Catalytic activity of Pd(II) and Pd(II)/DAB-R systems for the Heck arylation of olefins

Gabriela A. Grasa, Rohit Singh, Edwin D. Stevens, Steven P. Nolan *

Department of Chemistry, University of New Orleans, New Orleans, LA 70148-2820, USA

Abstract

Palladium-catalyzed reactions of aryl bromides with various olefins involving Pd(II)/diazabutadiene (DAB-R) systems have been investigated. The scope of a coupling process using Pd(II) sources and an α-diimine as ligand in the presence of Cs_2CO_3 as base was tested using various substrates. The $Pd(OAc)_2$/DAB-Cy (**1**, DAB-Cy = 1,4-dicyclohexyl-diazabutadiene) system presents the highest activity with respect to electron-neutral and electron-deficient aryl bromides in coupling with electron rich olefins. The synthesis and X-ray characterization of a Pd(II)-diazabutadiene ligand is reported. Extensive optimization experiments showed that another Pd(II) source, $Pd(acac)_2$ (acac = acetylacetonate), proved to activate aryl bromides at high temperatures, low catalyst loadings when the appropriate concentration of $^{n}Bu_4NBr$ additive was employed. The effect of the DAB-Cy ligand is important at very low catalyst loadings and high temperatures. $Pd(acac)_2$ and $Pd(acac)_2$/DAB-Cy precatalysts were very effective for the arylation of various olefins with aryl bromides with respect to reaction rate, catalyst loadings, and functional group tolerance.
© 2003 Elsevier Science B.V. All rights reserved.

Keywords: Heck coupling; Diazabutadienes; Palladium

1. Introduction

The Heck cross-coupling reaction of organohalides and pseudohalides with olefins has proven to be a powerful synthetic method for C–C bond formation [1], with wide applications from natural product [2] to fine chemicals synthesis [3]. In addition to its versatility, and unlike Kumada, Hiyama, Stille and other Pd-catalyzed cross-coupling reactions, which often employ expensive reagents, the Heck reaction presents the advantage of using cheap and easy available olefins as coupling partners.

Although Heck arylation and alkylation of olefins have proven to be one of the most versatile methods for C–C bond formation, various catalytic systems are used with a myriad of procedures involving different supporting ligands, metal source, solvent, additives or substrates [1]. Palladium–phosphine complexes have been em-

ployed as ancillary ligands [4] in controlling the reactivity and selectivity in the Heck cross-coupling reaction [1]. The main role of tertiary monophosphine ligands is to stabilize the zerovalent palladium as PdL_3 or PdL_4 species, which can enter the catalytic cycle and consequently prevent the formation of inactive palladium black. Important examples of the use of phosphines are found in the work of Fu [5], Hartwig [6] and Beller [7] who have made use of sterically demanding, electron rich tertiary phosphines as catalyst modifiers in the Heck aryl olefination reactions. The ligand properties in these cases make possible the activation of the less reactive aryl bromides and aryl chlorides as coupling partners in the Heck reaction. However, despite their effectiveness in controlling reactivity and selectivity transition-metal catalyzed transformations [4], tertiary monophosphines and their palladium complexes are often air-sensitive and are subject to P–C bond degradation at elevated temperatures [8], commonly employed under Heck conditions. Hence, higher phosphine concentrations are often needed with direct consequences on large-scale applications since tertiary electron-rich phosphines are unrecoverable from reac-

* Corresponding author. Tel.: +1-504-286-6311; fax: +1-504-280-6860.
E-mail address: snolan@uno.edu (S.P. Nolan).

tion mixtures and sometimes more expensive than palladium. A notable exception is the very thermally stable palladacycle formed by the reaction of Pd(OAc)$_2$ and tris(*o*-tolyl)phosphine, which represents a very active catalyst for aryl bromides and activated aryl chlorides, albeit under harsh conditions [9]. To this point, bidentate chelating phosphines can form more stable palladium complexes (Pd/L = 1/1) for Heck reactions and therefore an excess of ligand and higher palladium loadings can be avoided. To date, few catalytic systems using electron-rich bidentate phosphines 1,4-bis(diisopropylphosphino)butane and bis(diisopropylphosphino)propane [10] as catalyst modifiers have been reported effective for the Heck reaction of aryl chlorides.

Nucleophilic *N*-heterocyclic carbenes (NHC) [11], the imidazol-2-ylidenes, have attracted extensive attention due to their similar electronic and steric properties to basic phosphines. Unlike many phosphines, NHC ligands show a considerable stabilizing effect in organometallic systems [12] with respect to heat, moisture and air. As a result, NHC ligands have been employed efficiently for the cross-coupling of aryl halides with olefins [13].

Alternative catalytic systems represent the less explored palladium–nitrogen containing ancillary ligand complexes. A Pd(II) cyclometallated imine catalyst for the Suzuki and Heck reactions of aryl iodides and mainly activated aryl bromides has been reported by Milstein [14,15], but the system requires high reaction temperatures and reaction times. Ligands containing the 1,4-diaza-1,3-butadiene skeleton (DAB-R, Scheme 1) have attracted much interest. The coordination versatility of these ligands, a consequence of the flexibility of the NCCN backbone and the σ-donating and low π-accepting properties, reflects the very interesting properties of DAB-R–metal complexes [16]. However, relatively less investigated is the influence of DAB-R as a supporting ligand in various catalytic processes. Few Pd–diimine-catalyzed reactions, such as olefin polymerization [17] and alkyne co-cyclotrimerization [18] have been reported. We now wish to report an extended study on the use of these ligands as alternative catalyst modifiers along with the influence of various factors such as base, solvent, Pd(II) source, additive concentra-

tion, catalyst loading, and temperature on the cross-coupling of olefins with aryl halides.

2. Results and discussions

The α-diimines or 1,4-diazabutadienes represent a class of ligands of interest not only due to their σ-donating and low π-accepting abilities [6], but also due to cost-effective issues. These ligands are easily accessible by one step syntheses from the corresponding α-diketo compounds and various amines [19]. Further ring closure can afford the synthesis of various imidazolium salts, precursors of NHC ligands [20]. Alternatively, Pd(II)-α-diimine complexes can be easily synthesized from Pd(OAc)$_2$ in ether at room temperature with the formation of square planar Pd(DAB-R)(OAc)$_2$ complexes (Scheme 2).

We previously reported a general and efficient methodology for the Suzuki–Miyaura cross-coupling reaction of aryl bromides and activated aryl chlorides with aryl boronic acids based on the Pd(OAc)$_2$/DAB-R complexes generated in situ (Scheme 3). The Pd(OAc)$_2$/DAB-R system is very efficient in the Suzuki–Miyaura cross-coupling reaction of aryl bromides with aryl boronic acids in terms of reactivity, reaction temperature, reaction time and air-stability [21a]. Similar systems employing Pd–6 (6 = bis(arylimino)acenaphthene or Ph-BIAN) have been also reported to catalyze the coupling of alkyl or allyl halides or aryl iodides with organomagnesium, tin and zinc reagents [21b,21c].

2.1. Choice of DAB-R supporting ligands for Heck reaction of 4-bromotoluene with n-butylacrylate

Since the use of DAB-R as supporting ligand for the Suzuki–Miyaura cross-coupling reaction represents an interesting alternative to existing catalytic systems based on the use of tertiary phosphine ligands, we were interested to determine whether the Heck coupling of aryl bromides with olefins could be affected by Pd(II)-diimine complexes. We observed that the coupling of 4-bromotoluene and 1.5 equivalents of the activated olefin *n*-butylacrylate, in the presence of 3 mol% of Pd(OAc)$_2$, 3 mol% DAB-Cy (1) and 1.5 equivalents Cs$_2$CO$_3$ in *N*,*N*-dimethylacetamide (DMAc) at 100 °C proceeded to give 4-methylstyrene in 93% yield (Table 1, entry 2). The beneficial ligand effect was proven by running the control reaction in the absence of ligand (Table 1, entry 1), since it is known that naked palladium can catalyze the Heck reaction of olefins with activated aryl bromides [22].

Investigation of other diazabutadiene ligands led to the observation that alkyl-diazabutadienes (Table 1, entries 3 and 8) are superior supporting ligands for the
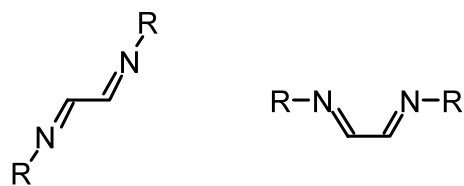
R = aryl and alkyl

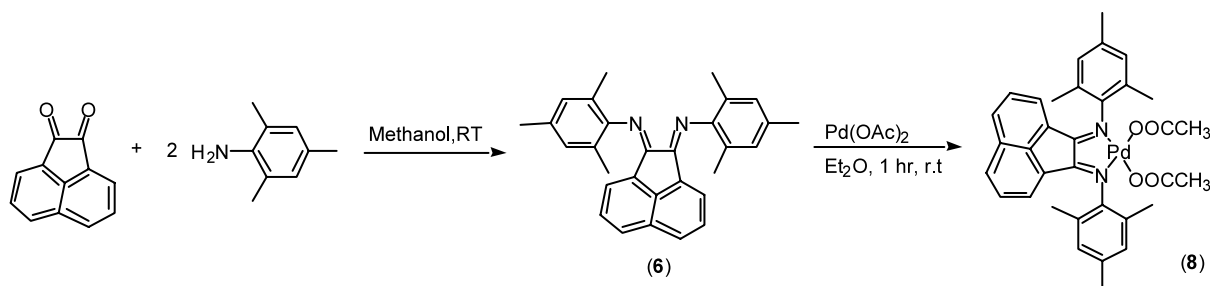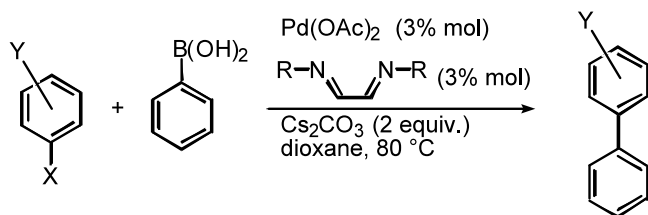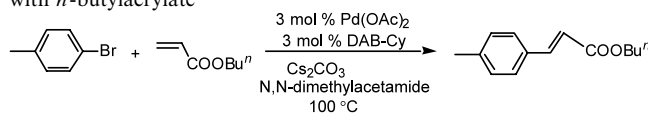Scheme 1. Diazabutadiene (DAB-R) ligands.

Scheme 2. Synthesis of a Pd(DAB-R)(OAc)$_2$ complex.

Scheme 3. Pd(OAc)$_2$/DAB-R catalytic systems for Suzuki–Miyaura reaction.

Table 1
Influence of DAB-R ligand on the Heck coupling of 4-bromotoluene with n-butylacrylate

entry	ligand	yield [b,c,d]
1	No L	52
2	(1)	93
3	(2)	81
4	(3)	32
5	(4)	33
6	(5)	75
7	(6)	47
8	(7)	82

(a) *Reaction conditions:* 1 mmol 4-bromotoluene, 1.5 mmol *n*-butylacrylate, 3 ml DMAc, 3 mol% Pd(OAc)$_2$, 3 mol% DAB-Cy, 1.5 mmol Cs$_2$CO$_3$, 5 h. (b) GC yields (diethyleneglycol di-*n*-butlyl ether used as internal standard, average of two runs).

Pd-catalyzed Heck reaction compared to aryl-diazabutadienes (Table 1, entries 4–7). This reactivity trend is in agreement with the stronger donating ability of alkyl substituents making the ligand more electron rich. However, it is important to note that the steric bulk of the ligand (usually very significant in the reductive elimination step in other coupling reactions), is not very important in this case, with the least sterically demanding DAB-Cy ligand being the most active ligand in the alky-substituted DAB-R series. Moreover, this tendency is in agreement with the general observation that the steric bulk of the ligand does not significantly affect the outcome of Pd-free phosphine-catalyzed Heck reactions [1a].

2.2. Reaction conditions optimization of Pd(OAc)$_2$/DAB-Cy-catalyzed Heck reaction

An investigation of the influence of the base suggested that the strong base Cs$_2$CO$_3$ was the reagent of choice. K$_2$CO$_3$ and KOAc also affect the Heck coupling of 4-bromotoluene with *n*-butylacrylate leading to moderate yields in 5 h. (Table 2). NaOAc, an effective base in combination with the phosphine palladacycle catalyst for the Heck reaction [9], showed no activity under our conditions (Table 2, entry 5). Moreover, Cy$_2$NMe, a very effective additive for the Pd$_2$(dba)$_3$/P(^{t}Bu)$_3$-catalyzed Heck reaction [5b], also proved to be less effective in the present system.

A survey of other solvents as reaction media showed that the polar aprotic DMAc is the most suitable solvent in combination with the Pd(OAc)$_2$/DAB-Cy system. The more polar solvent *N*-methylpyrrolidinone (NMP), used also as medium for Heck reactions [9c,23], led to low conversions (Table 2, entry 7). As expected ethereal solvents, which represent more suitable media for Pd/phosphine catalytic systems [5], did not influence the outcome of the model reaction (Table 2, entry 8). This reaction could be performed in air as well, but requires longer reaction times to lead to a moderate yield since (Table 2, entry 2).

It is well known that quaternary ammonium salts show a beneficial effect on the coupling of aryl halides with olefins [24]. We determined that 5 mol% *tetra-n-*

Table 2
Influence of the base and solvent on the Heck coupling of 4-bromotoluene with n-butylacrylate
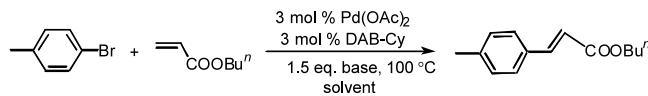
Entry	Solvent	Base	Time (h)	Yield(%) [a]
1	DMAc	Cs_2CO_3	5	93
2	DMAc	Cs_2CO_3	24	57 [b]
3	DMAc	Cs_2CO_3/5% $^nBu_4NBr$	3	95
4	DMAc	K_2CO_3	5	49
5	DMAc	NaOAc	5	NR [c]
6	DMAc	KOAc	5	47
6	DMAc	Cy_2NMe	5	15
7	NMP	Cs_2CO_3	5	30
8	DME	Cs_2CO_3	6	12

Reaction conditions: 1 mmol 4-bromotoluene, 1.5 mmol n-butylacrylate, 3 ml solvent, 3 mol% $Pd(OAc)_2$, 3 mol% DAB-Cy, 1.5 mmol base.

[a] GC yields (diethyleneglycol di-n-butlyl ether used as internal standard, average of two runs).

[b] Reaction performed in the air.

[c] NR, no reaction.

butylammonium bromide ($^nBu_4NBr$) gave a higher conversion in a shorter reaction time for the model reaction (Table 2, entries 1 and 3). This result is in agreement with studies performed by Amatore and Jutand [25], who have shown that halide anionic species $Pd^0L_2X^-$ could act as active intermediates in the Heck reaction catalyzed by underligated/phosphine-free systems. Higher amounts of $^nBu_4NBr$ (10 and 15 mol%) led to significantly lower yields. This could be due to the formation of coordinatively saturated Pd–bromide ionic species. Optimization experiments performed on the influence of the amount of the base and olefin on the model reaction, showed that the optimum combination base/olefin is 1.5 equivalents Cs_2CO_2 and 1.5 equivalents olefin [26].

2.3. Functional group tolerance of the $Pd(OAc)_2$/DAB-Cy-catalyzed Heck reaction of aryl bromides with olefins

As illustrated in Table 3, the palladium-catalyzed Heck reaction of aryl bromides with various olefins with the assistance provided by the DAB-Cy ancillary ligand (**1**) proved active and highly regioselective, with the formation of the terminally substituted olefin (> 99:1 Z selectivity). While neutral and activated aryl bromides were converted to the corresponding trans-n-butylcinnamates in high isolated yields using the optimized reaction conditions (Table 3, entries 1 and 2), unactivated aryl bromides such as 4-bromoanisole led to low conversions.

The effect of the olefin substrates in the Heck reactions was also examined. Unlike methylacrylate, which led to low conversion (Table 3, entry 3), we found that the less active styrene leads to 97% isolated yield in only 1 h. *Para*-substituted styrenes led to excellent yields of the desired products (Table 3, entries 6–9 and 14), while sterically hindered substrates led to low conversions, even under prolonged reaction times (Table 3, entries 12 and 13). Attempts to couple 4-bromotoluene with *meta*-substituted styrenes like 3-nitrostyrene resulted in low yields. The lower reaction rate may be explained in terms of the different electronic properties of *meta*-substituted styrenes [27].

This catalytic system was very active for more challenging olefins such as 1-hexene, which led to 1-aryl substituted hexene as the major product in only 2 h. Heck reactions involving the less active ethene usually require high pressure [3b]. We found that the $Pd(OAc)_2$/DAB-Cy system activates ethene in the reaction with 4-bromotoluene at atmospheric pressure with the formation of 4-methylstyrene in 58% isolated yield. However, since this system is very active for the coupling of aryl bromides with styrenes, a part of the resulting styrene participates also in reaction with 4-bromotoluene with the formation of p-substituted stilbene (Table 3, entry 5). Efforts to couple activated aryl chlorides were not successful when this catalytic system was employed.

2.4. Synthesis and structural characterization of $Pd(DAB'-Mes)(OAc)_2$

In order to gain some insight with regard to the behavior of the $Pd(OAc)_2$/DAB-R systems in the Heck arylation of olefins we synthesized a Pd-α-diimine complex by the reaction of $Pd(OAc)_2$ with diimine **6** (DAB'-Mes). A thermal stability study showed that this complex decomposes slowly in $CDCl_2$ at 40 °C. Although, we were not able to obtain the oxidative addition product of this complex with 4-bromoacetophenone, probably due to its instability, we assume that the acetate ligands are thermally decoordinated and the resulting species are reduced in the presence of the base or olefin [1] to highly active $Pd(0)(DAB-R)^-$-solvent stabilized species that activate the aryl bromide towards oxidative addition [28]. Moreover, the activity and lifetime of these active species could be improved by the stabilization effect brought by halide anions [9].

To unequivocally establish the structure of Pd(DAB'-Mes)(OAc)_2 (**8**) complex, single-crystals suitable for X-ray diffraction were grown by slow diffusion of a diluted $Pd(OAc)_2$/THF solution into a diluted DAB'-Mes (**6**)/THF solution. The ORTEP diagram of Pd(DAB'-Mes)(OAc)_2 (**8**) is presented in Fig. 1 as are selected bond lengths and angles. As shown in the ORTEP structure (Fig. 1), **8** adopts a slightly distorted square planar coordination geometry around the palladium center (the

Table 3
Functional group tolerance of the Pd(OAc)$_2$/DAB-Cy-catalyzed Heck reaction of aryl bromides with olefins

entry	aryl halide	olefin	product	time (h)	yield(%)[b]
1	Me—⬡—Br	⬟COOBu^n	Me—⬡—CH=CH—COOBu^n	3	95
2	Me(O)C—⬡—Br	⬟COOBu^n	Me(O)C—⬡—CH=CH—COOBu^n	0.5	99
3	Me—⬡—Br	⬟COOMe	Me—⬡—CH=CH—COOMe	5	30[d]
4	Me—⬡—Br	⬟Bu^n	Me—⬡—CH=CH—Bu^n	2	93[e]
5	Me—⬡—Br	⬟	Me—⬡—CH=CH$_2$	14	58[c]
6	Me—⬡—Br	⬟Ph	Me—⬡—CH=CH—Ph	1	97
7	Me—⬡—Br	⬟⬡OMe	Me—⬡—CH=CH—⬡—OMe	2.5	98
8	Me(O)C—⬡—Br	⬟⬡OMe	Me(O)C—⬡—CH=CH—⬡—OMe	0.5	85
9	Me—⬡—Br	⬟⬡NH$_2$	Me—⬡—CH=CH—⬡—NH$_2$	1	90
10	Me—⬡—Br	⬟⬡O$_2$N	Me—⬡—CH=CH—⬡—NO$_2$	24	63[d]
11	Me—⬡—Br	⬟⬡Cl	Me—⬡—CH=CH—⬡—Cl	24	45[d]
12	⬡(Br)(CN)	⬟⬡Me	⬡(CN)—CH=CH—⬡—Me	24	23[d]
13	Me—⬡—Br	⬟⬡(Me)(Me)(Me)	Me—⬡—CH=CH—⬡(Me)(Me)(Me)	24	20[d]
14	MeO—⬡—Br	⬟Ph	MeO—⬡—CH=CH—Ph	24	90

(a) *Reaction conditions:* 1 mmol 4-bromotoluene, olefin, 3 ml DMAc, 3 mol% Pd(OAc)$_2$, 3 mol% DAB-Cy, 5% ^{n}Bu$_4$NBr, 1.5 mmol Cs$_2$CO$_3$. (b) Isolated yield, average of two runs. (c) 10% 4,4′-dimethyl-*trans*-stilbene was isolated. (d) GC conversion. (e) *E*:*Z* = 20:1 as determined by ^{1}H-NMR, terminal:internal = 3:1.

sum of the bond angles around Pd is 360.14° with inequivalent Pd–N and, respectively Pd–O bonds. Also, the N–Pd–N bite angle in the rigid five-membered palladacycle is smaller than 90° due to the pressure imposed by the bulky mesityl substituents.

This observation is important, since the chelating planar ligand leaves the space below and above the plane free, possibly favoring the migratory insertion of the olefin at the end position with high selectivity for the formation of the terminally substituted olefin [29]. This is in agreement with theoretical studies performed on cationic phenylpalladium(II)diimine catalysts and on the influence of the electronic and steric effects of the ligand on the selectivity of the Heck reactions, which
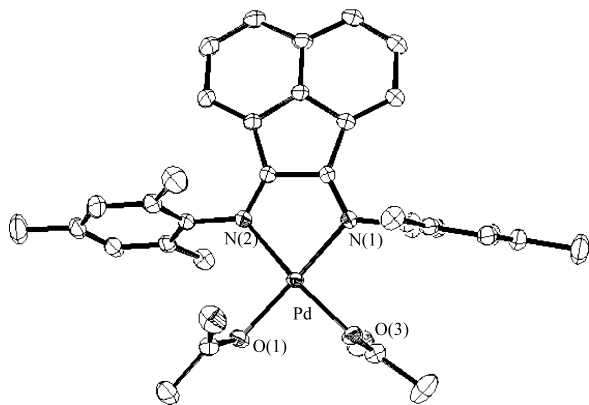
Fig. 1. ORTEP diagram of Pd(DAB′-Mes)(OAc)$_2$ (8). Thermal ellipsoids are drawn at 50% probability. Selected bond lengths (Å) and angles (°): Pd–O(1), 2.0027(9); Pd–O(3), 2.0079(9); Pd–N(1), 2.0278(4); Pd–N(2), 2.0183(10); O(1)–Pd–O(3), 89.97(4); O(1)–Pd–N(2), 92.79(4); O(3)–Pd–N(2), 175.07(4).

showed that while electronic effects are minor, steric effects have a major influence on the regiochemistry of the migratory insertion step [30].

2.5. Influence of the Pd source on the Heck coupling of 4-bromotoluene with styrene

Given the fact that the Pd(OAc)$_2$/DAB-Cy system is not very efficient for hindered and electron-rich aryl bromides at high temperatures and high catalyst loading, we were interested to determine whether other Pd sources would improve the yields obtained. Pd(dba)$_2$ and Pd(C$_6$H$_5$CN)$_2$Cl$_2$/DAB-Cy systems gave low conversions using 3 mol% catalyst, 5 mol% ^{n}Bu$_4$NBr, Cs$_2$CO$_3$ as base and DMAc at 100 °C. We were pleased to find out that using Pd(acac)$_2$ (acac = acetylacetonate) as precatalyst [31,32] the reaction of 4-bromotoluene

with styrene proceeds with a lower catalyst loading at lower temperature (Schemes 4 and 5).

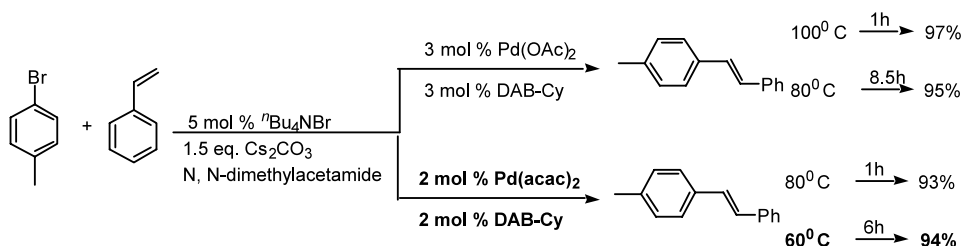### 2.6. Reaction conditions optimization for the Pd(acac)$_2$/ DAB-Cy-catalyzed Heck reaction

Optimization experiments showed that the reaction of 4-bromotoluene with styrene can be run with as low as 1 mol% Pd(acac)$_2$ using 5 mol% ^{n}Bu$_4$NBr in a very short reaction time and with high conversion (Table 5, entry 9). ^{n}Bu$_4$NBr additive has a significant effect on the coupling of 4-bromotoluene with styrene. When no ^{n}Bu$_4$NBr was used t–he reaction rate decreases significantly (Table 5, entries 4, 6 and 7), probably due to slow generation of Pd(0) species [33].

Running the control reaction (no ligand), we observed that Pd(acac)$_2$ is also an active catalyst at higher loadings and higher temperatures with slightly longer reaction times (Table 4, entries 2, 5 and 6).

This is not surprising, since it is known that non-ligated Pd(0) species are highly active and therefore able to activate aryl halides with respect to oxidative addition [25,34]. In this case, the Pd(0) species generated from Pd(acac)$_2$ appear to be very active and sufficiently stable at high temperatures in order to support oxidative addition. However, at 60 °C, the activity of the Pd(acac)$_2$ catalyst decreases significantly, while at the same temperature we observed a significant ligand effect (Table 4, entries 11 and 12). As a general trend, the ligand effect increases as the reaction temperature decreases; that is the Pd(acac)$_2$ catalyst is thermally activated at high temperature and requires the assistance provided by the supporting ligand DAB-Cy in order to form the active catalytic species under milder conditions.
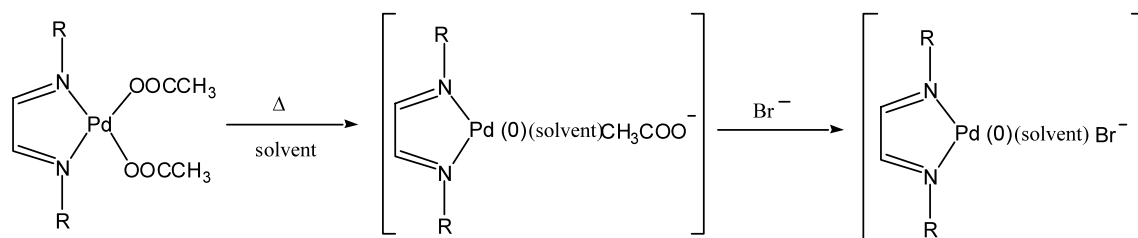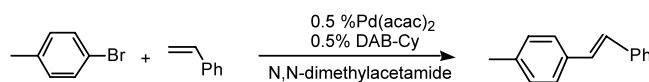

Scheme 4. Formation of active Pd(0) species.

Scheme 5. Pd(II)/DAB-Cy-catalyzed Heck reaction of 4-bromotoluene with styrene.

Table 4
Reaction conditions optimization of the Heck reaction of 4-bromotoluene with styrene
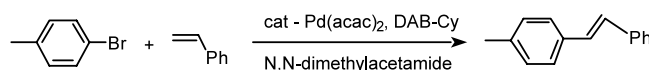

Entry	T (°C)	Pd(acac)$_2$/DAB-Cy	^{n}Bu$_4$NBr	Time (h)	Yield (%) [a]
1	100	0.03/0.03	0.05	1	97
2		0.03/–	0.05	1.5	95
3	80	0.03/0.03	0.05	1	95
4		0.02/0.02	0.05	1	93
5		0.02/–	0.05	3	93
6		0.02/0.02	–	2	NR
7				18	93
8		0.015/0.015	0.05	2	98
9		0.01/0.01	0.05	2.5	97
10		**0.005/0.005**	**0.05**	**20**	**10** [b]
11	60	0.02/0.02	0.05	6	94
12		0.02/–	0.05	9	22
13	RT	0.02/0.02	0.05	24	NR

Reaction conditions: 1 mmol 4-bromotoluene, 1.5 mmol styrene, 3 ml DMAc, Pd(acac)$_2$, DAB-Cy, ^{n}Bu$_4$NBr, 1.5 mmol Cs$_2$CO$_3$.
[a] GC yields(diethyleneglycol di-n-butyl ether used as internal standard, average of two runs).
[b] *Reaction conditions:* 2 mmol 4-bromotoluene, 3 mmol styrene, 6 ml DMAc, 3 mmol Cs$_2$CO$_3$.

Table 5
Influence of ^{n}Bu$_4$NBr concentration on the Heck reaction of 4-bromotoluene with styrene

Entry	T (°C)	0.005 mmol DAB-Cy	^{n}Bu$_4$NBr (mmol)	Time (h)	Yield (%) [a]
1	100		0.05	24	30
2			**0.10**	**1**	**92**
3			0.15	1	75
4			0.20	24	40
5		**No DAB-Cy**	**0.10**	**1**	**90**
6	80		0.10	3	43
7				9	95
8		No DAB-Cy	0.10	3	48
9				9	96
10	60		0.10	24	74
11		No DAB-Cy	0.10	24	62
12			**0.15**	**24**	**90**
13		**No DAB-Cy**	**0.15**	**24**	**86**
14			0.20	24	44
15		No DAB-Cy	0.20	24	50
16	120	0.001 Pd(acac)$_2$/0.001 DAB-Cy	0.10	24	70
17		0.001 Pd(acac)$_2$	0.10	24	43

Reaction conditions: 2 mmol 4-bromotoluene, 3 mmol styrene, 6 ml DMAc, 3 mmol Cs$_2$CO$_3$.
[a] GC yields(diethyleneglycol di-n-butyl ether used as internal standard, average of two runs).

Table 6
Functional group tolerance of the Heck coupling
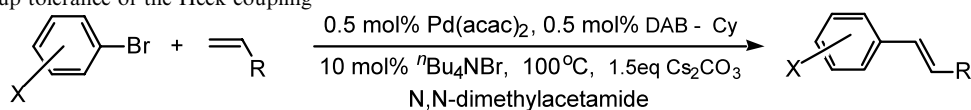
entry	aryl halide	olefin	product	time (h)	yield(%)[b] DAB-Cy	no ligand
1				6	58[c]	50[c]
2				6	70	52[c]
3				1	90[d]	89[d]
4				1	40[c]	80[e]
5				24	70[c]	57[c]
6				1	90	84
7				3	90	85
8				1	98	95
9				3	42[c]	25[c]
10				3	51[c]	99
11				3	99[f]	90[f]
12				3	94	90
13				1	95[f]	68[f]
14				6	90[f]	80[f,g]
15				6	88[f]	73[f,g]

(a) *Reaction conditions:* 1 mmol aryl halide, 1.5 mmol olefin, 3 ml DMAc, 10 mol% ^{n}Bu$_4$NBr, 1.5 mmol Cs$_2$CO$_3$. (b) Isolated yield, average of two runs. (c) GC conversion. (d) $E:Z = 20:1$ as determined by ^{1}H-NMR, terminal/internal = 4/1. (e) $E:Z = 20:1$ as determined by ^{1}H-NMR, terminal:internal = 8:1. (f) 1 mol% Pd(acac)$_2$ was used. (g) 24 h.

2.7. Influence of ^{n}Bu$_4$NBr additive

Since the reaction of 4-bromotoluene with styrene turns using as little as 0.5 mol% Pd(acac)$_2$ as precatalyst, we decided to investigate the influence of the additive concentration. We observed that the optimum bromide concentration at 100 and 80 °C is 10 mol%, with no significant ligand effect at these temperatures.

Decreasing the temperature to 60 °C and using as low as 0.5 mol% Pd(acac)$_2$ the optimum concentration of ^{n}Bu$_4$NBr increased to 1 mol%. The reaction rate decreases with the temperature perhaps due to higher

concentrations of coordinatively saturated species at lower temperatures. We believe that at lower temperatures, besides its activation quality, ^{n}Bu$_4$NBr serves also as transfer reagent for the insoluble base/solvent/substrates heterogeneous system [24,35]. Moreover, the concentration of ^{n}Bu$_4$NBr additive is also important, since higher bromide concentrations can lead to co-ordinative saturation, and hence deactivation of Pd(0) species. A significant ligand effect was observed when the catalyst loading was reduced to 0.1 mol%. The role of ^{n}Bu$_4$NBr additive concentration is threefold: (i) activation of Pd(0) species with the formation of anionic species; (ii) stabilization low coordinated Pd(0) species; (iii) phase transfer catalyst for the inorganic base/polar solvent/organic substrates/product phases [35].

2.8. Functional group tolerance of the Pd(acac)$_2$/DAB-Cy-catalyzed Heck reaction of arylbromides with olefins

Since the coupling of styrene with 4-bromotoluene is accelerated at 100 °C, we decided to investigate the functional group tolerance at this temperature. Coupling of electron-neutral and activated aryl bromides with styrenes proceeded with as little as 0.5 mol% Pd(acac)$_2$, in very short reaction times, giving the corresponding *trans*-stilbenes in excellent isolated yields (Table 6, entries 6–8). Acrylates proved to be poorer coupling partners under these reaction conditions, when either Pd(acac)$_2$ or Pd(acac)$_2$/DAB-Cy catalysts were employed (Table 6, entries 1 and 2). Surprisingly, unactivated olefins like 1-hexene and 1-octene lead to excellent yields and high selectivity in terminal *Z* olefin in very short reaction times when either the Pd(acac)$_2$ or Pd(acac)$_2$/DAB-Cy system was employed as the catalyst.

More difficult substrates such as 4-bromoanisole and sterically hindered substrates were converted to the corresponding products in high yields and with short reaction times using 1 mol% Pd(acac)$_2$, with no significant change when DAB-Cy was used as a supporting ligand.

3. Conclusions

In summary, optimization studies of the Pd(II)-catalyzed arylation of olefins have shown that, generally, there is no good or universal formula for this reaction when diazabutadiene ligands are employed. Pd(OAc)$_2$ in combination with the DAB-Cy ligand showed high activity with respect to coupling of electron-neutral and electron-deficient aryl bromides with a series of olefins, with excellent activity and selectivity for styrenes. Square planar Pd(II)(DAB-R)(OAc)$_2$ complexes are excellent precatalysts for Pd(0)(DAB-R)$^-$ ionic species generated in the polar solvent DMAc.

Pd(acac)$_2$ proved to be a very active and efficient catalyst precursor with respect to reaction rate, catalyst loadings, and functional group tolerance in the coupling of a wide range of aryl bromides with both electron-deficient or electron-rich olefins. Extensive optimization experiments showed that using the more active Pd(acac)$_2$ salt the reaction can be performed in certain cases without the support provided by the DAB-R ligand. Using the proper concentration of additive, Heck olefination can be performed in mild conditions (important factors for thermally labile substrates), under low catalyst loadings and with high conversions, which are important factors for industrial scale applications. Moreover, we observed that optimization of additive concentration is more important than the role of the ancillary ligand, which sometime is overestimated in coupling chemistry. However, at lower catalyst loadings, the DAB-Cy ligand shows a beneficial effect on the activity and productivity of the Pd(acac)$_2$ precatalyst. To this end, we can conclude that generally, unlike other Pd-catalyzed couplings, good results for the Heck reaction of aryl halides with olefins are often the consequence of the appropriate overlapping of a multitude of factors, such as olefin, base, and additive concentration, solvent, Pd source and supporting ligand.

4. Experimental

4.1. General information

All reactions were carried out under an atmosphere of dry argon using standard Schlenk techniques or in a MBraun glovebox containing less than 1 ppm of oxygen and water. NMR spectra were recorded using Varian 400 or 300 MHz spectrometers. GC analyses were performed on a Hewlett-Packard HP 5890 II equipped with a FID and a HP-5 column. Diazabutadiene ligands **1**–**7** were synthesized according to the literature methods [18,19].

4.2. Synthesis of Pd(DAB′-Mes)(OAc)$_2$ (**8**)

Pd(OAc)$_2$ (10 mg, 0.045 mmol) was dissolved in 5 ml diethyl ether and added to a 5 ml diethyl ether solution of DAB′-Mes (**6**). The deep red solution was stirred at room temperature for 2 h and the resulting precipitate filtered, washed with cold diethyl ether and dried under vacuo (microcrystalline deep red powder: 26 mg, 0.04 mmol, 89%); ^{1}H-NMR (CD$_2$Cl$_2$, 400 MHz), δ (ppm): 8.15 (d, $J = 8.4$ Hz, 2H), 7.54 (t, $J = 8$ Hz, 2H), 7.04 (s, 4H), 6.88 (d, $J = 7.2$ Hz, 2H), 2.46 (s, 12H), 2.35 (s, 6H), 1.31 (s, 6H); ^{13}C-NMR (CD$_2$Cl$_2$, 400 MHz), δ (ppm): 177.4, 174.3, 148, 140.3, 139, 132.8, 131.9, 130.7, 130, 129.8, 125.5, 125.1, 21.9, 21.4, 18.4%.

4.3. X-ray diffraction measurements

Single crystals of **8** were obtained by slow diffusion of a diluted THF solution of DAB′-Mes (**6**) into a diluted THF solution of Pd(OAc)$_2$. A single crystal was placed in a capillary tube and mounted on a Bruker SMART CCD X-ray diffractometer. Data were collected using Mo–K$_\alpha$ radiation at 150 K. The structures were solved using direct methods (SHELXS-86) and refined by full-matrix least-squares techniques. Selected bond distances and angles are shown in Table 4.

4.4. Pd(OAc)$_2$/DAB-R cross-coupling reactions of aryl halides olefins

General procedure: Under an atmosphere of argon DMAc (3 ml), aryl halide (1 mmol), Cs$_2$CO$_3$ (1.5 mmol), 5 mol% ^{n}Bu$_4$NBr and olefin (1.5 mmol) were added in turn to a Schlenk tube charged with 3 mol% Pd(OAc)$_2$, 3 mol% DAB-R, and a magnetic stirring bar. The Schlenk tube was placed in an oil bath at 100 °C and stirred. The reaction was monitored by GC. In some cases, the yields were determined by GC, using diethyleneglycol di-*n*-butyl ether as internal standard. The mixture was then allowed to cool at room temperature. The mixture was purified either directly by flash chromatography, or filtered through a pad of celite, concentrated, and then purified by flash chromatography using hexanes or hexanes:ethyl acetate = 15:1.

4.5. Pd(acac)$_2$/DAB-R cross-coupling reactions of aryl halides olefins

General procedure: Under an atmosphere of argon DMAc (6 ml), aryl halide (2 mmol), Cs$_2$CO$_3$ (3 mmol), ^{n}Bu$_4$NBr and olefin (3 mmol) were added in turn to a Schlenk tube charged with 0.5 mol% Pd(OAc)$_2$, 0.5 mol% DAB-R, and a magnetic stirring bar. The Schlenk tube was placed in an oil bath at 100 °C and stirred. The reaction was monitored by GC. In some cases, the yields were determined by GC, using diethyleneglycol di-*n*-butyl ether as internal standard. The mixture was then allowed to cool at room temperature. The mixture was purified either directly by flash chromatography, or filtered through a pad of celite, concentrated, and then purified by flash chromatography using hexanes or hexanes:ethyl acetate = 15:1

5. Supplementary material

Experimental procedures, characterization of new compounds, and references to known compounds are provided. Crystallographic data for the structural analysis has been deposited with the Cambridge Crystallographic Data Center, CCDC No. 206310 for compound **8**. Copies of this information may be obtained free of charge from the Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ UK (Fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk).

References

[1] (a) I. Beletskaya, A.V. Cheprakov, Chem. Rev. 100 (2000) 3009;
(b) N.J. Whitcombe, K.K. Hii, S.E. Gibson, Tetrahedron 57 (2001) 7446;
(c) G.T. Crisp, Chem. Soc. Rev. 27 (1998) 427;
(d) J.T. Link, L.E. Overman, in: F. Diedrich, P.J. Stang (Eds.), Metal-Catalyzed Cross-Coupling Reactions, Wiley-VCH, Weinheim, 1998;
(e) M.T. Reetz, in: S.G. Davies, S.-I. Murahashi (Eds.), Transition Metal Catalyzed Reactions, Blackwell Science, Oxford, 1999;
(f) H.A. Dieck, R.F. Heck, J. Org. Chem. 40 (1975) 1083;
(g) H.A. Dieck, R.F. Heck, J. Am. Chem. Soc. 96 (1974) 1133;
(h) R.F. Heck, in: B.M. Trost, I. Fleming (Eds.), Comprehensive Organic Synthesis, vol. 4, Pergamon Press, Oxford, 1991;
(i) J. Tsuji, Palladium Reagents and Catalysts, Wiley, Chichester, 1995.
[2] (a) J.-M. Gaudin, Tetrahedron Lett. 32 (1991) 6113;
(b) L.E. Overman, D.J. Ricca, V.D. Tran, J. Am. Chem. Soc. 115 (1993) 2042;
(c) L.F. Tietze, W. Buhr, Angew. Chem. Int. Ed. 34 (1995) 1366.
[3] (a) R.R. Bader, P. Baumeister, H.-U. Blaser, Chimia 50 (1996) 99;
(b) T.-C. Wu, US patent 5536870, 1996;
(c) A. Eisenstadt, in: F.E. Herkes (Ed.), Catalysis of Organic Reactions, Marcel Dekker, New York, 1998.
[4] Applications of phosphine ligands in homogeneous catalysis: (a) G.W. Parshall, S. Ittel, Homogenous Catalysis, J. Willey and Sons, New York, 1992;
(b) L.H. Pignolet, Homogenous Catalysis with Metal Phosphine Complexes, Plenum, New York, 1983.
[5] (a) A.F. Littke, G.C. Fu, J. Org. Chem. 64 (1999) 10;
(b) A.F. Litke, G.C. Fu, J. Am. Chem. Soc. 123 (2001) 6989.
[6] K.H. Shaughnessy, P. Kim, J.F. Hartwig, J. Am. Chem. Soc. 121 (1999) 2123.
[7] A. Ehrentraut, A. Zapf, M. Beller, Synlett 11 (2000) 1589.
[8] J.P. Collman, L.S. Hegedus, J.R. Norton, R.G. Finke, Principles and Applications of Organotransition Metal Chemistry, University Science, Mill Valley, CA, 1987.
[9] (a) A. Spencer, J. Organomet. Chem. 258 (1983) 101;
(b) W.A. Herrmann, C. Brossmer, K. Öfele, C.-P. Reisinger, T. Priermeier, M. Beller, H. Fischer, Angew. Chem. Int. Ed. 34 (1995) 1844;
(c) A. Zapf, M. Beller, Chem. Eur. J. 13 (2001) 2908.
[10] (a) M. Portnoy, Y. Ben-David, I. Rouso, D. Milstein, Organometallics 13 (1994) 3465;
(b) M. Portnoy, Y. Ben-David, M. Gozin, D. Milstein, Organometallics 11 (1992) 1995;

(c) M. Portnoy, D. Milstein, Organometallics 12 (1993) 1655;
(d) M. Portnoy, Y. Ben-David, I. Rouso, D. Milstein, Organometallics 13 (1993) 4734.

[11] For comprehensive reviews see: M. Regitz, Angew. Chem. Int. Ed. 35 (1996) 725;
(b) A.J. Arduengo III, R. Krafczyc, Chem. Zeit. 32 (1998) 6;
(c) W.A. Herrmann, C. Kocher, Angew. Chem. Int. Ed. 36 (1997) 2163;
(d) W.A. Herrmann, Angew. Chem. Int. Ed. 41 (2002) 1290;
(e) D. Bourissou, O. Guerret, F.P. Gabbaï, G. Bertrand, Chem. Rev. 100 (2000) 39.

[12] (a) J. Huang, E.D. Stevens, S.P. Nolan, J.L. Petersen, J. Am. Chem. Soc. 121 (1999) 2674;
(b) J. Huang, H. Schanz, E.D. Stevens, S.P. Nolan, Organometallics 18 (1999) 2370.

[13] (a) C. Yang, H.M. Lee, S.P. Nolan, Org. Lett. 3 (2001) 1511;
(b) C. Yang, S.P. Nolan, Synlett (2001) 1539;
(c) J. Schwarz, V.P.W. Böhm, M.G. Gardiner, M. Grosche, W.A. Herrmann, W. Hieringer, G. Raudaschl-Sieber, Chem. Eur. J. 6 (2000) 1773;
(d) A.A.D. Tulloch, A.A. Danopoulos, R.P. Tooze, S.M. Cafferkey, S. Kleinhenz, M.B. Hursthouse, Chem. Commun. (2000) 1247;
(e) D.S. McGuinness, K.J. Cavell, Organometallics 19 (2000) 741;
(f) D.S. McGuinness, K.J. Cavell, Organometallics 18 (1999) 1596;
(g) W.A. Herrmann, J. Fischer, M. Elison, C. Kocher, G.R.J. Artus, Chem. Eur. J. 2 (1996) 772;
(h) W.A. Herrmann, M. Elison, J. Fischer, C. Kocher, G.R.J. Artus, Angew. Chem. Int. Ed. 34 (1995) 2371.

[14] H. Weissman, D. Milstein, Chem. Commun. 9 (1999) 1901.

[15] (a) M. Ohff, A. Ohff, D. Milstein, Chem. Commun. (1999) 357;
(b) M. Nowotny, U. Hanefeld, H. van Koningsveld, T. Maschmeyer, Chem. Commun. (2000) 1877.

[16] (a) P. Mathur, S. Ghosh, A. Sarkar, A.L. Rheingold, I.A. Guzei, J. Organomet. Chem. 566 (1998) 159;
(b) J.F. Lehmann, S.G. Urquhart, L.E. Ennis, A.P. Hitchcock, K. Hatano, K.S. Gupta, M.K. Denk, Organometallics 18 (1999) 1862;
(c) S. Greulich, W. Kaim, A. Stange, H. Stoll, J. Fiedler, S. Zalis, Inorg. Chem. 35 (1996) 3998;
(d) J. Breuer, W.-H. Fruhauf, W.J.J. Smeets, A.L. Spek, Inorg. Chim. Acta 291 (1999) 438;
(e) G. van Koten, K. Vrieze, Adv. Organomet. Chem. 21 (1982) 151;
(f) R. van Asselt, C.J. Elsevier, W.J.J. Smeets, A.L. Spek, R. Benedix, R. Neth, Recl. Trav. Chim. Pay Bas 113 (1994) 88.

[17] (a) L.K. Johnson, C.M. Killian, M.S. Brookhart, J. Am. Chem. Soc. 117 (1995) 6414;
(b) C.M. Killian, D.J. Tempel, L.K. Johnson, M.S. Brookhart, J. Am. Chem. Soc. 118 (1996) 11664;
(c) D.J. Tempel, L.K. Johnson, R.L. Huff, P.S. White, M.S. Brookhart, J. Am. Chem. Soc. 122 (2000) 6686 (and references cited).

[18] (a) H. van der Poel, G. van Koten, M. Kokkes, C.H. Stam, Inorg. Chem. 20 (1981) 2941;
(b) H. tom Dieck, H. Bruder, J. Chem. Soc. Chem. Commun. 9 (1977) 24.

[19] (a) J.M. Kliegman, R.K. Barnes, Tetrahedron 26 (1970) 2555;
(b) A.J. Arduengo, III, R. Krafczyk, R. Schmutzler, A. Craig, A. Hugh, J.R. Goerlich, J. William, Tetrahedron 55 (1999) 14523;
(c) H. tom Dieck, I.W. Renk, K.D. Franz, J. Organomet. Chem. 94 (1975) 417.

[20] (a) A.J. Arduengo III, US patent 5 077 414, 1991;
(b) A.J. Arduengo, III, H.V.R. Dias, R.L. Harlow, M. Kline, J. Am. Chem. Soc. 114 (1992) 5530.

[21a] G.A. Grasa, A.C. Hillier, S.P. Nolan, Org. Lett. 3 (2001) 1077.

[21b] R. van Asselt, C.J. Elsevier, Organometallics 11 (1992) 1999.

[21c] R. van Asselt, C.J. Elsevier, Tetrahedron 50 (1994) 323.

[22] (a) M. Moreno-Manas, M. Perez, R. Pleixtas, Tetrahedron. Lett. 37 (1996) 7449;
(b) M. Moreno-Manas, R. Pleixats, A. Roglans, Synlett 10 (1997) 1157.

[23] (a) M. Ohff, A. Ohff, M.E.v.d. Boom, D. Milstein, J. Am. Chem. Soc. 119 (1997) 11687;
(b) F. Miyazaki, K. Yamaguchi, M. Shibasaki, Tetrahedron Lett. 40 (1999) 7379.

[24] (a) T. Jeffery, J. Chem. Soc. Chem. Commun. (1984) 1287;
(b) T. Jeffery, Tetrahedron Lett. 26 (1985) 2667;
(c) T. Jeffery, Synthesis 1 (1987) 70.

[25] C. Amatore, A. Jutand, Acc. Chem. Res. 33 (2000) 314.

[26] The yield of the reaction was lowered significantly when lower (e.g. 1.2 eq.) or higher (e.g. 2 eq.) amounts of base, respectively olefin are used.

[27] J. March, Advanced Organic Chemistry, Wiley, New York, 1992, pp. 278–286.

[28] For polar route (cationic mechanism) see: (a) W. Cabri, I. Candiani, S. DeBernardinis, F. Francalanci, S. Penco, R. Santi, R. J. Org. Chem. 56 (1991) 5796;
(b) W. Cabri, I. Candiani, A. Bedeschi, R. Santi, J. Org. Chem. 58 (1993) 7421;
(c) Y. Sato, M. Sodeoka, M. Shibasaki, Chem. Lett. 10 (1990) 1953;
(d) F. Ozawa, A. Kubo, T. Hayashi, J. Am. Chem. Soc. 113 (1991) 1417.

[29] (a) M. Larhed, C.-M. Anderson, A. Hallberg, Tetrahedron 50 (1994) 285;
(b) K. Olofsson, M. Larhed, A. Hallberg, J. Org. Chem. 63 (1998) 5076.

[30] H. von Schenck, B. Åkermark, M. Svensson, Organometallics 21 (2002) 2248.

[31] Pd(acac)$_2$ has been employed as precatalyst for the Heck reaction of aryl iodides in superheated water (R. Reardon, S. Metts, C. Crittendon, P. Daugherity, E.G. Parsons, Organometallics 14 (1995) 3810) or as source for synthesis of cyclopalladated imine catalysts ([15b]).

[32] Pd(acac)$_2$ is used mainly as precatalyst for telomerization reaction of dienes: (a) H. Karlheintz, B. Gruber, K.J. Weese, Tetrahedron Lett. 35 (1994) 4541;
(b) E.A. Petrushkina, V.I. Bregadze, Metalloorg. Khim. 5 (1992) 1161;
(c) M.I. Zakharkin, V.V. Guseva, D.D. Sulaimankulova, E.A. Petrushkina, Zh. Org. Chem. 23 (1987) 1654;
(d) T. Ito, Y. Takami, Bull. Chem. Soc. Jpn 51 (1978) 1220.

[33] W.A. Hermann, M. Elison, J. Fischer, C. Koecher, C.R.J. Artus, Angew. Chem. Int. Ed. 34 (1995) 2371.

[34] (a) C. Güertler, S.L. Buchwald, Chem. Eur. J. 5 (1999) 3107;
(b) P.H. Dussault, C.T. Eary, J. Am. Chem. Soc. 120 (1998) 7133.

[35] The Pd(acac)$_2$/DAB-Cy catalyst can be recycled three times without significant loss of activity. A typical procedure involves extraction of the product with hexanes (hexanes and DMAc are not miscible at room temperature), and addition of base and substrates (3 mol% Pd(acac)$_2$/DAB-Cy, run 1:97% in 1 h; run 2:91% in 12 h; run 3: 85% in 24 h).