Letter

Direct ortho Arylation of Anisoles via the Formation of Four-Membered Lithiumcycles/Palladacycles

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Abstract We report here our latest discovery on the directed lithiation and palladium-catalyzed arylation of anisoles. During this research, the formation of a four-membered lithiumcycle followed by transmetalation to the corresponding palladacycle has been achieved, which is difficult to be obtained from palladium-catalyzed C–H activation processes. This approach has provided an alternative way of introducing functionalities to arenes such as anisoles, thioanisoles, and anilines. This approach also features an excellent monoselectivity compared with reactions under transition-metal-catalyzed conditions.

Key words directed lithiation, lithiumcycle, transmetalation, monoselectivity, palladium-catalyzed arylation

The utilization of transition metals for the activation of arene C-H bonds for further functionalization is one of the most efficient strategies for the exploration of molecular diversity.¹ The C-H activation of arenes with no coordinative groups will normally lead to the products in less site-selective fashion. The introduction of directing groups in arenes has attracted great attention for ortho-selective functionalgroup installation.² Our group has made contributions in the direct access of heteroaromatic systems via ortho C-H activation-annulation strategies.³ More interestingly, the directed meta-4 and para-selective⁵ C-H activation have been developed in the last five years. Within the field of directed C-H activation under transition-metal-catalyzed conditions, the formation of five-membered transitionmetal complexes are preferred intermediates, which could give rise to the corresponding functionalized arenes. As shown in Scheme 1 (a) with imine 1 as an example, the five-membered metallocycle 2 is formed, which is then further converted into the functionalized arene 3. The direct



formation of four-membered metallocycle **6** is very scarcely studied. With anisole (**4a**) for example, the direct arylation under transition-metal-catalyzed conditions would be very challenging because the direct formation of four-membered metallocycle **6** from anisole (**4a**) is less favored (Scheme 1, b). However, the use of the DoM (directed *ortho*-metalation) strategy by directed *ortho* lithiation⁶ followed by the transmetalation between lithium and a transition metal such as palladium would be a good alternative to facilitate the formation of four-membered metallocycle **6**.⁷⁻¹⁰ The further reaction of metallocycle **6** will lead to *ortho*-substituted anisole **7** (Scheme 1, b).



Scheme 1 Directed metalation-functionalization and directed lithiation-transmetalation-functionalization of arenes

Tamoxifen (**8**, Figure 1), an anticancer agent¹¹ which is also being used for the treatment of the McCune–Albright syndrome,¹² is a drug molecule containing the anisole core structure. Anisole derivatives or tamoxifen (**8**) could be used as precursors for the further functionalization with regard to the late-stage molecular modification for the lead and optimizations for drug discovery.



In the directed *ortho*-lithiation process, the unique size for the lithium ion makes a four-membered coordinative intermediate possible. The directed lithiation followed by the reaction with various electrophiles has been very well studied.⁶ However, the direct lithiation and transmetalation of organolithium with palladium for the direct introduction of arenes has not been very well studied. Inspired by Murahashi/Moritani^{9c} and Feringa¹³, we explored directed *ortho*-lithiation and palladium-catalyzed arylation processes. We herein report our latest discoveries on the directed lithiation and palladium-catalyzed *ortho* arylation for the access of a class of arylated anisole derivatives as shown in Scheme 2.



We chose anisole (4a) as our model substrate for the lithiation reactions. As one of our research focus, we were interested in the utilization of *n*-BuLi under mild conditions instead of the less stable and more expensive t-BuLi and s-BuLi for the deprotonation at low temperature. A number of commonly available amine ligands were studied. The lithiation at room temperature in the absence of a ligand was inefficient; the desired silvlated anisole 7b was isolated in 21% yield after lithiation and trapping with TMSCI (Table 1, entry 1). The use of TMEDA at both 0.4 M and 0.2 M were both giving the desired product in nearly quantitative yield (Table 1, entries 2 and 3). The triamine additive PMDTA¹⁴ with *n*-BuLi was nearly as good as the use of TMEDA (Table 1, entry 4). The results from the reaction at 0 °C are comparable to those at room temperature, however, the reaction at -20 °C provided the desired arene 7b in slightly lower yield of 79% (Table 1, entries 5 and 6).

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 Table 1
 The Directed Lithiation and Trapping with Trimethylsilyl Chloride^a

		1. ⁿ BuLi, ligand, Et _z 2. TMSCI	0, temp.	U TMS
	4a	7b		
Entry	Ligand	Concn (M)	Temp (°C)	Yield of 7b (%)
1	-	0.4	r.t.	21
2	TMEDA	0.4	r.t.	99
3	TMEDA	0.2	r.t.	99
4	PMDTA	0.4	r.t.	92
5	TMEDA	0.4	0	97
6	TMEDA	0.4	-20	79

^a Reaction conditions: anisole **4a** (0.2 mmol), *n*-BuLi (2.4 M, 0.125 mL, 1.5 equiv), TMEDA (34.8 mg, 1.5 equiv) in Et_2O (0.4 M, 0.5 mL), r.t. 0.5 h, TMSCI (0.1 mL).

Table 2 The Directed Lithiation and Palladium-Catalyzed Arylation^a



Entry	PhX	Pd catalyst	Ligand	Temp (°C)	Yield of 7a (%)
1	PhBr	$Pd_2(dba)_3$	XPhos	r.t.	12
2	PhBr	Pd ₂ (dba) ₃	SPhos	r.t.	6
3	PhBr	$Pd_2(dba)_3$	DavePhos	r.t.	<5
4	PhBr	Pd ₂ (dba) ₃	XantPhos	r.t.	<5
5	PhBr	$Pd_2(dba)_3$	$P(t-Bu)_3$	r.t.	34
6	PhBr	$Pd(PPh_3)_2Cl_2$	$P(t-Bu)_3$	r.t.	10
7	PhBr	$Pd(PPh_3)_4$	$P(t-Bu)_3$	r.t.	12
8	PhBr	Pd(Pt-Bu ₃) ₂	$P(t-Bu)_3$	r.t.	31
9	PhBr	$Pd_2(dba)_3$	$P(t-Bu)_3$	50	49
10	PhI	$Pd_2(dba)_3$	$P(t-Bu)_3$	50	57
11ª	PhI	Pd ₂ (dba) ₃	$P(t-Bu)_3$	0-50	65

^a Reaction conditions: anisole **4a** (0.2 mmol), *n*-BuLi (2.4 M, 0.125 mL, 1.5 equiv), TMEDA (34.8 mg, 1.5 equiv) in Et₂O (0.4 M, 0.5 mL), r.t. 0.5 h, then aryl halides (ArX, X = Br or I, 2 equiv), Pd₂(dba)₃ (9.2 mg, 5 mol%) and P(t-Bu)₃ (1.0 M in toluene, 0.04 mL, 20 mol%) in toluene (0.4 mL). ^b The lithiated reaction mixture was added at 0 °C then warm up to 50 °C.

With the optimal conditions for the lithiation step in hand, the transition-metal catalyst/ligand screening was also carried out. In order to speed up the oxidative addition processes, a number of electron-rich phosphine ligands was evaluated. After treatment of lithiated anisole 4a with 5 mol% of Pd₂(dba)₃ in the presence of 20% of XPhos ligand at room temperature for three hours, the desired arylated product 3b was isolated in 12% yield (Table 2, entry 1). Biaryl phosphine ligands such as SPhos, DavePhos, and Xant-Phos were also examined; unfortunately, the desired product 7a was only isolated in rather low yields (Table 2, entries 2–4). The increase of the reaction temperature to 50 °C led to the desired product 7a in 49% yield (Table 2, entry 9). The addition of organolithium prepared at 0 °C then slowly warm up to 50 °C. The use of PhI instead of PhBr gave the desired product in 57% yield (Table 2, entry 10). Compared to the lithium-palladium coupling reactions developed by Feringa, where they were calculated reaction yields based on the use of aryl halides with excess use of commercially available organolithium reagents, our yields were calculated based on the amount of anisoles used.

Under our optimized conditions, reactions with a number of aryl halides were evaluated. The corresponding arylated products with aryl halides were all successfully obtained in useful to good yields (Scheme 3). Reactions of arenes bearing both electron-rich and electron-deficient substituents at the *para* position went smoothly and the desired products **7a–g** were obtained. More interestingly, coupling reactions for the introduction of bicyclic and tricyclic ring systems have also shown to be fruitful, the corresponding arylated products **7j–1** were successfully obtained. In addition, coupling with a heteroaromatic system is also possible; the desired product **7m** was isolated in 30% yield.

The utilization of alkyl bromides and chloride were also studied. It seemed that the reactions with alkyl bromides gave similar results as the ones using alkyl iodides, however, reaction with alkyl chloride was less efficient due to the low conversion.

Reactions with a number of representative directed arenes were also evaluated. The results are shown in Scheme 4. The use of substituted anisoles provided the corresponding phenyl-substituted anisoles in moderate to useful yields. The low yielding with halo-substituted anisoles is due to the strong base mediated reduction reaction. The dehalogenated product **7a** was formed together with our desired products **7n** and **7o**, respectively. The side reaction was even more favored when *meta*-Cl-substituted anisole was utilized. No desired product formed with only 10% of anisole, **7a** was isolated. The N- and S-containing directing groups have also been demonstrated to be efficient lithiation directing groups for the palladium-catalyzed direct arylation processes. Tamoxifen derivatives **8a** and **8b** have also been obtained albeit with low yields.



Scheme 3 Synthesis of monoarylated anisoles. *Reagents and conditions*: anisole **4a** (0.2 mmol), *n*-BuLi (2.4 M, 0.125 mL, 1.5 equiv), TMEDA (34.8 mg, 1.5 equiv) in Et₂O (0.4 M, 0.5 mL), r.t. 0.5 h, then aryl halides (ArX, X = Br or I, 2 equiv), $Pd_2(dba)_3$ (9.2 mg, 5 mol%) and $P(t-Bu)_3$ (1.0 M in toluene, 0.04 mL, 20 mol%) in toluene (0.4 mL), 0–50 °C. ^a Transmetalation with ZnCl₂ (2.0 equiv) proceeded.

The proposed reaction mechanism is shown in Scheme 5. The reaction starts from the addition of a palladium(0) species in the presence of an electron-rich ligand onto ArX to give palladium(II) intermediate **9**. After the ligand deassociation, palladium species **10** forms. Transmetalation occurs when lithiated anisole **5** reacts with palladium species **10** to provide the four-membered palladacycle **11**. The transmetalation processes between organolithium and aryl palladium species have been studied previously in the Murahashi group.¹⁵ The desired product **7a** is obtained after reductive elimination of palladium complex **11** to regenerate the palladium(0) catalyst which is ready for the next catalytic cycle.

In conclusion, we have studied the directed lithiation procedure as well as the direct transmetalation processes for the access of arylated anisoles in useful to good yields.¹⁶ This has made the direct arylation of anisoles possible as a good alternative for access a range of anisoles, thioanisoles, and anilines.

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Scheme 4 Direct arylation of various arenes. Reagents and conditions: arene 4 (0.2 mmol), n-BuLi (2.4 M, 0.125 mL, 1.5 equiv), TMEDA (34.8 mg, 1.5 equiv) in Et₂O (0.4 M, 0.5 mL), r.t. 0.5 h, then PhI (2 equiv), Pd₂(dba)₃ (9.2 mg, 5 mol%) and P(t-Bu)₃ (1.0 M in toluene, 0.04 mL, 20 mol%) in toluene (0.4 mL).



Scheme 5 The plausible reaction mechanism

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Supporting Information

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(16) General Procedure for Direct ortho Arylation of Anisoles

A 5 mL well-dried round-bottomed flask was charged with nitrogen through Schlenk line. To a solution of the corresponding substrate (0.2 mmol) and TMEDA (34.8 mg, 1.5 equiv) in Et₂O (0.4 M, 0.5 mL), n-BuLi (2.4 M, 0.125 mL, 1.5 equiv) was added dropwise at r.t. Then the reaction was allowed to stir for 0.5 h at r.t.

In another 10 mL well-dried flask, the arvl halides (ArX, X = Br or I, 2 equiv), $Pd_2(dba)_3$ (9.2 mg, 5 mol%) and $P(t-Bu)_3$ (1.0 M in Tol, 0.04 mL, 20 mol%) were dissolved in toluene (0.4 mL), and the solution was stirred for 5 min. Then the above organolithium solution was added dropwise at 0 °C, and the reaction was then allowed to stir at 50 °C for another 3 h. The mixture was quenched with sat. aq NH₄Cl, extracted with EtOAc (3×5 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under vacuo. The residue was purified by column chromatography to get the product.

(Z)-2-{[5-(1,2-Diphenylbut-1-en-1-yl)-3'-methoxy-(1,1'biphenyl)-2-yl]oxy}-N,N-dimethylethanamine (8a)

Following the general procedure, the amine 8a was obtained after column chromatography as a colorless oil (X = I, 26 mg, 27 % yield). ¹H NMR (600 MHz, CDCl₃): δ = 7.35 (t, J = 6.5 Hz, 2 H), 7.29-7.20 (m, 5 H), 7.19-7.13 (m, 4 H), 6.86 (s, 1 H), 6.77 (d, J = 8.0 Hz, 2 H), 6.69 (m, 2 H), 6.64 (d, J = 8.0 Hz, 1 H), 3.94 (t, J = 5.0 Hz, 2 H), 3.76 (s, 3 H), 2.59 (t, J = 5.0 Hz, 2 H), 2.46 (q, J = 6.5 Hz, 2 H), 2.21 (s, 6 H), 0.93 (t, J = 7.0 Hz, 3 H). ¹³C NMR (151 MHz, $CDCl_3$): $\delta = 158.9, 153.7, 143.6, 142.6, 141.6, 139.8, 138.1, 135.7, 143.6, 142.6, 141.6, 139.8, 138.1, 135.7, 143.6, 142.6, 141.6, 139.8, 138.1, 135.7, 143.6, 142.6, 141.6, 139.8, 138.1, 135.7, 143.6, 142.6, 141.6, 139.8, 138.1, 135.7, 143.6, 142.6, 141.6, 139.8, 138.1, 135.7, 143.6, 142.6, 141.6, 139.8, 138.1, 135.7, 143.6, 142.6, 141.6, 139.8, 138.1, 135.7, 143.6, 142.6, 141.6, 139.8, 138.1, 135.7, 143.6, 145.6,$ 133.7, 130.8, 129.8, 129.5, 129.3, 128.4, 128.1, 128.0, 126.6, 126.1, 122.2, 114.7, 112.7, 111.6, 66.7, 58.0, 55.3, 45.9, 29.1, 13.6. ESI-HRMS: *m*/*z* [M + H]⁺ calcd for (C₃₃H₃₆NO₂): 478.2746; found: 478.2745.