ORGANIC LETTERS
2013
Vol. 15, No. 23
6042–6045

Two-Component, Three-Molecule Reactions between 2,3-Dihydroinden-1-ones and Aryl Chlorides Catalyzed by an *N*-Heterocyclic Carbene–Palladium(II)–1-Methylimidazole Complex

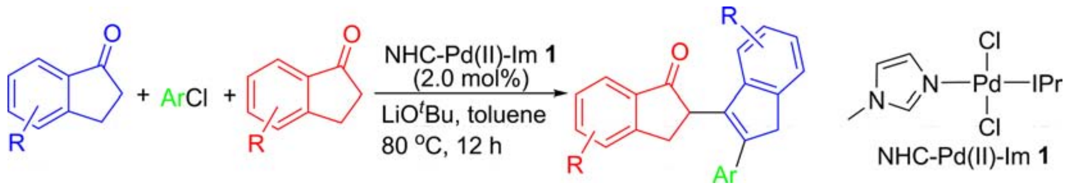
Hui-Ying Yin,[†] Meng-Yuan Liu,[†] and Li-Xiong Shao*,[†,‡]

College of Chemistry and Materials Engineering, Wenzhou University, Chashan University Town, Wenzhou, Zhejiang Province 325035, People's Republic of China, and College of Chemistry and Life Sciences, Zhejiang Normal University, Jinhua, Zhejiang Province 321004, People's Republic of China

Shaolix@wzu.edu.cn

Received October 11, 2013

ABSTRACT



The two-component, three-molecule reactions between 2,3-dihydroinden-1-ones and aryl chlorides were achieved in the presence of an NHC–Pd(II)–Im complex. Under the optimal conditions, all reactions performed well to give the corresponding products in moderate to high yields.

Pioneered by the group of Miura,[1] Buchwald,[2] and Hartwig,[3] the palladium-catalyzed α-arylation of carbonyl compounds, which was usually promoted by the introduction of phosphine ligands, has become one of the most useful methods for the formation of $C(sp^2)-C(sp^3)$ bonds.[4] During the past decade, *N*-heterocyclic carbenes (NHCs), with the advantages of higher air-, moisture-, and thermal-stability over their phosphine counterparts, have showed good catalytic activity along with palladium salts in the α-arylation of ketones.[5] Very recently, we have also successfully synthesized a well-defined *N*-heterocyclic carbene–Pd(II)–1-methylimidazole [NHC–Pd(II)–Im] complex **1** and found it to be an efficient catalyst in the α-arylation of carbonyl compounds such as aryl alkyl ketones and 2-oxindoles with aryl chlorides.[6] These results thus prompted us to further investigate the catalytic activity of NHC–Pd(II)–Im complex **1** toward the α-arylation of other carbonyl compounds.

Recently, metals such as palladium and nickel catalyzed reactions of 2,3-dihydroinden-1-ones with aryl chlorides,

---

[†] Wenzhou University.

[‡] Zhejiang Normal University.

(1) Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1740–1742.

(2) Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 11108–11109.

(3) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1997**, *119*, 12382–12383.

(4) For some reviews, please see: (a) Culkin, D. A.; Hartwig, J. F. *Acc. Chem. Res.* **2003**, *36*, 234–245. (b) Bellina, F.; Rossi, R. *Chem. Rev.* **2010**, *110*, 1082–1146. (c) Johansson, C. C. C.; Colacot, T. J. *Angew. Chem., Int. Ed.* **2010**, *49*, 676–707. (d) Novak, P.; Martin, R. *Curr. Org. Chem.* **2011**, *15*, 3233–3262.

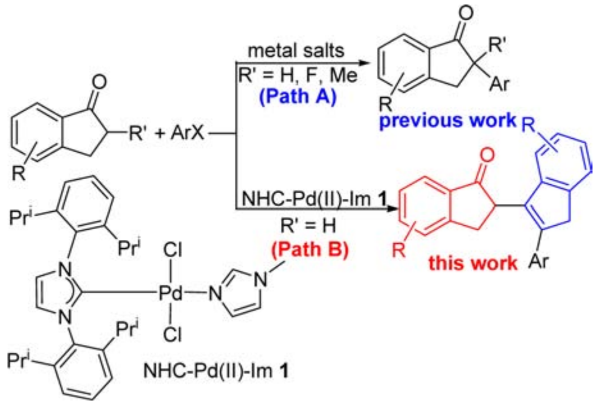
(5) (a) Lee, S.; Beare, N. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 8410–8411. (b) Viciu, M. S.; Germaneau, R. F.; Nolan, S. P. *Org. Lett.* **2002**, *4*, 4053–4056. (c) Viciu, M. S.; Kelly, R. A., III; Stevens, E. D.; Naud, F.; Studer, M.; Nolan, S. P. *Org. Lett.* **2003**, *5*, 1479–1482. (d) Navarro, O.; Marion, N.; Scott, N. M.; González, J.; Amoroso, D.; Bell, A.; Nolan, S. P. *Tetrahedron* **2005**, *61*, 9716–9722. (e) Navarro, O.; Marion, N.; Oonishi, Y.; Kelly, R. A., III; Nolan, S. P. *J. Org. Chem.* **2006**, *71*, 685–692. (f) Marion, N.; Ecarnot, E. C.; Navarro, O.; Amoroso, D.; Bell, A.; Nolan, S. P. *J. Org. Chem.* **2006**, *71*, 3816–3821. (g) Marion, N.; de Frémont, P.; Puijk, I. M.; Ecarnot, E. C.; Amoroso, D.; Bell, A.; Nolan, S. P. *Adv. Synth. Catal.* **2007**, *349*, 2380–2384. (h) Cao, C.-S.; Wang, L.-L.; Cai, Z.-Y.; Zhang, L.-Q.; Guo, J.; Pang, G.-S.; Shi, Y.-H. *Eur. J. Org. Chem.* **2011**, 1570–1574. (i) Zhang, J.-L.; Yang, X.-Q.; Cui, X.-L.; Wu, Y.-J. *Tetrahedron* **2011**, *67*, 8800–8807.

(6) (a) Xiao, Z.-K.; Shao, L.-X. *Synthesis* **2012**, *44*, 711–716. (b) Xiao, Z.-K.; Yin, H.-Y.; Shao, L.-X. *Org. Lett.* **2013**, *15*, 1254–1257.

10.1021/ol4029447

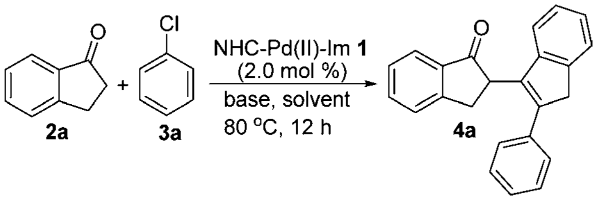
bromides, and triflates have been reported to give the normal α-arylated products in the presence of phosphine, NHC, and *N*,*O* ligands, respectively (Scheme 1, Path A).[7] However, to our pleasure, when the reactions between 2,3-dihydroinden-1-ones and aryl chlorides were carried out in the presence of NHC−Pd(II)−Im complex **1**, the two-component, three-molecule reactions were achieved in moderate to good yields (Scheme 1, Path B). Herein, we report these preliminary results in detail.

Scheme 1. Metal Catalyzed α-Arylation of 2,3-Dihydroinden-1-ones



An initial trial was carried out using 2,3-dihydroinden-1-one **2a** (1.2 mmol) and chlorobenzene **3a** (0.6 mmol) as the substrates, in the presence of NHC−Pd(II)−Im complex **1** (2.0 mol %) and LiO^{t}Bu (4.0 equiv) in toluene (1.0 mL) at 80 °C for 12 h, and product **4a** was formed in 61% yield (Table 1, entry 1). The structure of product **4a** was unambiguously determined by X-ray single crystal diffraction (Figure 1).[8] Subsequently, the ratio of **2a** and **3a** was adjusted to 1:1 and the yield of **4a** was not disturbed in this case (Table 1, entry 2). Finally, the best yield was achieved when the ratio of **2a** and **3a** was adjusted to 4:3, and product **4a** was obtained in 69% yield (Table 1, entry 3). Based on these results, a variety of bases were then screened. It was found that, in the presence of NaO^{t}Bu, product **4a** can be obtained in 45% yield (Table 1, entry 5), while, in the presence of other bases such as KO^{t}Bu, K_2CO_3, Na_2CO_3, NaOH, KOH, Li_2CO_3, Cs_2CO_3, $Na_3PO_4\cdot 12H_2O$, and $K_3PO_4\cdot 3H_2O$, almost no desired product was detected (ND) (Table 1, entries 4, 6−13).

Table 1. Optimization for the Reaction Conditions



2a **3a** **4a**

entry[a]	2a:3a	solvent	base	yield/%[b]
1	2:1	toluene	LiO^{t}Bu	61
2	1:1	toluene	LiO^{t}Bu	60
3	4:3	toluene	LiO^{t}Bu	69
4	4:3	toluene	KO^{t}Bu	ND
5	4:3	toluene	NaO^{t}Bu	45
6	4:3	toluene	K_2CO_3	ND
7	4:3	toluene	Na_2CO_3	ND
8	4:3	toluene	NaOH	<5
9	4:3	toluene	KOH	trace
10	4:3	toluene	Li_2CO_3	ND
11	4:3	toluene	Cs_2CO_3	ND
12	4:3	toluene	$Na_3PO_4\cdot 12H_2O$	ND
13	4:3	toluene	$K_3PO_4\cdot 3H_2O$	ND
14	4:3	THF	LiO^{t}Bu	ND
15	4:3	CH_3CN	LiO^{t}Bu	ND
16	4:3	Dioxane	LiO^{t}Bu	ND
17	4:3	DMF	LiO^{t}Bu	ND
18	4:3	DMSO	LiO^{t}Bu	ND

[a] All reactions were carried out using **2a**, **3a** (0.6 mmol), base (4.0 equiv), **1** (2.0 mol %) in solvent (1.0 mL) at 80 °C for 12 h. [b] Isolated yields.

Furthermore, the effect of solvents was also investigated. It was found that in the presence of all other solvents such as THF, CH_3CN, dioxane, DMF, and DMSO, no desired product can be detected (Table 1, entries 14−18).[9]

With the optimal conditions in hand, the scope and limitations of this reaction were first examined using 2,3-dihydroinden-1-one **2a** and a variety of aryl chlorides **3** as the substrates. The results are summarized in Table 2. A wide range of aryl chlorides **3** bearing an electron-rich or -poor group on the phenyl rings gave the corresponding products **4** in acceptable to high yields (Table 2, entries 1−10). Sterically hindered substituents such as 2-Me, 2-OMe, 2-F, and 2,6-Me_2 groups on the phenyl rings of aryl chlorides **3** did not affect the reactions, giving the expected products **4b**, **4e**, **4g**, and **4k** in good to high yields

---

(7) (a) Åhman, J.; Wolfe, J. P.; Troutman, M. V.; Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 1918–1919. (b) Ehrentraut, A.; Zapf, A.; Beller, M. *Adv. Synth. Catal.* **2002**, *344*, 209–217. (c) Chen, G.-S.; Kwong, F. Y.; Chan, H. O.; Yu, W.-Y.; Chan, A. S. C. *Chem. Commun.* **2006**, 1413–1415. (d) Liao, X.-B.; Weng, Z.-Q.; Buchwald, S. L. *J. Am. Chem. Soc.* **2008**, *130*, 195–200. (e) Grasa, G. A.; Colacot, T. J. *Org. Process Res. Dev.* **2008**, *12*, 522–529. (f) Ranganath, K. V. S.; Kloesges, J.; Schäfer, A. H.; Glorius, F. *Angew. Chem., Int. Ed.* **2010**, *49*, 7786–7789. (g) Ge, S.-Z.; Hartwig, J. F. *J. Am .Chem. Soc.* **2011**, *133*, 16330–16333. (h) Guo, C.; Wang, R.-W.; Guo, Y.; Qing, F.-L. *J. Fluorine Chem.* **2012**, *133*, 86–96. (i) Richter, C.; Ranganath, K. V. S.; Glorius, F. *Adv. Synth. Catal.* **2012**, *354*, 377–382.

(8) The crystal data of product **4a** has been deposited in CCDC with number 951405, and please see in the Supporting Information for more details.

(9) Some other well-known NHC−Pd complexes from Nolan, Organ, and Tu's groups with high catalytic activity in cross-coupling reactions have also been checked for the reaction between **2a** and **3a** under the optimal conditions, and similar good results were achieved, respectively (see Supporting Information for more details). For selected papers, please see: (a) Viciu, M. S.; Germaneau, R. F.; Nolan, S. P. *Org. Lett.* **2002**, *4*, 4053–4056. (b) Viciu, M. S.; Navarro, O.; Germaneau, R. F.; Kelly, R. A., III; Sommer, W.; Marion, N.; Stevens, E. D.; Cavallo, L.; Nolan, S. P. *Organometallics* **2004**, *23*, 1629–1635. (c) O'Brien, C. J.; Kantchev, E. A. B.; Valente, C.; Hadei, N.; Chass, G. A.; Lough, A.; Hopkinson, A. C.; Organ, M. G. *Chem.—Eur. J.* **2006**, *12*, 4743–4748. (d) Organ, M. G.; Calimsiz, S.; Sayah, M.; Hoi, K. H.; Lough, A. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 2383–2387. (e) Tu, T.; Fang, W.-W.; Jiang, J. *Chem. Commun.* **2011**, *47*, 12358–12360. (f) Tu, T.; Sun, Z.-M.; Fang, W.-W.; Xu, M.-Z.; Zhou, Y.-F. *Org. Lett.* **2012**, *14*, 4250–4253.

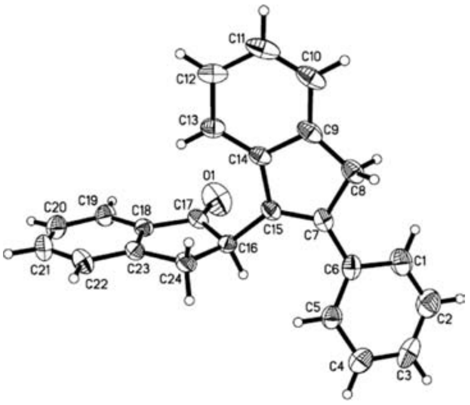
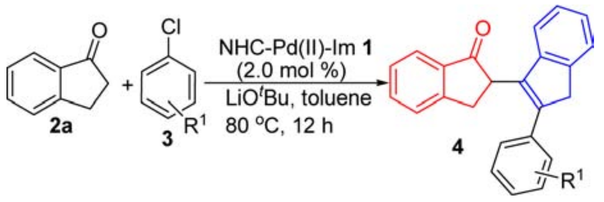
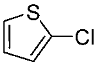


Figure 1. ORTEP drawing of product **4a**.

Table 2. NHC−Pd(II)−Im **1** Catalyzed Reactions of 2,3- Dihydroinden-1-one **2a** with Aryl Chlorides **3**



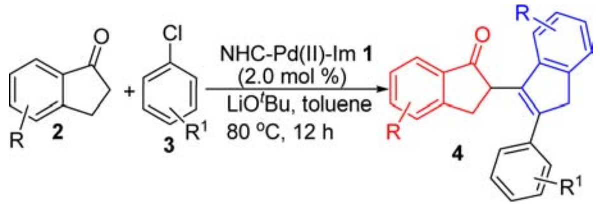
entry^a	**3** (R^1)	yield/%^{b}
1	**3b** (2-Me)	**4b**, 73
2	**3c** (3-Me)	**4c**, 69
3	**3d** (4-Me)	**4d**, 58
4	**3e** (2-OMe)	**4e**, 79
5	**3f** (3-OMe)	**4f**, 54
6	**3g** (2-F)	**4g**, 85
7	**3h** (3-F)	**4h**, 83
8	**3i** (4-F)	**4i**, 50
9	**3j** (4-vinyl)	**4j**, 70
10	**3k** (2,6-Me$_2$)	**4k**, 76
11	**3l**  S Cl	**4l**, 47

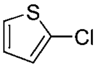
^{a} All reactions were carried out using **2a** (0.8 mmol), **3** (0.6 mmol), LiO^{t}Bu (4.0 equiv), **1** (2.0 mol %) in toluene (1.0 mL) at 80 °C for 12 h. ^{b} Isolated yields.

(Table 2, entries 1, 4, 6, and 10). Furthermore, heteroaryl chloride such as 2-chlorothiophene **3l** was also found to be an effective substrate in this reaction to give the desired product **4l** in 47% yield (Table 2, entry 11).

Encouraged by the above results, the optimized conditions were further investigated using variations of 2,3-dihydroinden-1-ones **2** and aryl chlorides **3** as the substrates. To our pleasure, for the reactions with various combinations of substrates **2** and **3**, moderate to high yields of the desired products **4** can be achieved. Substituents on both substrates of **2** and **3** almost did not affect the reactions, whether they were electron-rich, -poor, or sterically hindered groups. For example, sterically hindered 4-*F*-2,3-dihydroinden-1-one **2d** worked well with all the aryl chlorides **3** tested (Table 3, entries 12−14). In addition, the reactions involving sterically hindered aryl chlorides **3** with 2-Me, 2-MeO, 2-F, and 2,6-Me$_2$ groups on the phenyl rings also took place smoothly in all cases to give the corresponding products **4** in moderate to high yields (Table 3, entries 2, 5−7, 9, 11, 13, 14, 16, and 17). Furthermore, for the reaction between 4-methyl-2,3-dihydroinden-1-one **2b** and 2-chlorothiophene **3l**, product **4t** can be obtained in 55% yield (Table 3, entry 8).

Table 3. NHC-Pd(II)-Im **1** Catalyzed Reactions of 2,3-Dihydroinden-1-ones **2** with Aryl Chlorides **3**



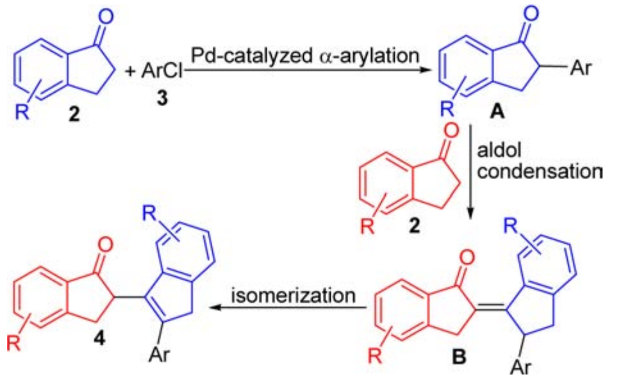
entry^a	**2** (R)	**3** (R^1)	yield/%^{b}
1	**2b** (6-Me)	**3a** (H)	**4m**, 60
2	**2b**	**3b** (2-Me)	**4n**, 84
3	**2b**	**3c** (3-Me)	**4o**, 71
4	**2b**	**3d** (4-Me)	**4p**, 60
5	**2b**	**3e** (2-OMe)	**4q**, 85
6	**2b**	**3g** (2-F)	**4r**, 90
7	**2b**	**3k** (2,6-Me$_2$)	**4s**, 69
8	**2b**	**3l**  S Cl	**4t**, 55
9	**2c** (5-OMe)	**3g**	**4u**, 69
10	**2c**	**3c**	**4v**, 52
11	**2c**	**3e**	**4w**, 60
12	**2d** (4-F)	**3b**	**4x**, 85
13	**2d**	**3e**	**4y**, 84
14	**2d**	**3g**	**4z**, 75
15	**2e** (6-F)	**3a**	**4aa**, 62
16	**2e**	**3e**	**4ab**, 82
17	**2e**	**3g**	**4ac**, 83

^{a} All reactions were carried out using **2** (0.8 mmol), **3** (0.6 mmol), LiO^{t}Bu (4.0 equiv), **1** (2.0 mol %) in toluene (1.0 mL) at 80 °C for 12 h. ^{b} Isolated yields.

Although the real mechanism for this reaction is unclear at this stage, a plausible pathway for the formation of products **4** is shown below on the basis of the results described above (Scheme 2): first, the Pd-catalyzed α-arylation between 2,3-dihydroinden-1-ones **2** and aryl chlorides **3** will afford the normal α-arylated intermediate **A**. Subsequently, intermediate **A** was subjected to aldol condensation with another molecule **2** to give intermediate **B**, which will be transformed to the final products **4** by isomerization.

In conclusion, we have reported novel NHC−Pd(II) complex catalyzed two-component, three-molecule

Scheme 2. Plausible Pathway for the Formation of Products **4**



reactions between 2,3-dihydroinden-1-ones **2** and aryl chlorides **3**. It seems that three steps such as Pd-catalyzed α-arylation, subsequent aldol condensation, and final isomerization are involved in the reactions. Furthermore, a broad range of substrates are tolerant in the reactions. For instance, both substrates bearing electron-rich, -poor, and sterically hindered substituents can give the corresponding products in acceptable to high yields. The reactions involving heteroaryl chloride also work well to give the desired products in acceptable yields.

Acknowledgment. Financial support from the Natural Science Foundation of Zhejiang Province (No. LY12-B02012) and the Open Research Fund of Top Key Discipline of Chemistry in Zhejiang Provincial Colleges and Key Laboratory of the Ministry of Education for Advanced Catalysis Materials (Zhejiang Normal University) (No. ZJHX201305) is greatly appreciated.

Supporting Information Available. Full experimental details and X-ray data of compound **4a** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.