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Tetrahedron Letters 49 (2008) 1706–1709
Tetrahedron Letters

New 2-(2-pyridyl)piperidines: synthesis, complexation of palladium and catalytic activity in Suzuki reaction ☆

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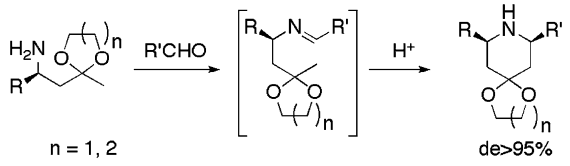
Received 26 September 2007; revised 19 December 2007; accepted 21 December 2007
Available online 8 January 2008

Abstract

The syntheses of novel 2-(2-pyridyl)-6-alkyl piperidines are reported using intramolecular Mannich-based methodology. Preliminary evaluation of the catalytic activity of the corresponding (diamine)Pd(II) complexes in the preparation of biaryl derivatives through Suzuki-type coupling reaction showed high to quantitative conversions and catalyst loadings as low as 10^{-3} mol %.

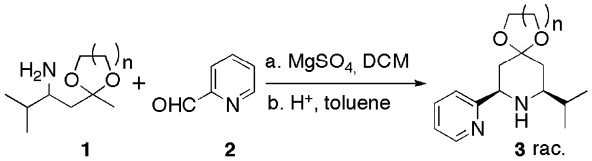
Vicinal diamines are common functional motifs in bioactive compounds.[1] Over the course of the past decades, 1,2-diamine derivatives also found applications as tools in organic synthesis[2] and in transition-metal-assisted catalysis.[3] Despite increasing reports in the latter area, there is a steady demand for original, easily accessible diamine ligands. As part of a programme directed towards the preparation of new aza-heterocycles and their applications to the design of new ligands,[4] we envisioned the preparation of 2-(2-aryl)-6-alkyl piperidines.

These compounds could be easily obtained through an intramolecular Mannich type reaction between a protected β-amino ketone and an aromatic aldehyde, which led predominantly to the 2,6-cis derivatives[5] (Scheme 1). This reaction is of wide scope as it can be applied to obtain various R and R′ substituents and this methodology has been successfully applied to the synthesis of numerous alkaloids.[6,7] We wish to report herein the synthesis of new 2-(2-pyridyl)-6-isopropyl-*cis* piperidine derivatives (Scheme 2) and their corresponding Pd(II) complexes together with the evaluation of their potential catalytic activity through the Suzuki coupling reaction.[8]



Scheme 1.

Indeed, in the last three decades, the Suzuki reaction has become one of the most popular and general catalytic way to create carbon–carbon bonds and thus found widespread applications in organic synthesis. Many active catalytic systems have been developed[9] to improve the stability of



Scheme 2.

☆ This work has been presented at JCO (Journées de Chimie Organique) at Palaiseau in September 2007.

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doi:10.1016/j.tetlet.2007.12.125

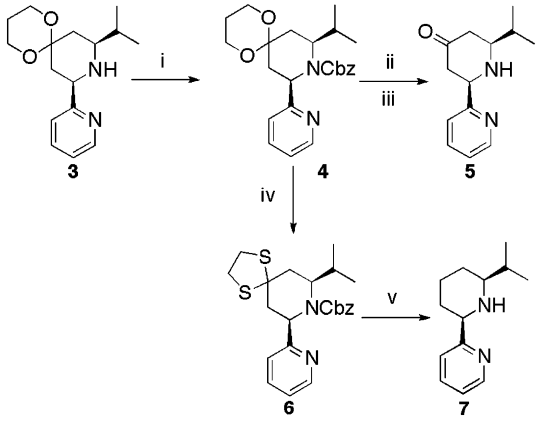
palladium-based catalyst and to increase their efficiency. Besides bis-phosphine ligands, several nitrogen containing ligands have proved to be useful for the preparation of biaryl-type compounds.[4,10a–f] However, little attention has been paid to the use of piperidyl compounds as potent transition metal ligands. To the best of our knowledge, pyridine-piperidine bidentate ligands have not been yet described in palladium based catalysis.

So, aminoketal **1** was easily prepared in three steps and good overall yield (80%) by Michael addition of phthalimide to 5-methyl-3-hexen-2-one in the presence of Triton B® as the catalyst, followed by acetalization with 1,3 propane diol and hydrazonolysis of the phthalimide moiety. Condensation of **1** with commercially available 2-pyridine carboxaldehyde **2**, under our standard acidic cyclization conditions,[6a,b] cleanly afforded the expected 2,6-cis-disubstituted piperidine **3** in high yield (80%) and high diastereoselectivity (up to 95%) (Scheme 2). Relative configuration of piperidine **3** was unambiguously established from the ^{1}H NMR data, notably with the signals relative to axial H-3 and axial H-5 showing typical coupling constants for a 2,6-diequatorial disubstitution in a chair conformation.[5]

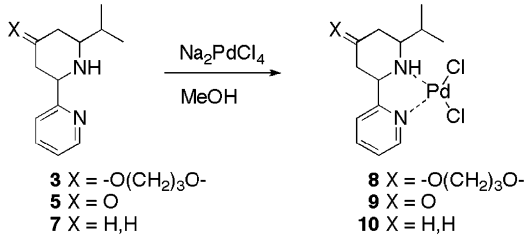
We next envisioned the modification and/or rigidification of the piperidine backbone, which may strongly influence the catalytic process, and turned our attention to keto and dihydro derivatives **5** and **7**. Cleavage of the dioxane appendage of compound **3** was then achieved in two steps since we have demonstrated that deacetalization was best realized if the nitrogen of the piperidine ring was protected. Thus, the treatment of piperidine **3** with benzyl chloroformate in biphasic medium[11] led to carbamate **4** in very good yield. Then, the reaction of **4** with trifluoroacetic acid followed by catalytic hydrogenation furnished piperidone **5**. On the other hand, treatment of **4** with an excess of ethanedithiol in dichloromethane in the presence of BF_3. Et_2O afforded quantitatively the dithiolane derivative **6**. Subsequent hydrogenolysis of **6** was completely and cleanly achieved in the presence of freshly prepared W_2 Raney-nickel in refluxing methanol and furnished piperidine **7**[12] in good overall yield (Scheme 3).

Compounds **3**, **5** and **7** were now treated with Na_2PdCl_4 under classical conditions[13] to give the expected Pd (II) complexes **8**–**10** in high yields (Scheme 4). The reaction proceeds smoothly at room temperature in freshly distilled methanol. After 24 h, the precipitated complexes are collected by filtration. These palladium complexes are stable on air and they could be either purified by silica gel chromatography if necessary. NMR data of complexes **8**–**10** were in good agreement with their respective structure. Indeed, characteristic positive shieldings ranging from 0.08 to 0.43 ppm for pyridine protons were observed between ligands **3**, **5**, **7** and their complexes **8**–**10**, thus confirming coordination by the metal centre.

Having in hands a set of three new complexes, we started to evaluate their catalytic activity in Suzuki-type reactions. Preliminary results based on the preparation of 4-biphenylcarbaldehyde **11**, as model compound (Scheme 5), are

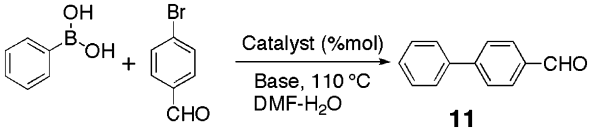


Scheme 3. Reagents and conditions: (i) CBzCl, CH_2Cl_2, Na_2CO_3; (ii) TFA aq 40%; (iii) H_2, Pd/C; (iv) $HS(CH_2)_2SH$, $BF_3(OEt)_2$, CH_2Cl_2; (v) H_2, Raney-Ni, EtOH.



Scheme 4.

shown in Table 1. Classical reaction conditions (K_2CO_3 as the base and a mixture of DMF/H_2O (95:5) as the solvent) were first used. Gratifyingly, the model compound could be quantitatively obtained using 1% of catalyst **8** (Table 1, entry 1). Subsequent reaction analysis was performed by ^{1}H NMR spectroscopy of crude reaction mixtures to give an accurate assessment of product distribution based on the chemical shift of the aldehyde proton of both the product and the substrate. Interestingly, decrease of the catalyst loading to 0.1 and further to 0.01 mol % led to quantitative conversion within 1 h 30 min (entries 2 and 3, respectively). In addition, reaction times could be optimized to 30 min by changing the base, moving from K_2CO_3 to Cs_2CO_3 or $K_3PO_4{\cdot}7H_2O$ (entries 4 and 5) without the loss of catalytic activity. Although if complete conversion could be observed in the latter case, a small amount of benzaldehyde, arising from hydrodehalogenation of the starting halide, was concomitantly obtained (less than 5%, entry 5). It is also worth noting that optimal reaction temperature was 110 °C. Effectively, decreasing of the reaction temperature resulted in prolonged heating time for the same quantitative yield.



Scheme 5.

Table 1
Optimization of reaction conditions[a] at 110 °C

E	mol % Cat.	Complex	Base	Time	Yield[b] (%) (conversion)
1	1	**8**	K_2CO_3	1 h 30 min	96
2	0.1	**8**	K_2CO_3	1 h 30 min	(>98)
3	0.01	**8**	K_2CO_3	1 h 30 min	(>98)
4	0.01	**8**	Cs_2CO_3	30 min	(>98)
5	0.01	**8**	$K_3PO_4{\cdot}7H_2O$	30 min	(>98)[c]
6	0.01	**9**	$K_3PO_4{\cdot}7H_2O$	2 h	80
7	0.01	**10**	$K_3PO_4{\cdot}7H_2O$	30 min	(>98)
8	0.006	**10**	$K_3PO_4{\cdot}7H_2O$	30 min	90

[a] Reaction conditions: 4-bromobenzaldehyde (0.5 mmol), phenylboronic acid (0.55 mmol), base (1.25 mmol) 1 ml DMF/H_2O (95:5).
[b] Isolated yields.
[c] Obtained as a 95:5 mixture of expected biphenyl product and benzaldehyde.

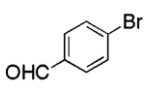
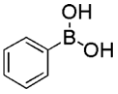
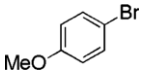
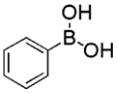
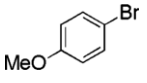
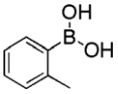
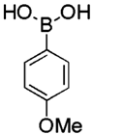
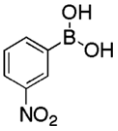
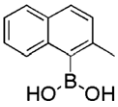
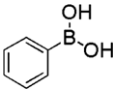
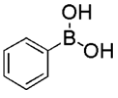
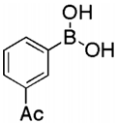
We next evaluated the catalytic activity of complexes **9** and **10**. Complex **9** bearing the keto moiety revealed less effective than the ketal analogue **8** (entry 6). The more rigid conformation of the piperidone cycle may account for the observed lesser activity. Finally, complex **10**[14] used as the catalyst proved efficient in the Suzuki-type reaction. Indeed, catalyst loading as low as 1×10^{-2} and 6×10^{-3} allowed the preparation of **11** in quantitative and 90% yield, respectively, within 30 min (entries 7 and 8). In addition, no reduction of the starting halide leading to benzaldehyde could be observed under these conditions. Catalytic system based on complex **10** thus seems to be the catalyst of choice in these reactions from practical considerations.

Then, catalyst **10** was used in a variety of Suzuki-type coupling reactions and the results obtained were collected as shown in Table 2. We first examined the influence of the substitution of both the aromatic halide and boronic acid, by electron withdrawing or electron donating groups on the formation of the coupling product. The latter are well tolerated in this reaction leading to quantitative yields of the corresponding biaryls (entries 2, 3 and 5). Even the presence of a strong withdrawing NO_2 substituent on the aromatic boronic acid afforded the expected biphenyl compound in 85% yield after 5 h (entry 5). As illustrated in compounds **13**, **15**, **16**, under our conditions, the coupling reactions seem not to be sensitive to *ortho*-substitution pattern of both the aromatic halide and boronic acid. In addition, naphthalene bromides have been successfully coupled with (4-methoxyphenyl)boronic acid and (2-methylnaphthyl)boronic acid, using 6×10^{-3} mol % catalyst loading, affording compounds **14** and **16** in high yields (entries 4 and 6).

Finally, the coupling reaction of phenylboronic acid with both π-excessive and π-deficient heterocycles was carried out leading to **17** and **18**, respectively, in nearly quantitative yields (entries 7 and 8).

In summary, new 2-(2-pyridyl)-6-isopropyl *cis* piperidines have been successfully synthesized using intramolecular Mannich methodology. These new bidendate strained ligands with two different chelation sites permit the preparation of new palladium(II) complexes. Preliminary evaluation of the catalytic activity of these complexes addresses the potentiality of this new ligand series in the preparation of biaryls through Suzuki-type coupling reactions. Further development of both the asymmetric synthesis of such ligands and the asymmetric Suzuki reaction is now under investigation.

Table 2
Suzuki reaction[15] of aryl halide with boronic acid using complex **10** as the catalyst[a]

E	Ar–Br	Boronic acid	Mol %	Time	Yield[b] (%)
1			6×10^{-3}	30 min	90
2			10^{-2}	1 h	99
3			6×10^{-2}	2 h	99
4			6×10^{-3}	1 h	95
5			6×10^{-2}	2 h 5 h	66 85
6			6×10^{-3}	2 h	95
7			6×10^{-2}	2 h	99
8			6×10^{-2}	2 h	99
9			6×10^{-2}	12 h	50

[a] Reaction conditions: aryl halide (0.5 mmol) boronic acid (0.55 mmol), $K_3PO_4{\cdot}7H_2O$ (1.25 mmol), DMF/H_2O (95:5) 1 ml, 110 °C.
[b] Isolated yields.

Acknowledgements

We are grateful to MENRT-France for a Grant (B. Puget) and the CNRS, the Université de Versailles-Saint-Quentin-en-Yvelines and ENSCCF for financial support.

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12. Spectral data ^{1}H NMR: δ_H (300 MHz, $CDCl_3$) 8.52 (d, $J = 3.0$ Hz, 1H), 7.76 (td, $J = 7.7$ Hz, $J = 0.8$ Hz, 1H), 7.48 (d, $J = 7.7$ Hz, 1H), 7.27 (td, $J = 7.4$ Hz, $J = 1.2$ Hz, 1H), 4.38 (dd, $J = 12.0$ Hz, $J = 2.8$ Hz, 1H), 3.22 (m, 1H), 2.44 (m, 1H), 1.83–2.09 (m, 5H), 1.61 (m, 2H); 1.07 (d, $J = 6.8$ Hz, 3H); 1.01 (d, $J = 6.8$ Hz, 3H). ^{13}C NMR: δ_C (75 MHz, $CDCl_3$) 155.6, 149.2, 137.9, 124 122.6, 62.2, 60.3, 30.3, 30.1, 23.3, 22.5, 19.4, 16.7.
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14. Spectral data ^{1}H NMR: δ_H (400 MHz, $CDCl_3$, one drop DMSO-d_6) 8.85 (dd, $J = 5.1$ Hz, $J = 0.6$ Hz, 1H), 7.74 (td, $J = 7.7$ Hz, $J = 1.3$ Hz, 1H), 7.18 (d, $J = 7.4$ Hz, 1H), 7.13 (td, $J = 7.4$ Hz, $J = 1.3$ Hz, 1H); 5.40 (m, 1H), 3.60 (dt, $J = 12.0$ Hz, $J = 2.8$ Hz, 1H), 2.80 (m, 1H), 1.64–1.89 (m, 5H), 1.26–1.41 (m, 2H); 0,84 (d, $J = 6.6$ Hz, 3H), 0.60 (d, $J = 6.6$ Hz, 3H).
^{13}C NMR: δ_C (100 MHz, $CDCl_3$, one drop DMSO-d_6) 149.9, 139.4, 123.5, 120.4, 71.1, 70.6, 34.8, 28.8, 26.0, 24.5, 20.4, 19.7.
15. Typical experimental procedure for the Suzuki reaction:
A mixture of *p*-bromobenzaldehyde (0.50 mmol, 92 mg), phenyl boronic acid (0.55 mmol, 67 mg), Pd-complex **10** (6×10^{-3} mol %, 330 μl of a 1/100 diluted 9 mM solution in 95:5 DMF/H_2O) and $K_3PO_4 \cdot 7H_2O$ (1.25 mmol, 423 mg) in 1 ml DMF/H_2O (95:5) freshly prepared with degassed and distilled solvents was stirred at 110 °C for 30 min. After the mixture was washed with water, extracted with ether, dried over magnesium sulfate and concentrated under vacuum, the residue was purified by flash column chromatography (petroleum ether) to afford biphenyl-4-carbaldehyde **11** (82 mg, 90%).