹H NMR spectroscopy (internal standard: DMF). ^b TON = mmol **7**/mmol **1**. ^c Isolated yield.

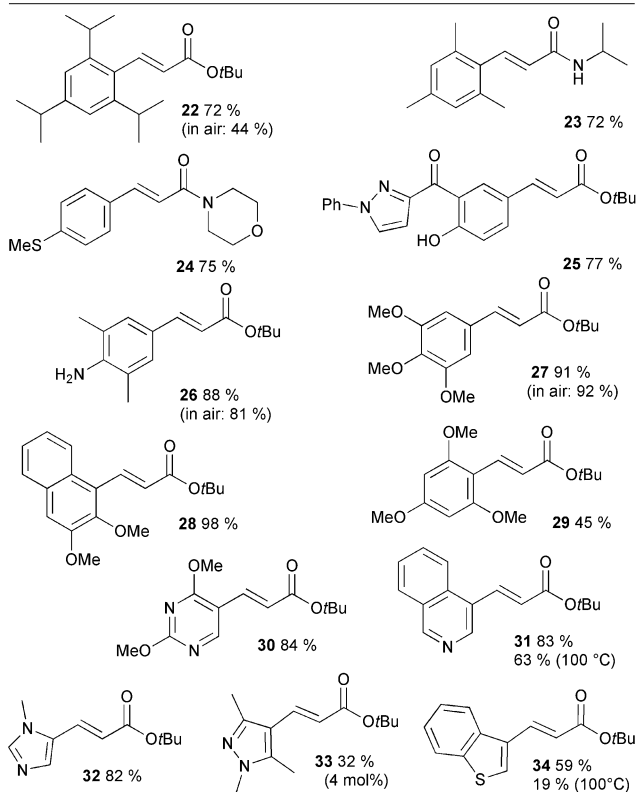
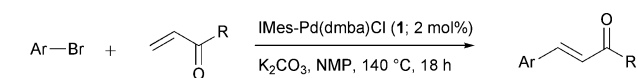
a substrate that was recently suggested as a benchmark for testing of new Pd-catalysis.¹⁶ The colorless solution of precatalyst **1** and the substrates in NMP turned orange within 1–5 min of heating, indicative of palladacycle decomposition and the formation of catalytically active IMes-Pd(0) species. The solution retained this color throughout the reaction, implying little or no formation of Pd-black in accord with the established notion of the excellent thermal stability of NHC-Pd complexes. The catalyst showed excellent productivity, reaching a maximum TON of 5.22 × 10⁵ for arylbromide **5**. Notably, a 54% yield for the product **7** was obtained even when precatalyst **1** was employed at 10 ppm, a concentration comparable with the FDA-established limit for Pd in active pharmaceutical ingredients. Under the standard conditions, a variety of simple bromoarenes underwent Heck–Mizoroki coupling with *tert*-butyl acrylate (**6**) (Scheme 3). Heck–Mizoroki couplings of the three bromotoluene isomers (*o*-, *m*- and *p*-), 2-bromonaphthalene and the double coupling of *p*-dibromobenzene proceeded in excellent yields (81–96%) in the presence of 2 equiv. of K₂CO₃ (products **8**–**12**). Similarly, electron-deficient fluorinated bromobenzene derivatives were excellent substrates (products **13** and **14**). The coupling of other electron-deficient bromobenzenes was less effective under these conditions (A)—even though the starting materials were completely consumed, the yields of the corresponding *t*Bu cinnamate derivatives (**15** and **16**) were moderate (60 and 36%, respectively). The appearance of an intense dark brown–black color suggested that the most likely reason for the low yields would be either product or starting material degradation. A change to milder conditions (2 equiv. of *i*Pr₂NEt, 120 °C, B) led to much higher yields. Electron-rich substrates coupled well under standard conditions (A) (**18**: 91% and **19**: 94%), and so did simple heteroaryl bromides (**20**: 87% and **21**: 91%). Extensive attempts at Heck–Mizoroki couplings of deactivated aryl chlorides (*p*-chloroanisole or *p*-chlorotoluene) were unsuccessful. It should be noted that unlike the facile Suzuki–Miyaura coupling or Buchwald–Hartwig amination of deactivated aryl chlorides, Heck–Mizoroki reaction for these substrates mediated by NHC-Pd catalysts has been a long standing and as yet unsolved problem.³¹



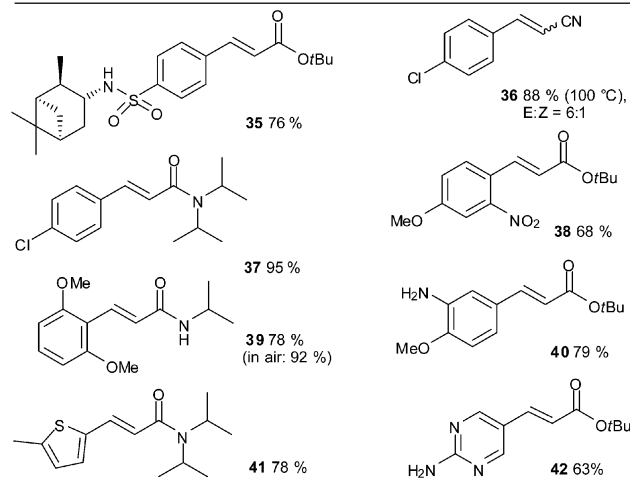
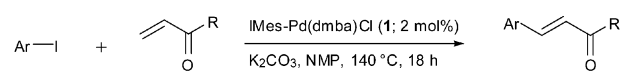
Scheme 3 Preparative Heck–Mizoroki couplings of simple aryl bromides mediated by IMes-Pd(dmab)Cl (**1**) (0.5 mol%). Conditions A: K₂CO₃ (2 equiv.), 140 °C. Conditions B: *i*Pr₂NEt (2 equiv.), 120 °C. The reaction times were not minimized. The yields shown are for chromatographically homogeneous materials, average of two runs.

Heck–Mizoroki reaction of functionalized bromo- and iodoarenes with acrylate and styrene derivatives

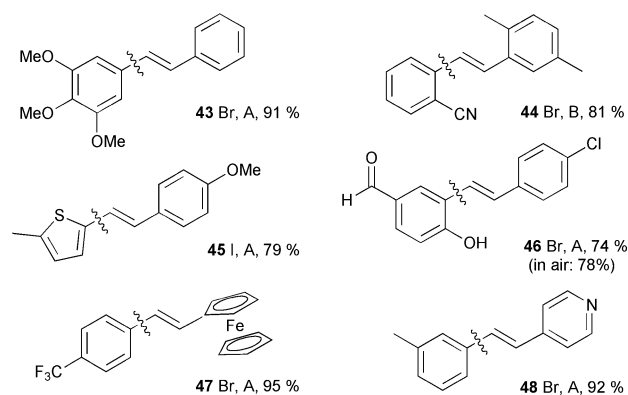
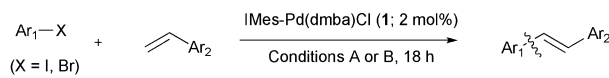
Encouraged by these results, we explored preparative Heck–Mizoroki couplings of a wider range of more challenging, functionalized and heterocyclic aryl bromides (Schemes 4 and 6) and iodides (Schemes 5 and 6) with a wider range of acrylate (Schemes 4 and 5) and styrene (Scheme 6) derivatives. Electron-deficient substrates coupled well (**44**: 81%, **47**: 95%). Particularly, the coupling of an iodobenzene derivative carrying the pharmaceutically important *p*-sulfonylamido functionality was facile (**35**: 76%). Couplings of *p*-chloriodobenzene (**36**: 88% and **37**: 95%) and *p*-chlorostyrene (**46**: 74%) proceeded in high yields indicating that the IMes-Pd catalyst is tolerant to aryl chlorides. Importantly, couplings of deactivated arylhalides with two *o*-alkyl substituents (**22** and **23**: 72%), free anilines (**26**: 88%, **40**: 79% and **42**: 63%), phenols (**25**: 77% and **46**: 74%), or highly electron-rich substrates with multiple methoxy substituents (**27**: 91%, **28**: 98%, **29**: 45%, with 55% starting bromide recovered, **30**: 84%, **39**: 78%, **43**: 91%) all proceeded in good to excellent yields. The coupling of a thioether-substituted arylbromide (**24**, 75% yield) and an aryl iodide containing a nitro and methoxy group (**38**, 68%) were also facile. Notably, for some substrates, good yields were observed even at 100 °C (**31**: 63% and **36**: 88%). The couplings of substituted thiophenes (**34**: 59% and **41**: 78%) and a relatively simple quinoline substrate (**31**: 83%) proceeded well. The success of the Heck–Mizoroki coupling of heterocycles containing



Scheme 4 Preparative Heck–Mizoroki couplings of more challenging aryl bromides with acrylate derivatives mediated by IMes-Pd(dmba)Cl (**1**) (2 mol%). The reaction times were not minimized. The yields shown are for chromatographically homogeneous materials, average of two runs.



Scheme 5 Preparative Heck–Mizoroki couplings of aryl iodides with acrylate derivatives mediated by IMes-Pd(dmba)Cl (**1**) (2 mol%). The reaction times were not minimized. The yields shown are for chromatographically homogeneous materials, average of two runs.



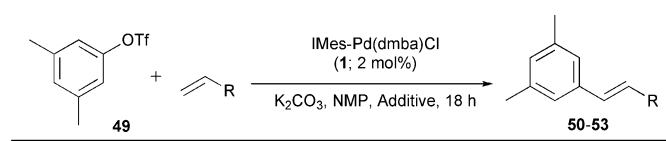
Scheme 6 Preparative Heck–Mizoroki couplings of aryl bromides and iodides with styrene derivatives and analogs mediated by IMes-Pd(dmba)Cl (**1**) (2 mol%). Conditions A: K_2CO_3 (2 equiv.), 140 °C. Conditions B: $i\text{Pr}_2\text{NEt}$ (2 equiv.), 120 °C. The reaction times were not minimized. The yields shown are for chromatographically homogeneous materials, average of two runs.

two N-atoms was dependent on the nature of the heterocycle. Whereas high yields were observed for the couplings of pyrimidine (**30**: 84% and **42**: 63%) and imidazole (**32**: 82%) derivatives, 4-bromo-1,3,5-trimethylpyrazole, a very difficult substrate,⁵⁷ yielded product **33** in 32% yield and 49% of the starting bromide was recovered. With respect to the Heck acceptors, acrylate esters,⁵⁸ amides and acrylonitrile and various styrene derivatives (Scheme 6; **43–46**: 74–91%) were all suitable. In particular, the first Heck–Mizoroki couplings of vinylferrocene (**47**: 95%) and 4-vinylpyridine (**48**: 92%) with NHC-Pd catalyst are noteworthy. The Heck–Mizoroki protocol mediated by IMes-Pd(dmba)Cl can be carried out in aerobic conditions without a significant decrease in yields (**22**: 44 vs 72%; **26**: 81 vs 88%; **27**: 92 vs 91%; **39**: 92 vs 78%; **46**: 78 vs 74% for aerobic and anaerobic conditions, respectively)

Heck–Mizoroki reaction of aryltriflates with acrylate and styrene derivatives

Aryltriflates are highly active substrates; however, no examples of the Heck–Mizoroki reaction of aryltriflates mediated by NHC-Pd catalysts have been reported to date. We explored the coupling of triflate **49** with a variety of Heck–Mizoroki acceptors (Table 2). Under standard conditions (A), complete degradation of the triflate with no product formation was observed in the presence of a number of common bases. The use of halide additives proved to be more promising—whereas 1 equiv. of Bu_4NCl and Bu_4NI gave approx. 15% yield of **50**, 69% was achieved with Bu_4NBr (TBAB). The addition of 4 Å molecular sieves to suppress base-promoted hydrolysis of the triflate by adventitious moisture led to a further increase of the yield to 93% (quantitative ^1H NMR spectroscopy; 79% isolated yield). However, decreasing the amount of TBAB to 0.1 equiv. was detrimental, resulting in only 37% of **50**, with the remaining starting material recovered. Under optimized conditions, triflate **49** underwent Heck–Mizoroki couplings with

Table 2 Heck–Mizoroki couplings of aryl triflate **49** with styrene and acrylate derivatives mediated by IMes–Pd(dmba)Cl (**1**) (2 mol%). The reaction times were not minimized. The yields shown are the average of two runs



Entry	R	Additive	Yield, %
1	COO <i>t</i> Bu	None	< 3 ^{a,b}
2	COO <i>t</i> Bu	Bu ₄ NCl (1 equiv.)	13 ^b (50)
3	COO <i>t</i> Bu	Bu ₄ NBr (1 equiv.)	69 ^b
4	COO <i>t</i> Bu	Bu ₄ NI (1 equiv.)	19 ^b
5	COO <i>t</i> Bu	Bu ₄ NBr (1 equiv.), 4 Å MS	93 ^b /79 ^c
6	COO <i>t</i> Bu	Bu ₄ NBr (0.1 equiv.), 4 Å MS	37 ^b
7	CON <i>i</i> Pr ₂	Bu ₄ NBr (1 equiv.), 4 Å MS	64 ^c (51)
8	4-MeOC ₆ H ₄ -	Bu ₄ NBr (1 equiv.), 4 Å MS	73 ^c (52)
9	4-ClC ₆ H ₄ -	Bu ₄ NBr (1 equiv.), 4 Å MS	56 ^c (53)

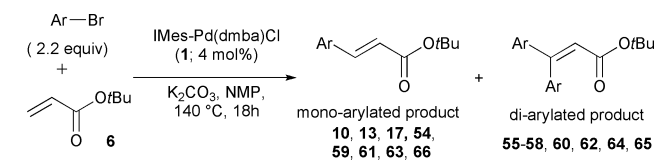
^a Na₂CO₃, Cs₂CO₃, NaOAc, *i*Pr₂NEt, (*n*C₈H₁₇)₃N, Cy₂NMe (Cy = cyclohexyl) and DBU (1,4-diazabicyclo[3.2.0]undecane) were also ineffective. ^b The yield (+/–4%) was determined by quantitative ¹H NMR spectroscopy (internal standard DMF). ^c Isolated yields of analytically pure materials after column chromatography.

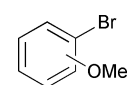
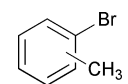
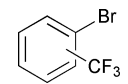
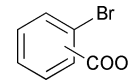
N,N-diisopropylacrylamide (**51**: 64%) 4-methoxystyrene (**52**: 73%) and 4-chlorostyrene (**53**: 56%).

Double Heck–Mizoroki reactions

When more than 2 equiv. of aryl halide are used, the cinnamate initially formed undergoes a second Heck–Mizoroki reaction to yield a β,β-diarylacrylate. Isolated cases of Heck–Mizoroki diarylations of acrylates and styrene mediated by NHC–Pd catalysts are known.^{35,59} However, there have not been complete studies on how the steric and electronic properties of the substituent on the aryl halide can affect the outcome of the double arylation reaction mediated by NHC–Pd catalysts. We undertook a systematic evaluation of the efficiency of the double Heck–Mizoroki reaction (4 mol% of **1**) between *tert*-butyl acrylate (**6**) and *o*-, *m*- and *p*-isomers of bromoanisole and bromotoluene as representative electron-rich aryl bromides, and bromobenzotrifluoride and methyl bromobenzoate as electron-deficient, respectively. All *o*-substituted aryl bromides, (Table 3) gave exclusively monoarylated products (**10**, **54**, **59**, **63**; 62–100% yields). For electron-rich *m*- and *p*-substituted aryl bromides, β,β-diarylacrylates (**55–58**; 81–92% yields) were obtained exclusively.⁶⁰ On the other hand, electron-deficient *m*- and *p*-substituted aryl bromides generally gave mixtures of mono- (**13**, **17**, **61**, **66**; 41–63% yields) and diarylated products (**60**, **62**, **64**, **65**; 6–24% yields) with the mono-arylated products (cinnamates) being major the major ones. These results imply that both electronic and steric effects affect the product distribution considering that methyl and trifluoromethyl substituents are virtually identical in size. We further attempted to obtain diarylated product from *o*-bromoanisole (**54**) with different Pd-catalysts (Scheme 7 and Table 4). Complex **1** (100%) was the best catalyst of all complexes tested, supporting our choice of IMes as a privileged ligand for Heck–Mizoroki reaction (Fig. 1). Cyclopalladated *N,N*-dimethylbenzylamine (dmba) ligated with other 1,3-diarylimidazol-2-ylidenes (**68** and **70**),

Table 3 Double Heck–Mizoroki arylation of electron-rich and electron-deficient aryl bromides with *tert*-butyl acrylate (**6**). The reaction times were not minimized. The yields shown are the average of two runs



Entry	Ar–Br	Di-/mono-arylation, %		
		<i>o</i> -	<i>m</i> -	<i>p</i> -
1		0/100 (54)	92(55)/0	91(56)/0
2		0/86 (10)	81(57)/0	84 (58)/0
3		0/62 (59)	24 (60)/41 (61) ^a	21 (62)/59 (13) ^a
4		0/89 (63) ^b	6 (64)/63 (17) ^b	6 (65)/55 (66) ^b

^a The mono- and diarylated products were obtained as inseparable mixtures. The yields were determined by ¹H NMR spectroscopy. ^b In the presence of 4 Å molecular sieves.

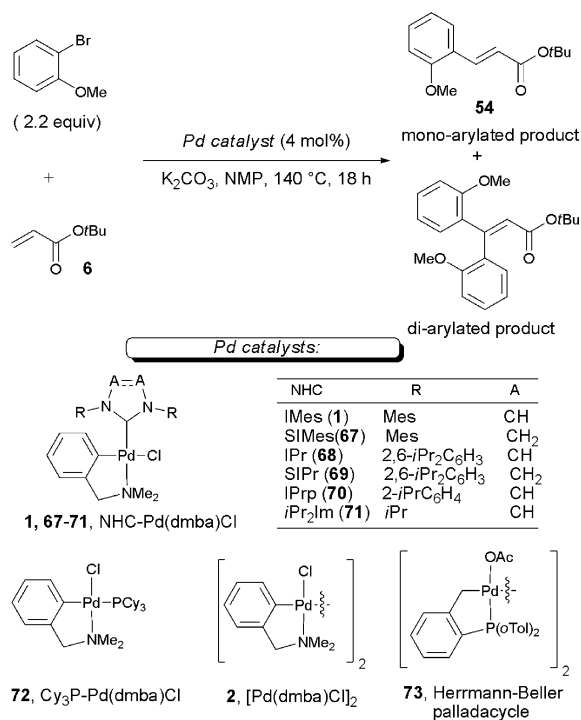
1,3-diaryl-4,5-dihydroimidazol-2-ylidenes (**67** and **69**) and simple 1,3-diisopropylimidazol-2-ylidene (**71**), recently synthesized in our group,⁵⁶ all gave lower yields (31–76%). The corresponding tricyclohexylphosphine complex (**73**)⁴¹ and the parent dimeric palladacycle (**2**)⁵⁴ also gave high yields of **66** (73 and 63%, respectively). In comparison, the Herrmann–Beller palladacycle (**73**)^{14,15} performed rather poorly. A high yield (86%) was also observed with [Pd(PPh₃)₄]. Disappointingly, no catalyst yielded even a trace of the desired diarylated product, revealing an important limitation in the current scope of the Heck–Mizoroki catalysts.⁶¹

Importantly, the results of our double Heck–Mizoroki reaction experiments demonstrate that, unlike phosphane–Pd and ligandless Pd catalysts, which show higher activity for electron-deficient (hence known as “activated”) aryl halides, IMes–Pd shows higher activity for electron-rich or “deactivated” aryl bromides. Recent comparative computational studies on the complete cycle of the Heck–Mizoroki reaction mediated by phosphane–Pd and NHC–Pd catalysts by Lee *et al.* have shown that for NHC–Pd catalysts the olefin binding–migratory insertion step (Scheme 1) proceeding from a cationic NHC–Pd species is the rate-limiting step, whereas for phosphane–Pd catalysts, the oxidative addition is the rate-limiting step.⁶² Our results are consistent with such a mechanism. Oxidation of the aryl bromide to the monoligated NHC–Pd(0) species, the active catalyst (Fig. 1), yields a new NHC–Pd(II)–Br moiety σ-bonded to an aryl substituent. Conceivably, the more electron rich the aryl group, the higher the electron density on the Pd atom and the higher the propensity of the bromide ion to leave the coordination sphere of Pd during the olefin binding/migratory insertion step.

Table 4 Effect of the catalyst structure on the outcome of the double Heck–Mizoroki reaction between *o*-bromoanisole (2.2 equiv.) and *tert*-butyl acrylate (**6**) (Scheme 7). The yields shown are the average of two runs

Entry	Catalyst (4 mol%) ^a	Mono-/di-arylation, % ^b
1	IMes-Pd(dmba)Cl (1)	100/0
2	SIMes-Pd(dmba)Cl (67)	76/0
3	IPr-Pd(dmba)Cl (68)	41/0
4	SIPr-Pd(dmba)Cl (69)	73/0
5	IPr ^p -Pd(dmba)Cl (70)	31/0
6	<i>i</i> Pr ₂ Im-Pd(dmba)Cl (71)	58/0
7	Cy ₃ P-Pd(dmba)Cl (72) ^c	73/0
8	Herrmann-Beller palladacycle (73)	21/0
9	[Pd(PPh ₃) ₄]	86/0
10	[Pd(dmba)Cl] ₂ (2)	63/0

^a Relative to the limiting reagent, *tert*-butyl acrylate (**6**). ^b The remaining unreacted *o*-bromoanisole was recovered. In some cases, 2,2'-dimethoxybiphenyl arising from homocoupling of *o*-bromoanisole was isolated as a minor product (<10%). ^c Cy = cyclohexyl.



Scheme 7 Double Heck–Mizoroki reaction between *o*-bromoanisole and *tert*-butyl acrylate (**6**) mediated by various Pd catalysts. The reaction times were not minimized.

Experimental section

Large scale synthesis of IMes-Pd(dmba)Cl

A two necked flask (1 L) was charged with a large, egg-shaped magnetic stirrer bar, PdCl₂ (32.3 g, 182 mmol), CH₃CN (370 mL; HPLC grade) and *N,N*-dimethylbenzylamine (**4**) (29 mL, 25.8 g, 191 mmol). One of the necks was equipped with a reflux condenser and the other was closed with a glass stopper. The mixture was heated at reflux until a clear, dark orange solution was formed and

PdCl₂ dissolved completely (approx. 25 min). Finely powdered K₂CO₃ (62.9 g, 455 mmol) was added in one portion and the mixture was stirred under reflux until the solution changed color to bright canary yellow (approx. 5 min). IMes-HCl (**3**) (65.1 g, 191 mmol) was added in one portion and the reflux continued for another 30 min. After cooling, the mixture was diluted with CH₂Cl₂, filtered and the volatiles removed under vacuum. IMes-Pd(dmba)Cl (**1**) (95.2 g, 90% yield, white crystalline solid) was crystallized from CH₃CN (30 mL), filtered and dried under high vacuum; mp 225–230 °C (with decomposition); ¹H NMR (CDCl₃, 400 MHz): δ 7.10 (s, 2H), 6.99 (s, 2H), 6.83–6.76 (m, 4H), 6.70 (td, *J* = 7.6, 1.2 Hz, 1H), 6.58 (dd, *J* = 7.2, 1.2 Hz, 1H), 3.53 (s, 2H), 2.45 (s, 6H), 2.44 (s, 6H), 2.29 (s, 6H), 2.23 (s, 6H); ¹³C NMR (CDCl₃, 100 MHz): δ 175.6, 149.3, 147.6, 138.3, 138.3, 137.4, 136.2, 133.9, 129.4, 128.7, 123.9, 123.2, 123.0, 121.2, 72.2, 50.0, 21.1, 20.2, 19.8; Anal. calcd for C₃₀H₃₆ClN₃Pd (580.50): C, 62.07; H, 6.25; N, 7.24. Found: C, 62.02; H, 6.37; N, 7.40.

Stock solution of the catalyst

The required amount of IMes-Pd(dmba)Cl (**1**) (7.26 mg/mL for 0.5 mol% or 29.03 mg/mL for 2 mol%) was dissolved in reagent grade NMP and the solution degassed by purging with Ar for 10–20 min.

General procedure for Heck–Mizoroki reaction (A)

To a vial with a magnetic stirrer bar, the arylbromide (1 mmol), the olefin (1.5 mmol at 0.5 mol% or 1.2 mmol at 2 mol% **1**) were weighed in (if solids) or added *via* syringe (if liquids), followed by addition of K₂CO₃ (276 mg, 2.0 mmol). Stock solution of IMes-Pd(dmba)Cl (**1**) (400 μL) was added and the atmosphere above the reaction mixture was purged with Ar over 30 sec. The vial was closed with a screw cap and heated at 140 °C with vigorous stirring over 18 h. Two reactions were done side by side. After cooling, the combined reaction mixtures were filtered with CH₂Cl₂ (total 20 mL). The crude product was loaded directly over a short pad of silica gel and purified by flash chromatography. For experiments conducted in-air, the same procedure was followed except the purging of precatalyst stock solution and reaction vial with Ar was omitted.

(*E*)-3-(4-(Methylthio)phenyl)-1-(morpholine-1'-yl)-prop-2-en-1-one (**24**)

Following procedure A (2 mol% **1**), 4-bromothioanisole (203 mg) and *N*-acryloyl morpholine (150 μL, 169 mg) were used. The reactions were cooled and combined after filtration (CH₂Cl₂, total of 30 mL), washed with water (5 × 20 mL), dried (MgSO₄), and the volatiles removed under reduced pressure. Product **24** (169 mg, 75%) was obtained as a white solid after column chromatography on silica gel (ethyl acetate gradient in hexane-CH₂Cl₂ (5:1, vol/vol): 0 to 25%, 25 min); mp 113–119 °C; ¹H NMR (CDCl₃, 400 MHz): δ 7.66 (d, *J* = 15.4 Hz, 1H), 7.44 (m, 2H), 7.22 (m, 2H), 6.80 (d, *J* = 15.4 Hz, 1H), 3.73 (m, 8H), 2.49 (s, 3H); ¹³C NMR (CDCl₃, 100 MHz): δ 165.7, 142.7, 141.1, 131.7, 128.2, 126.1, 115.4, 66.9, 15.3; Anal. calcd for C₁₄H₁₇NO₂S (263.36): C, 63.85; H, 6.51; N, 5.32. Found: C, 64.03; H, 6.51; N, 5.20.

General procedure for Heck–Mizoroki reaction (B)

To a vial with a magnetic stirrer bar, the arylbromide (1 mmol), the olefin (1.5 mmol at 0.5 mol% or 1.2 mmol at 2 mol% **1**) were weighed in (if solids) or added *via* syringe (if liquids). *i*Pr₂NEt (350 μ L, 258 mg, 2.0 mmol) and stock solution of IMes–Pd(dmba)Cl (**1**) (400 μ L) were added and the atmosphere above the reaction mixture was purged with Ar over 30 sec. The vial was closed with a screw cap and heated at 120 °C with vigorous stirring over 18 h. Two reactions were done side by side. After cooling, the combined reaction mixtures were filtered under dilution with CH₂Cl₂ (total 20 mL). The crude product was loaded directly over a short pad of silica gel and purified by flash chromatography.

2-(2,5-Dimethylstyryl)benzotrile (44)

Following procedure B (2 mol% **1**), from 2-bromobenzotrile (182 mg) and 2,5-dimethylstyrene (175 μ L, 159 mg), **44** (188 mg, 81%) was obtained as white solid after column chromatography on silica gel (ethyl acetate gradient in hexane: 0%, 10 min, then 0 to 10%, 10 min); mp 72–76 °C; ¹H NMR (CDCl₃, 400 MHz): δ 7.80 (d, *J* = 8.1 Hz, 1H), 7.66 (d, *J* = 7.8 Hz, 1H), 7.60 (t, *J* = 7.6 Hz, 1H), 7.55–7.50 (m, 2H), 7.37 (s, 1H), 7.33 (d, *J* = 8.2 Hz, 1H), 7.13–7.07 (m, 2H), 2.37 (s, 3H); ¹³C NMR (CDCl₃, 400 MHz): δ 141.0, 135.9, 135.0, 133.4, 133.2, 132.8, 131.4, 130.5, 129.5, 127.5, 126.4, 125.5, 125.0, 118.2, 111.1, 21.1, 19.5; Anal. calcd for C₁₇H₁₅N (233.31): C, 87.52; H, 6.48; N, 6.00. Found: C, 87.38; H, 6.66; N, 5.91.

General procedure for Heck–Mizoroki reaction of aryltriflates (C)

A vial was charged with a magnetic stirrer bar, 3,5-dimethylphenyl trifluoromethanesulfonate (**49**) (190 μ L, 254 mg, 1 mmol), the olefin (1.2 mmol), TBAB (322 mg, 1 mmol), K₂CO₃ (276 mg, 2.0 mmol) and powdered molecular sieves (4 Å; approx. 500 mg). Stock solution of IMes–Pd(dmba)Cl (2 mol% **1**; 400 μ L) was added and the atmosphere above the reaction mixture was purged with Ar over 30 sec. The vial was closed with a screw cap and heated at 140 °C with vigorous stirring over 18 h. Two reactions were done side by side. After cooling, the reactions were combined after filtration (CH₂Cl₂, total of 30 mL), washed with water (5 \times 20 mL), dried (MgSO₄), and the volatiles removed under reduced pressure. The crude product was loaded directly onto a short pad of silica gel and purified by flash chromatography.

1-(4-Chlorostyryl)-3,5-dimethylbenzene (53)

Following procedure C (2 mol% **1**), from 4-chlorostyrene (145 μ L, 167 mg), **53** (136 mg, 56%) was obtained as a white solid after column chromatography on silica gel (ethyl acetate gradient in hexane: 0%, 10 min, then 0 to 15%, 20 min); mp 54–58 °C; ¹H NMR (CDCl₃, 400 MHz): δ 7.44 (m, 2H), 7.33 (m, 2H), 7.15 (s, 2H), 7.05 (s, 2H), 6.95 (s, 1H), 2.36 (s, 6H); ¹³C NMR (CDCl₃, 100 MHz): δ 138.2, 136.9, 133.0, 129.7, 129.5, 128.8, 127.6, 127.6, 127.0, 124.5, 21.3; Anal. calcd for C₁₆H₁₅Cl (242.09): C, 79.17; H, 6.23. Found: C, 79.59; H, 6.29.

General procedure for the double Heck–Mizoroki arylation reaction (D)

To a vial with a magnetic stirrer bar, the arylbromide (2.2 mmol), *tert*-butyl acrylate (**6**) (145 μ L, 128 mg, 1.0 mmol), K₂CO₃ (276 mg,

2.0 mmol) were weighed in (if solids) or added *via* syringe (if liquids). Stock solution of IMes–Pd(dmba)Cl (**1**) (4 mol%; 800 μ L) was added and the atmosphere above the reaction mixture was purged with Ar over 30 sec. The vial was closed with a screw cap and heated at 140 °C with vigorous stirring over 18 h. Two reactions were done side by side. After cooling, the combined reaction mixtures were filtered under dilution with CH₂Cl₂ (total 20 mL), washed with water (5 \times 20 mL), dried (MgSO₄), and the volatiles removed under reduced pressure. The crude product was loaded directly over a short pad of silica gel and purified by flash chromatography.

tert-Butyl 3,3-bis(3-methoxyphenyl)acrylate (55)

Following procedure D (4 mol% **1**), from 3-bromoanisole (275 μ L, 412 mg), **55** (313 mg, 92%) was obtained as a colorless oil after column chromatography on silica gel (ethyl acetate gradient in hexane: 0%, 5 min, then 0 to 20%, 20 min); ¹H NMR (CDCl₃, 400 MHz): δ 7.31–7.21 (m, 2H), 6.93–6.75 (m, 6H), 6.28 (s, 1H), 3.80 (s, 3H), 3.78 (s, 3H), 9.55 (s, 9H); ¹³C NMR (CDCl₃, 400 MHz): δ 165.8, 159.2, 153.8, 140.7, 129.3, 129.0, 121.7, 120.8, 120.1, 114.6, 114.5, 113.8, 113.6, 80.4, 55.3, 55.2, 27.8; Anal. calcd for C₂₁H₂₄O₄ (340.41): C, 74.09; H, 7.11. Found: C, 74.12; H, 7.12.

Conclusion

In conclusion, we have developed a novel NHC–palladacycle as a rationally designed precatalyst (**1**) with respect to both catalytic performance and practicality. Complex **1** is available in high yield in multi-gram amounts from inexpensive starting materials by virtue of a one-pot, three-component NHC–palladacycle synthesis, and is stable to air, moisture (even tolerating aqueous workup) and long-term shelf storage (>3 years). The catalyst can be either weighed in as a solid or dispensed as a stock solution in NMP, which can be stored for at least a week without losing its activity. The reactions are performed without any special techniques or glovebox—after addition of the coupling partners, the base and the catalyst stock solution in air, the atmosphere above the solution is simply purged with Ar. Moreover, the catalyst can be used in air without significant loss of activity (Tables 3–5). The small amount of NMP used (0.4 mL/mmol arylbromide) allows for direct isolation of the products by flash chromatography (R_f permitting) without the cumbersome, difficult-to-automate aqueous extractive workup step. In summary, these features render catalyst **1** particularly suitable for deployment in automated parallel synthesis workstations. Taken together, the results in this work validate the design principle (Fig. 1) that both a powerful ligand (in this case IMes) and suitable disposable ligands, which deliver the active catalyst smoothly and efficiently into the catalytic cycle, are necessary for high catalytic activity across a wide range of substrates. Importantly, this work has revealed that IMes–Pd is more active for electron rich, “deactivated” arylbromides as opposed to phosphane–Pd and ligandless Pd catalysts that show higher activity for electron-deficient, “activated” aryl bromides. The design and exploration of later generations of NHC–palladacycle precatalysts for other important Pd-mediated reactions based on this paradigm are underway.

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