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Synthesis of novel pillar[5]arene-based *N*-heterocyclic carbene ligands for Pd-catalysed Heck reactions

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ABSTRACT

Pillar[5]arene-based 1-benzylimidazole and 1-(9-anthracenylmethyl)imidazole salts were prepared for the first time as novel class supramolecular NHC ligands. These ligands, together with $PdCl_2(CH_3CN)_2$, were used as catalysts in the Heck coupling reactions of styrene and aryl halide derivatives. The 1-(9-anthracenylmethyl)imidazole salt exhibited better catalytic activity than the 1-benzylimidazole salt, owing to the steric bulk of the ligand. The novel pillar[5]arene-based imidazolium salt is a promising supramolecular skeleton for the construction of highly active catalysts.

Introduction

The Heck reaction, or palladium-catalysed arylation of olefins, has attracted increasing attention in the past decade and has become one of the most important selective C–C bond forming methods.[1–6] In recent years, *N*-heterocyclic carbenes (NHCs) have started to play a more important role than phosphine ligands in organometallic chemistry,[7–13] being easily modifiable and exhibiting outstanding catalytic performance in a variety of reactions.[14–16]

Pillar[n]arenes, first reported by Tomoki Ogoshi in 2008,[17] are a new class of macrocyclic hosts, which not only show unique symmetrical pillar-shaped architectures, but also exhibit other supramolecular macrocyclic host compounds excellent properties.[18–21] Just a few years after their discovery, pillar[n]arenes have already been widely used in molecular recognition,[22] self-assembly,[23] preparation of liquid crystals[24] and other fields. With the development of organometallic chemistry, many supramolecular organometallic complexes, such as metallacrown ethers (Fig. 1A),[25] metallacalixarenes (Fig. 1B)[26] and metalloporphyrins (Fig. 1C)[27] have been successfully obtained by coordination of transition metals to the supramolecular skeleton. These metal-containing macrocycles are widely applicable in the area of catalysis. Despite their widespread applications in supramolecular chemistry, the utilization of pillararenes in catalytic processes just begun.[28] As part of our current research on supramolecular *N*-heterocyclic carbenes, we have found that pillar[5]arene-based imidazolium salts, being *N*-heterocyclic carbene precursors, are promising organocatalysts.

Results and discussion

In this work, we prepared two novel pillar[5]arene-NHC ligands: 1-benzylimidazole hexafluorophosphate (**ligand 3a**) and 1-(9-anthracenylmethyl)imidazole hexafluorophosphate (**ligand 3b**) according to previously reported procedures.[29,30] The synthesis of NHC ligands is outlined in Scheme 1. Bromoethoxy pillar[5]arene **2** was prepared by stirring a mixture of 1,4-bis(2-bromoethoxy)benzene **1**, $BF_3{\cdot}Et_2O$, and paraformaldehyde in dry CH_2Cl_2 for 150 min under N_2 atmosphere. Ligand **3b** was prepared by refluxing **2** with excess 1-(9-anthracenylmethyl)imidazole in 1,4-dioxane, followed by anion exchange with PF_6^-.[31,32] Moreover, since the melting point of 1-benzylimidazole is relatively low, a solvent-free method was used to obtain high-purity **3a**. Compound **2** and excess 1-benzylimidazole were stirred at 150 °C in the absence of solvent, yielding **3a** after anion exchange with PF_6^-. The pillar[5]arene-NHC ligands were characterized by ^{1}H NMR, ^{13}C NMR, and IR spectroscopy. In the ^{1}H NMR spectra, the appearance of the imidazolium proton resonance at δ 9.50 and 9.43 (NCHN) supports the formation of the expected carbene precursors.

To evaluate the catalytic activity of novel pillar[5]arene-NHC ligands, they were tested in the Heck cross-coupling of styrene and aryl halide derivatives. We first chose ligand **3b** and $PdCl_2(CH_3CN)_2$ as a catalytic system to determine optimum conditions, including base, solvent, temperature, etc. Further investigations showed that the model substrates (styrene and aryl halide)

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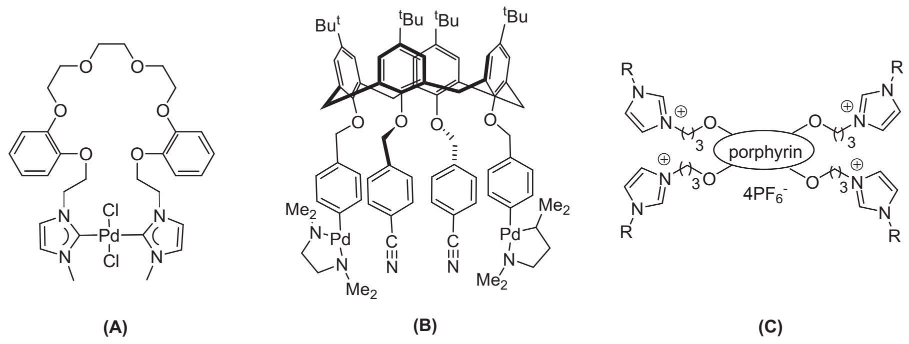
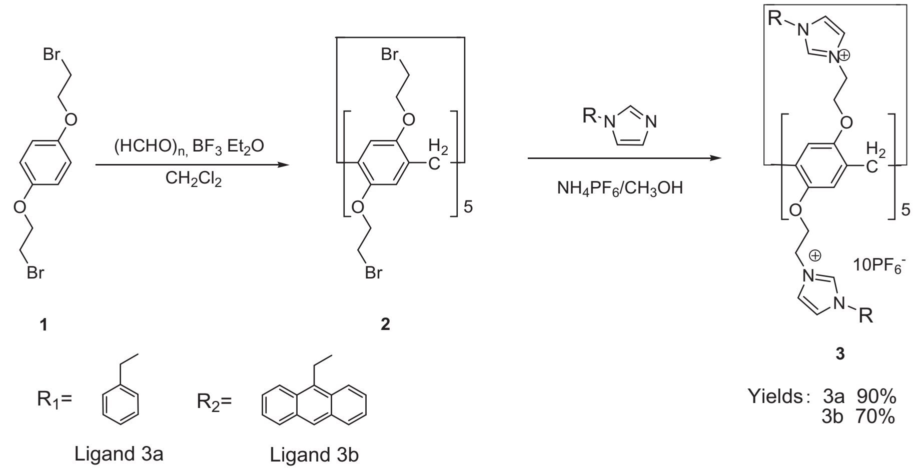


Figure 1. Structures of the complexes A, B and C.

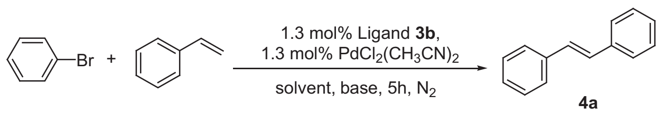


Scheme 1. Preparations of ligand **3a** and ligand **3b**.

efficiently formed the *trans*-stilbene coupling product (**4a**), with the results shown in Table 1.

Initially, among the several bases examined, a 30% yield of 4a was obtained by using KO^{t}Bu and NEt$_3$ in DMF at 120 °C for 5 h (Table 1, entries 1, and 2). Subsequently, we turned our attention to inorganic bases, known to be useful in Heck coupling.[33] K$_2$CO$_3$ (120 °C, 5 h) gave a low yield (Table 1, entry 3). However, when KOH was accidentally used as a base, the yield was significantly improved (Table 1, entry 4), Therefore, KOH, an inorganic strong base, was determined to be most suitable. Our re-optimization efforts were then focused on testing different types of solvents, Non-polar and polar protic solvents, afforded **4a** in less than 40% yield, whereas polar aprotic solvents (e.g., THF, DMF, or NMP) gave relatively high conversions (Table 1, entries 5–10). After some experimentation, we found NMP to be the best solvent for this reaction (Table 1, entry 10). More screening conditions are listed in the Supplementary data (Table S1).

Table 1
Optimization of reaction conditions[a]



Entry	Solvent	Base	Temp (°C)	Yield[b] (%)
1	DMF	KO^{t}Bu	120	24
2	DMF	NEt$_3$	120	33
3	DMF	K$_2$CO$_3$	120	25
4	DMF	KOH	120	71
5	Ethanol	KOH	100	30
6	DMSO	KOH	100	34
7	CH$_3$CN	KOH	85	31
8	THF	KOH	100	44
9	NMP	KOH	140	90
10	NMP	KOH	160	95

[a] Reaction condition: 0.73 mmol of aryl halide, 0.87 mmol styrene, 2.19 mmol of base, 1.3 mol% (9.49×10^{-3} mmol) of ligand **3b**, 1.3 mol% (9.49×10^{-3} mmol) of PdCl$_2$(CH$_3$CN)$_2$, 5 h, N$_2$.

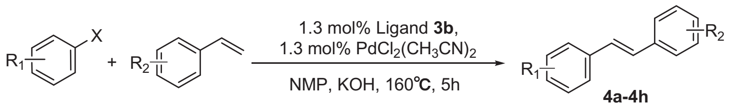
[b] Isolated yields after chromatographic purification.

With the optimized reaction conditions in hand, we set out to explore the substrate scope. A wide range of aryl halide derivatives were coupled with two different styrenes (R$_2$ = H, OMe), ligand **3b** and PdCl$_2$(CH$_3$CN)$_2$ as a catalytic system. The results are summarized in Table 2.

As shown in Table 2, all iodobenzene and bromobenzene derivatives were converted to the corresponding coupling products in excellent yields, despite the aromatic rings having electron-donating groups (Table 2, entries 2, 3, 5, 6, 8, 9, 11, 12, 14, and 15). The coupling of chlorobenzene derivatives also proceeded smoothly, furnishing the coupling products in moderate yields (Table 2, entries 1, 4, 7, 10, and 13). Additionally, we examined the coupling of various aryl bromides with 4-methoxystyrene, and found that aryl bromides bearing different substituents were efficiently converted to the corresponding coupling products in good yields (Table 2, entries 16–19).

In the last part of the study, we tried to explore the catalytic performance of different ligands; For this purpose, the performance of pillar[5]arene-based imidazolium salts **3a** and **3b** was compared for the coupling of aryl halides with styrene, with the results summarized in Table 3.

Table 2
Heck coupling reaction catalysed by ligand **3b**[a]



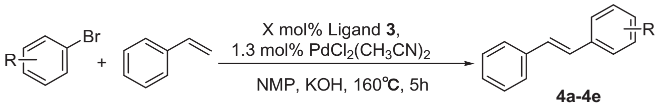
Entry	Product	R$_1$	X	R$_2$	Yield[b] (%)
1	**4a**	H	Cl	4-H	79
2	**4a**	H	Br	4-H	95
3	**4a**	H	I	4-H	99
4	**4b**	2-Me	Cl	4-H	71
5	**4b**	2-Me	Br	4-H	90
6	**4b**	2-Me	I	4-H	90
7	**4c**	4- Me	Cl	4-H	74
8	**4c**	4- Me	Br	4-H	90
9	**4c**	4- Me	I	4-H	94
10	**4d**	4-OMe	Cl	4-H	70
11	**4d**	4-OMe	Br	4-H	91
12	**4d**	4-OMe	I	4-H	95
13	**4e**	4-F	Cl	4-H	82
14	**4e**	4-F	Br	4-H	97
15	**4e**	4-F	I	4-H	99
16	**4d**	4-H	Br	4-OMe	92
17	**4f**	4-Me	Br	4-OMe	89
18	**4g**	4-OMe	Br	4-OMe	84
19	**4h**	4-F	Br	4-OMe	95

[a] Reaction condition: 0.73 mmol of Ar-X derivatives, 0.87 mmol styrene ($R_2 = H$, OMe), 2.19 mmol of KOH, 1.3 mol% (9.49×10^{-3} mmol) of ligand **3b**, 1.3 mol% (9.49×10^{-3} mmol) of PdCl$_2$(CH$_3$CN)$_2$, 160 °C, 5 h.

[b] Isolated yields after chromatographic purification.

As shown in Table 3, the activity of the two catalysts in the simple coupling of bromobenzene derivatives and styrene is quite different. It is surprising that the steric bulk of the ligand seems to have a large impact on the Heck coupling. Notably, when 1.3 mol % of the NHC-pillar[5]arene **3b** was used, all coupling reactions of bromobenzene derivatives and styrene afforded the desired products in considerable yields (entries 2, 4, 6, 8, and 10). However, the reaction yields were significantly reduced when 2.0 mol% of the NHC-pillar[5]arene **3a** were used (entries 1, 3, 5, 7, and 9). These facts suggest that the pillar[5]arene-based imidazolium salt **3b** exhibits higher catalytic activity, since the steric bulk of the NHC ligand may facilitate the formation of a catalytically active species, and enhance the reductive elimination step.[14,34,35]

Table 3
Heck coupling of aryl halide with different catalysts[a]



Entry	R	Ligands	Yield[b] (%)
1	H	Ligand **3a**	85
2	H	Ligand **3b**	95
3	2-Me	Ligand **3a**	72
4	2-Me	Ligand **3b**	90
5	4-Me	Ligand **3a**	80
6	4-Me	Ligand **3b**	90
7	4-OMe	Ligand **3a**	80
8	4-OMe	Ligand **3b**	91
9	4-F	Ligand **3a**	89
10	4-F	Ligand **3b**	97

[a] Reaction condition: 0.73 mmol of bromobenzene derivatives, 0.87 mmol styrene, 2.19 mmol of KOH, 2.0 mol% (14.6×10^{-3} mmol) of ligand **3a**, 1.3 mol% (9.49×10^{-3} mmol) of ligand **3b**, 1.3 mol% (9.49×10^{-3} mmol) of PdCl$_2$(CH$_3$CN)$_2$, 160 °C, 5 h.

[b] Isolated yields after chromatographic purification.

Conclusions

In this paper, we report the first-time synthesis of pillar[5]arene-based 1-benzylimidazole hexafluorophosphate (**ligand 3a**) and pillar[5]arene-based 1-(9-anthracenylmethyl)imidazole hexafluorophosphate (**ligand 3b**). The novel NHC-pillar[5]arene **3b** exhibited good catalytic activity in the Heck cross-coupling of styrene and aryl halide derivatives. The activities of the two catalysts were compared, showing the steric bulk of the ligand plays a very important role in this coupling reaction. Inspired by this, we are now pursuing the search for highly active supramolecular catalytic systems.

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Supplementary data

Supplementary data (full experimental procedures and ^{1}H NMR, ^{13}C NMR and IR spectra for compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.06.083.

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