Report

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Ryo Nishio, Stephane Wessely, Masaharu Sugiura, and Sh Kobayashi

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Synthesis of Acridone Derivatives Using Polymer-Supported Palladium and Scandium Catalysts

Ryo Nishio, Stephane Wessely, Masaharu Sugiura, and Shū Kobayashi*

Graduate School of Pharmaceutical Sciences, The University of Tokyo, The HFRE Division, ERATO, Japan Science and Technology Agency (JST), Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

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Library synthesis related to combinatorial chemistry plays a key role both in the search for lead structures of pharmacologically active compounds and in their optimization.[1] In this context, polymer-supported catalysts have become valuable tools offering advantages such as simplification of product workup, reuse of the catalyst, and facilitation of large-scale syntheses.[2,3] Herein, we describe a new method for the preparation of acridone derivatives using polymer-supported catalysts.

Acridone analogues are promising antiviral agents[4] as well as fluorescent labels[5] in biodiagnostics. In the field of antitumor binding agents, acridones are important precursors for the creation of acridine derivatives with potential anticancer activity.[6] Acridones are usually prepared by Ullmann condensation of anilines with 2-bromobenzoic acids to give *N*-phenyl anthranilic acids, which undergo ring closure with sulfuric acid.[7] However, this method requires harsh conditions and suffers from tedious workup and purification.

We planned to synthesize acridone derivatives using polymer-supported catalysts. Our synthetic strategy is shown in Scheme 1. The initial step involves the formation of *N*-phenyl anthranilic acid ester **5** according to the Pd-catalyzed amination.[8,9] Recently, we reported immobilization of palladium clusters onto polystyrene-based copolymers using the polymer incarcerated (PI) method.[10,11] These heterogeneous PI Pd catalysts are highly active for hydrogenation or carbon−carbon bond-forming reactions, such as Suzuki−Miyaura coupling and Heck reaction. Furthermore, these catalysts can be recovered quantitatively by simple filtration and reused several times without loss of activity. Therefore, we tried to apply those PI Pd catalysts to the amination step for the synthesis of acridone derivatives.

First, the effect of solvents and bases was examined in the model reaction of aryl bromide **1a** with aniline (**2a**) in the presence of PI Pd **3** and ligand **4a**[9] (Table 1). PI Pd **3** was prepared from $Pd(PPh_3)_4$ and polystyrene-based copolymer **9** according to a standard method[10] (Scheme 2). Leaching of the palladium was measured by fluorescence X-ray (XRF) analysis after removal of the catalyst. It was found that serious palladium leaching occurred when toluene was used as a solvent (entry 1); however, the addition of water and ethanol remarkably suppressed the leaching of palladium and showed higher catalytic activity (entries 2−5). Furthermore, the use of K_2CO_3 rather than K_3PO_4 as a base was more effective to suppress the leaching (entry 5).

To confirm the catalytic activity of PI Pd **3** in the amination of aryl halides, we briefly surveyed substrate generality of aryl halides and amines (Table 2). Both aryl iodides and bromides gave the desired products in good yields without leaching of palladium. Furthermore, aryl chloride also gave the aminated product in moderate yield without leaching of palladium (entry 8). In the case of secondary amines, such as morpholine, however, aminated products were obtained in lower yields, and leaching of Pd

Scheme 1. Procedure for the Synthesis of Acridone Derivatives

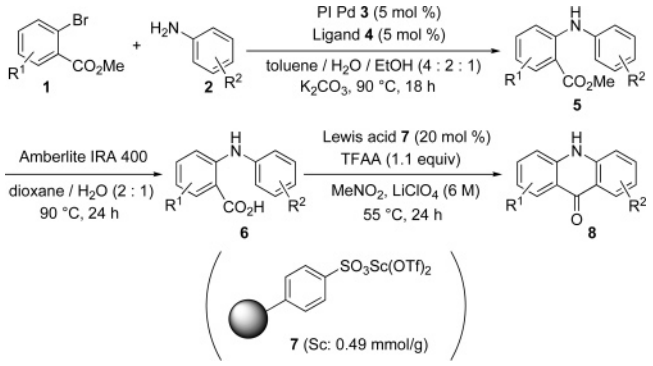
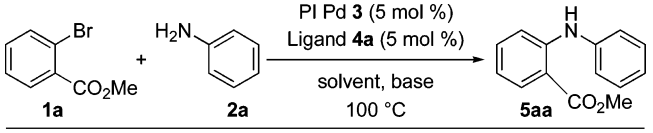


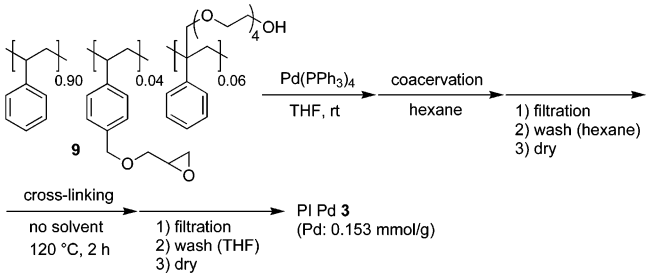
Table 1. Effect of Reaction Conditions in PI Pd-Catalyzed Amination



entry	solvent	base	time (h)	yield (%)[a]	leaching of Pd (%)[b,c]
1	toluene	K_3PO_4	18	46	46
2	toluene/H_2O (4:1)	K_3PO_4	18	78	7
3	toluene/H_2O (4:1)	K_2CO_3	12	34	nd
4	toluene/H_2O/EtOH (4:2:1)	K_3PO_4	12	78	2
5	toluene/H_2O/EtOH (4:2:1)	K_2CO_3	24	79	nd

[a] Isolated yield. [b] Determined by XRF analysis. [c] nd = not detected.

Scheme 2. Preparation of the Polymer-Incarcerated (PI) Pd Catalyst



* To whom correspondence should be addressed. E-mail: skobayas@mol.f.u-tokyo.ac.jp.

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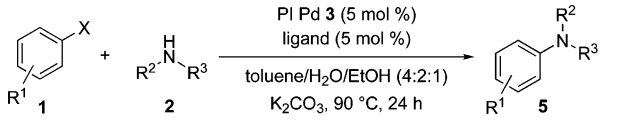
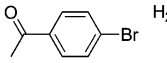
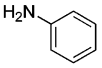
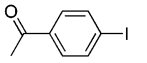
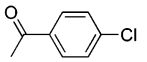
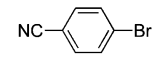
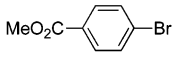
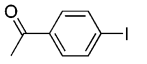
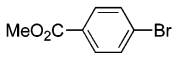
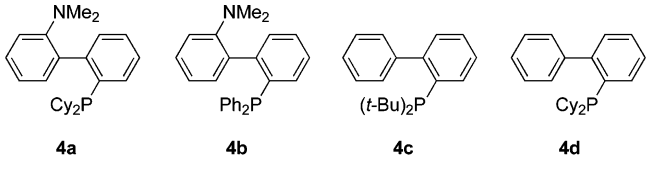
Table 2. PI Pd-catalyzed Amination[a]



entry	aryl halide	amine	ligand	yield (%)[b]	leaching of Pd (%)[f]
1			**4a**	72	nd
2			**4b**	70	nd
3			**4c**	68	nd
4[d]			**4d**	47	nd
5[d]			**4e**	trace	11
6			**5f**	trace	nd
7			**4c**	93	nd
8			**4c**	64	nd
9			**4c**	80	nd
10			**4c**	88	nd
11			**4c**	43	21
12[e]			**4c**	24	11

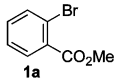
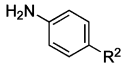
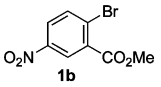
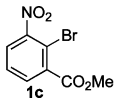
[a] Reaction conditions: 1.0 equiv of aryl halide, 1.3 equiv of amine, 1.5 equiv of K_2CO_3, 5 mol % of PI Pd **3** (Pd: 0.668 mmol/g), toluene/H_2O/EtOH (4:2:1), 90 °C. Workup conditions: reaction mixture was diluted with hexane, and the catalyst was filtered off. [b] Isolated yield. [c] Determined by XRF analysis. [d] Reaction time: 17 h. [e] Reaction time: 25 h. [f] nd = not detected.

was observed under the same reaction conditions (entries 11−12).



For the synthesis of acridone derivatives, we further examined substrates and reaction conditions. In the reaction of methyl-2-bromobenzoic acid ester **1a** with aniline (**2a**), it was found that the amination proceeded in the presence of PI Pd **3** (5 mol %) and ligand **4a** (5 mol %) in a toluene−water−ethanol (4:2:1) solvent system and K_2CO_3 as a stoichiometric base. Filtration of the reaction mixture from the catalyst and evaporation gave the crude product **5a**, which was then hydrolyzed by an excess amount of basic resin Amberlite IRA 400 (OH).[12,13] The resin was treated with acetic acid, and product **6aa** precipitated in high purity after addition of hot water.[14] Other substrates were investigated,

Table 3. The Synthesis of Acridone Derivatives

entry	aryl halide	amine	yield (%) of **6** (2 steps; **1**+**2**→**6**)	yield (%) of **8** (**6**→**8**)
1	 **1a**	 **2a** (R^2 = H)	**6aa** (70)	**8aa** (75)
2		**2b** (R^2 = Me)	**6ab** (65)	**8ab** (77)
3		**2c** (R^2 = Cl)	**6ac** (64)	**8ac** (74)
4		 **2e** (R^3 = Me)	**6ae** (54)	**8ae** (70)
5		**2f** (R^3 = F)	**6af** (59)	**8af** (72)
6		**2g** (R^3 = Cl)	**6ag** (57)	**8ag** (74)
7		 **2h**	**6ah** (65)	**8ah** (73)
8	 **1b**	**2a**	**6ba** (77)	**8ba** (70)
9		**2c**	**6bc** (56)	**8bc** (77)
10		**2d** (R^2 = OMe)	**6bd** (75)	**8bd** (72)
11	 **1c**	**2e**	**6be** (72)	**8be** (68)
12		**2b**	**6cb** (66)	**8cb** (72)

and the results are summarized in Table 3. The coupling reactions of several methyl 2-bromobenzoates (**1a**−**c**) with anilines (**2a**−**h**) proceeded smoothly in the presence of the PI Pd/**4a** catalyst. Hydrolysis of the corresponding adducts afforded *N*-phenyl anthranilic acids (**6**) in good overall yields (2 steps).

The final step of our synthetic route involves the ring closure of *N*-phenyl anthranilic acid (**6**) to acridone (**8**). Adaptation of previous studies concerning the catalytic Friedel−Crafts acylation[15] led to a finding that acridone (**8**) could be formed in a $MeNO_2$−$LiClO_4$ solution by the reaction of **6** with 1.1 equiv of trifluoroacetic anhydride in the presence of $Sc(OTf)_3$ as a Lewis acid catalyst. Similarly, formation of **8** was promoted by the previously described polymer-supported scandium catalyst (**7**).[16] The product could be easily obtained by filtration and precipitation in hot water. This synthetic protocol was applied to other aryl halides, and the acridones could be isolated in good yields (Table 3).

In summary, a convenient method for the preparation of acridone derivatives has been developed. The method is based on combined use of polymer-supported palladium and scandium catalysts in arylic amination and intramolecular Friedel−Crafts acylation reactions, respectively. The approach using several polymer-supported catalysts in multistep synthesis would be useful for construction of other compound libraries. Further studies along this line are now in progress.

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Supporting Information Available. Experimental procedures, spectral data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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