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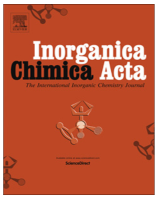

N-Heterocyclic carbene-palladium(II)-1-methylimidazole complex catalyzed α-arylation of symmetric dialkyl ketones with aryl chlorides

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ABSTRACT

N-Heterocyclic carbene-palladium(II)-1-methylimidazole [NHC-Pd(II)-Im] complex **1** showed efficient catalytic activity toward α-arylation of symmetric dialkyl ketones under mild conditions. It was found that the ratio of aryl chlorides and ketones drastically affected the reaction. When the ratio of aryl chlorides and ketones was 1:2, mono-arylated products can be obtained in good to high yields as the sole; while that of aryl chlorides and ketones was changed to 1:0.7, di- and mono-arylated products were obtained in good to high total yields at the same time, with the former as the major.

1. Introduction

Owing to the original contributions from Miura [1], Buchwald [2], and Hartwig [3], the palladium-catalyzed α-arylation of carbonyl compounds has been one of the most versatile methods for the formation of C(sp^2)–C(sp^3) bonds [4–7]. Traditionally, in order to improve the efficiency of such transformation, toxic, expensive, less available, electron-rich and sterically-hindered monodentate phosphine ligands were necessary. In addition, since Nolan's initial paper was reported in 2002, *N*-heterocyclic carbenes (NHCs), which usually had the advantages of higher air-, moisture-, and thermal-stability over their phosphine counterparts, were found to be excellent ligands in the palladium-catalyzed α-arylation of ketones [8–17]. However, despite the above abundant papers, the mono-arylation of symmetric dialkyl ketones still kept a big challenge in organic synthesis [18–20]. For example, in 2011, Stradiotto and co-workers reported the palladium-catalyzed mono-arylation of acetone with aryl chlorides and tosylates using 1–6 mol% P,N ligands [18]. In 2012, Ackermann and co-workers reported the palladium-catalyzed mono-arylation of acetone with aryl imidazolylsulfonates using 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl as the ligand, in high catalyst loadings [5.0 mol% $Pd(OAc)_2$ and 10.0 mol% ligand] [19]. In addition, all the phosphine ligands are not readily available. In the NHC-metal complexes catalyzed α-arylation reactions of ketones reported, only fewer examples on symmetric dialkyl ketones were involved, implying their limitations on the substrate generality. For example, in 2011, Shi and co-workers reported few examples on the NHC-Pd complex catalyzed α-arylation of dialkyl ketones, in which mono-arylated products can be only obtained when sterically hindered 1-bromo-2-methoxynaphthalene or bulky (3-chlorophenyl)-(phenyl)-methanone were used as the substrates [16]. Therefore, much room still remains for the mono-arylation of symmetric dialkyl ketones.

Recently, we have developed a well-defined and easily available *N*-heterocyclic carbene-Pd(II)-1-methylimidazole [NHC-Pd(II)-Im] complex **1** and found it to be efficient catalyst in the α-arylation of aryl alkyl ketones, oxindoles and 2,3-dihydroinden-1-ones [21–23]. In addition, we have also found that when 4-methoxyphenyl chloride **2a** and 3-pentanone **3a** were used as the substrates, the solvents and reaction time drastically affected the reaction. That is, when the ratio of **2a** to **3a** is 1.2:1 and the reaction was performed in DMF for 6 h, the mono-arylated product **4a** can be obtained in 42% yield as the sole one, while if the same reaction was performed in toluene for 3 h, the di-arylated product **5a** can be formed in 67% yield as the sole one (Scheme 1) [21]. These results thus prompted us to further investigate the NHC-Pd(II)-Im complex **1** catalyzed α-arylation of symmetric dialkyl ketones with aryl chlorides. Herein, we report these results in detail.

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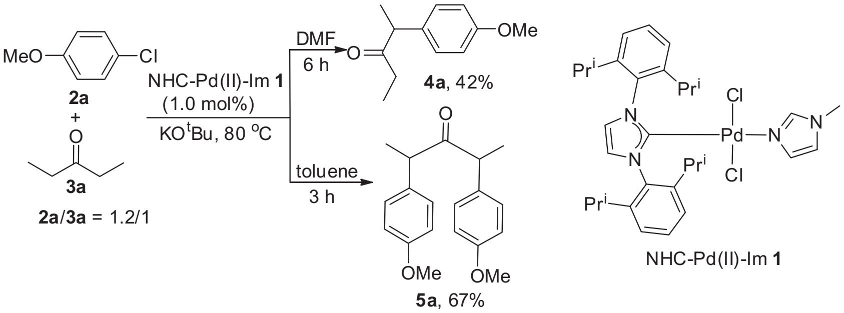


Scheme 1. NHC-Pd(II)-Im complex 1 catalyzed reaction of 4-methoxyphenyl chlorides **2a** with 3-pentanone **3a**.

2. Experimental

2.1. General remarks

Melting points are uncorrected. NMR spectra were recorded at 300/500 (for ^{1}H NMR) or 75/125 MHz (for ^{13}C NMR), respectively. ^{1}H NMR and ^{13}C NMR spectra recorded in $CDCl_3$ solutions were referenced to TMS (0.00 ppm) and the residual solvent peak (77.0 ppm), respectively. *J*-values are in Hz. Organic solvents used were dried by standard methods. The mass analyzer type for the high resolution mass spectra (HRMS) is quadrupole (for ESI). Other commercially obtained reagents were used without further purification. Flash column chromatography was performed on silica gel (300–400 mesh).

2.2. General procedure for the NHC-Pd(II)-Im complex 1 catalyzed α-arylation

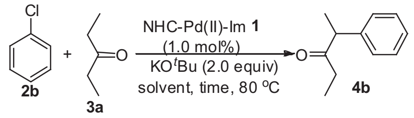
Under N_2 atmosphere, NHC-Pd(II)-Im complex **1** (6.5 mg, 1.0 mol%), KO^{t}Bu (224.4 mg, 2.0 mmol), toluene (1.0 mL), ketones **3** (2.0 mmol or 0.7 mmol), and aryl chlorides **2** (1.0 mmol) were successively added into a Schlenk reaction tube. The mixture was stirred at the specified temperature for the listed time shown in Tables 1–3. The reaction mixture was cooled to room temperature, then the solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography to give the pure products.

3. Results and discussion

Initial examinations were carried out using chlorobenzene **2b** and 3-pentanone **3a** as the model substrates, KO^{t}Bu (2.0 equiv) as the base, NHC-Pd(II)-Im complex **1** (1.0 mol%) as the catalyst, DMF as the solvent at 80 °C for 6 h, and the mono-arylated product **4b** can be obtained in 42% yield (Table 1, entry 1) [21], which still kept in 41% when the ratio of **2b** to **3a** was adjusted to 2:1 (Table 1, entry 3). When the reaction time was prolonged to 8 h, the yield of **4b** was slightly decreased to 37% (Table 1, entry 2). In addition, when the ratio of **2b** to **3a** was adjusted to 1:2, the yield of **4a** can be increased to 65% within 6 h (Table 1, entry 4). Considering of the reversibility of this reaction as previously reported [21], the reaction time was then decreased to 3 h, and the yield of **4a** can be actually increased to 78% (Table 1, entry 5). Finally, to our pleasure, when toluene was used as the solvent, the best result was achieved, giving product **4a** in 86% yield (Table 1, entry 6).

With the optimal conditions in hand, we then set out to test the reaction generality using a variety of aryl chlorides **2** and symmetric dialkyl ketones **3** such as 3-pentanone **3a** and 5-nonanone **3b** as the substrates. As can be seen from Table 2, all reactions took place well to give the expected mono-arylated products **4** in good to high yields. Substituents on the aryl chlorides had almost no effect on the reactions. For example, whether electron-rich substituents such as Me, OMe, NMe_2 or electron-poor substituent such as F atom were attached on the phenyl rings of aryl chlorides, all reactions gave products **4** in good to high yields. In addition, sterically-hindered substituents such as 2-Me, 2-OMe, even 2,6-Me_2 on the

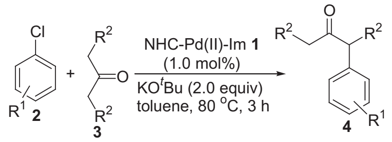
Table 1
Optimization for the NHC-Pd(II)-Im complex **1** catalyzed mono-arylation of 3-pentanone **3a** with chlorobenzene **2b**.



Entry[a]	**2b**:**3a**	Solvent	Time (h)	Yield (%)[b]
1	1.2:1	DMF	6	42
2	1.2:1	DMF	8	37
3	2:1	DMF	6	41
4	1:2	DMF	6	65
5	1:2	DMF	3	78
6	1:2	toluene	3	86

[a] All reactions were carried out using **1** (1.0 mol%), KO^{t}Bu (2.0 equiv), solvent (1.0 mL) at 80 °C.
[b] Isolated yields.

Table 2
NHC-Pd(II)-Im complex **1** catalyzed mono-arylation of symmetric dialkyl ketones **3** with aryl chlorides **2**.

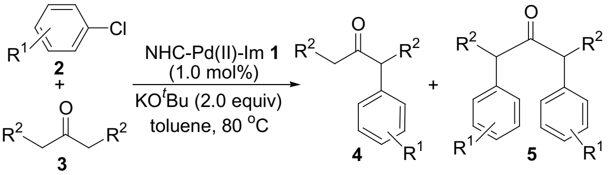


Entry[a]	**2** (R^1)	**3** (R^2)	Yield (%)[b]
1	**2a** (4-OMe)	**3a** (Me)	**4a**, 86
2	**2c** (4-Me)	**3a**	**4c**, 83
3	**2d** (3-Me)	**3a**	**4d**, 82
4	**2e** (2-Me)	**3a**	**4e**, 89
5	**2f** (2,6-Me_2)	**3a**	**4f**, 89
6	**2g** (4-F)	**3a**	**4g**, 80
7	**2h** (3-OMe)	**3a**	**4h**, 90
8	**2i** (2-OMe)	**3a**	**4i**, 89
9	**2j** (4-NMe_2)	**3a**	**4j**, 87
10	2a	**3b** (^{n}Pr)	**4k**, 83
11	**2b** (H)	**3b**	**4l**, 95
12	**2c**	**3b**	**4m**, 79
13	**2h**	**3b**	**4n**, 80
14	**2i**	**3b**	**4o**, 87

[a] All reactions were carried out using **2** (1.0 mmol), **3** (2.0 mmol), **1** (1.0 mol%), KO^{t}Bu (2.0 equiv), toluene (1.0 mL) at 80 °C for 3 h.
[b] Isolated yields.

Table 3

NHC-Pd(II)-Im complex **1** catalyzed mono- and di-arylation of symmetric dialkyl ketones **3** with aryl chlorides **2**.



Entry[a]	**2** (R^1)	**3** (R^2)	Time (h)	Yield (%)[b]	
1	**2b** (H)	**3a** (Me)	3	**4b**, 19	**5b**, 68
2	**2c** (4-Me)	**3a**	3	**4c**, 20	**5c**, 66
3	**2d** (3-Me)	**3a**	3	**4d**, 11	**5d**, 78
4	**2e** (2-Me)	**3a**	3	**4e**, 32	**5e**, 50
5	**2c**	**3b** (^{n}Pr)	12	**4m**, 19	**5f**, 67
6	**2d**	**3b**	12	**4p**, 22	**5g**, 65
7	**2a** (4-OMe)	**3b**	12	**4k**, 16	**5h**, 71

[a] All reactions were carried out using **2** (1.0 mmol), **3** (0.7 mmol), **1** (1.0 mol%), KO^{t}Bu (2.0 equiv), toluene (1.0 mL) at 80 °C.

[b] Isolated yields.

phenyl rings of aryl chlorides had no effect on the reactions (Table 2, entries 4, 5, 8 and 14).

Encouraged by the successful results of the mono-arylation between aryl chlorides **2** and symmetric dialkyl ketones **3**, we then turned our interest to the di-arylation reaction. Though in our preliminary investigations, when the reaction between 4-methoxyphenyl chloride **2a** (1.5 mmol) and 3-pentanone **3a** (1.0 mmol) was performed in toluene for 3 h, the di-arylated product **5a** can be obtained in 80% yield as the sole one [21], after some trials and errors, the best result can only be observed under such conditions. However, to our disappointment, using other aryl chlorides as the substrates, the di-arylated products cannot be formed as the sole one. That is, under these conditions, the di-arylated products **5** were obtained as the major, along with the mono-arylated products **4** as the minor. The results were shown in Table 3. It seems that substituents on the aryl chlorides did not affect the reactions. For all the aryl chlorides examined, all reactions performed well to give the mono-arylated products **4** and di-arylated products **5** in good to high total yields, with the latter as the major.

4. Conclusion

In conclusion, NHC-Pd(II)-Im complex **1** was found to be an efficient catalyst for the α-arylation of symmetric dialkyl ketones[1]. Under the optimal conditions, the mono-arylated products can be obtained in good to high yields as the sole using a variety of aryl chlorides as the substrates, providing an alternative, phosphine-free method for the mono-arylation of symmetric dialkyl ketones. It may be noted here that this is the first example of phosphine-free, NHC-Pd complex catalyzed α-mono-arylation of symmetric dialkyl ketones with such broad reaction generality. In addition, by tuning the ratio of aryl chlorides and symmetric dialkyl ketones, the mono-arylated and di-arylated products can be formed in good to high total yields at the same time, with the latter as the major.

Acknowledgements

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ica.2014.07.061. These data include MOL files and InChiKeys of the most important compounds described in this article.

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[1] Many efforts were tried for the mono- or di-arylation of other simple ketones such as acetone and cyclohexanone under the optimal or other reaction conditions, but no satisfactory result was achieved for these two substrates.