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Synthesis of Dibenzo[*b*,*f*][1,4]oxazepin-11(10*H*)-ones via Intramolecular Cyclocarbonylation Reactions Using PdI_2/Cytop 292 as the Catalytic System

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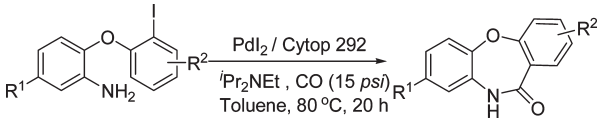

The intramolecular cyclocarbonylation of substituted 2-(2-iodophenoxy)anilines was catalyzed by PdI_2 and 1,3,5,7-tetramethyl-6-phenyl-2,4,8-trioxa-6-phospha-adamantane (Cytop 292) in an efficient manner. A series of substituted dibenzo[*b*,*f*][1,4]oxazepin-11(10*H*)-ones were prepared in good yields under mild reaction conditions.

Medium-sized heterocycles, especially seven- and eight-membered ring compounds, are receiving significant attention because of the existence of their structural units in some natural products.[1] In particular, dibenzo-fused oxazepinones, diazepinones, and azepinones are key elements for a number of biologically active molecules. For example, several dibenzo-[*b*,*e*][1,4]diazepin-11-one and dibenzo[*b*,*e*][1,4]diazepine derivatives have been shown to have anti-arrhythmic/defibrillatory activity.[2] Although these heterocycles can be prepared by conventional methods via multistep syntheses, the reactions often require rather stringent reaction conditions, and low yields of the products were obtained in some cases.[3] Therefore, it seems desirable to develop a general and effective route to synthesize medium-sized ring heterocycles.

The transition-metal-catalyzed carbonylation reaction is an effective tool for organic synthesis. It provides convenient and direct access to a large number of heterocycles.[4] Catalysts with added bulky, electron-rich phosphine ligands are useful for some of these applications.[5] During the past several years, a novel class of tertiary phosphine ligands based on a phospha-adamantane framework were successfully utilized for various palladium-catalyzed reactions[6] and for the rhodium-catalyzed hydroformylation of unsaturated esters.[7] They are readily made, stable to air, and inert to decomposition and have stereoelectronic properties similar to those of bulky phosphines. Furthermore, the ability to alter the aryl moiety of the phospha-adamantane ligand affords the opportunity to sterically and electronically fine-tune the phosphonite and hence generates transition-metal complexes with different catalytic potentials.

In 2005, a publication from our group demonstrated that palladium-complexed dendrimers supported on silica are efficient catalysts for the synthesis of medium-sized oxygen-, nitrogen-, or sulfur-containing heterocycles (Scheme 1).[8] In light of this research, we investigated the intramolecular cyclocarbonylation reactions of substituted 2-(2-iodophenoxy)-anilines to evaluate and compare the *in situ* generated palladium(II)−1,3,5,7-tetramethyl-6-phenyl-2,4,8-trioxa-6-phospha-adamantane (Cytop 292, Figure 1) catalytic system with the

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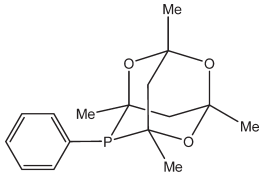


FIGURE 1. Structure of 1,3,5,7-tetramethyl-6-phenyl-2,4,8-trioxa-6-phospha-adamantane (Cytop 292).

SCHEME 1. Palladium-Complexed Dendrimers on Silica-Catalyzed Intramolecular Carbonylation Reactions

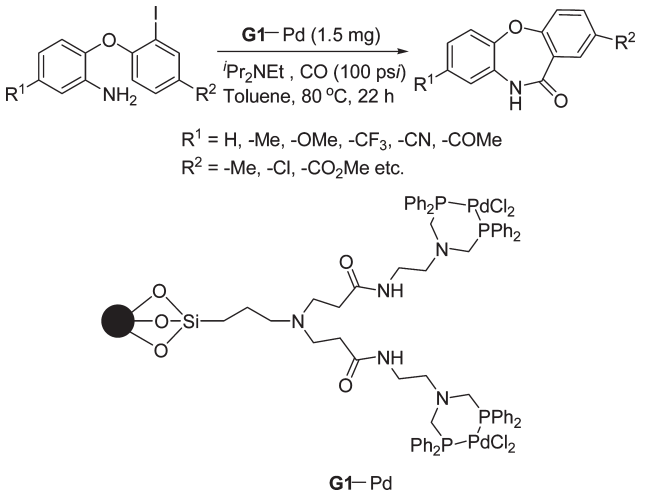
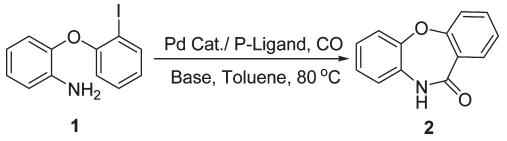


TABLE 1. Pd-Catalyzed Intramolecular Cyclocarbonylation of 2-(2-Iodophenoxy)aniline Using Different Catalytic Systems[a]

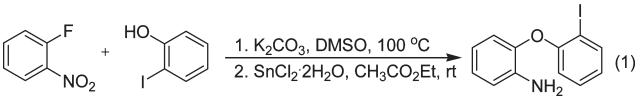


entry	catalyst	catalyst loading (mol %)	CO (psi)	base	yield (%)[b]
1	$Pd(OAc)_2$/Cytop 292	5	100	^{i}Pr$_2$NEt	86
2	$PdCl_2$/Cytop 292	5	100	^{i}Pr$_2$NEt	96
3	$Pd(PPh_3)_2Cl_2$/Cytop 292	5	100	^{i}Pr$_2$NEt	87
4[c]	$Pd_2(dba)_3$/Cytop 292	5	100	^{i}Pr$_2$NEt	87
5	PdI_2/Cytop 292	5	100	^{i}Pr$_2$NEt	99
6	$Pd(PCy_3)_2Cl_2$/Cytop 292	5	100	^{i}Pr$_2$NEt	tr
7[d]	PdI_2/PPh_3	5	100	^{i}Pr$_2$NEt	75
8	PdI_2/dppb	5	100	^{i}Pr$_2$NEt	tr
9	PdI_2/Cytop 292	5	100	DBU	78
10[e]	PdI_2/Cytop 292	5	100	^{i}Pr$_2$NEt	84
11	PdI_2/Cytop 292	5	15	^{i}Pr$_2$NEt	99
12[c]	PdI_2/Cytop 292	1	15	^{i}Pr$_2$NEt	82
13	**PdI_2/Cytop 292**	**2**	**15**	**^{i}Pr$_2$NEt**	**99**

[a]Reaction conditions: 2-(2-iodophenoxy)aniline (1 mmol), ^{i}Pr$_2$NEt or DBU (1.5 mmol), toluene or THF (5 mL), 80 °C, 20 h. [b]Isolated yield. [c]Substrate was not completely consumed. [d]20% substrate was recovered. [e]THF was used as solvent.

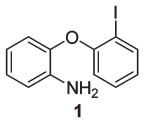
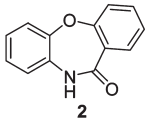
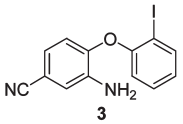
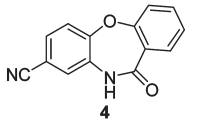
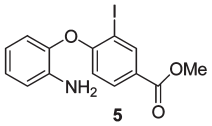
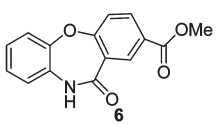
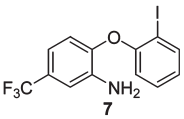
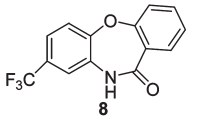
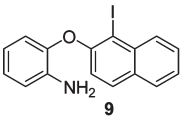
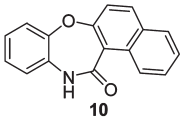
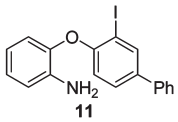
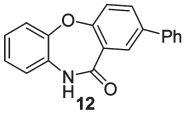
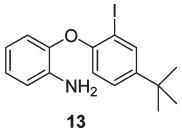
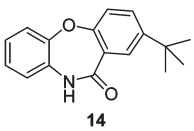
dendrimer-palladium catalytic system for the intramolecular cyclocarbonylation reaction.

2-(2-Iodophenoxy)aniline was prepared from 1-fluoro-2-nitrobenzene according to the literature (eq 1)[8] and used as a model substrate to perform the intramolecular cyclocarbonylation reaction under different reaction conditions. The results are shown in Table 1.



The results in Table 1 show that the intramolecular cyclocarbonylation reaction of 2-(2-iodophenoxy)aniline can be performed with different catalytic systems. With $Pd(OAc)_2$ or $PdCl_2$ as the catalyst and Cytop 292 as the ligand, the desired product was obtained in 86% and 96% isolated yields, respectively (Table 1, entries 1 and 2). When the reaction was catalyzed by $Pd(PPh_3)_2Cl_2$/Cytop 292 or $Pd_2(dba)_3$/Cytop 292, the product was isolated in 87% yield in both cases, but in the case of $Pd_2(dba)_3$/Cytop 292, 2-(2-iodophenoxy)aniline was not fully consumed (Table 1, entries 3 and 4). We were pleased to observe that the yield of the product was increased to 99% when PdI_2 /Cytop 292 was used as the catalytic system and ^{i}Pr$_2$NEt as the base under 100 psi CO pressure and 80 °C in toluene (Table 1, entry 5). In contrast, when $Pd(PCy_3)_2Cl_2$/Cytop 292 was used as the catalyst, only trace quantities of the product was formed

TABLE 2. Pd-Catalyzed Intramolecular Cyclocarbonylation of Substituted 2-(2-Iodophenoxy)anilines Using PdI_2/Cytop 292 as Catalytic System[a]

Entry	Substrate	Product	Yield(%)[b]
1			99
2			95
3			95
4			96
5			91
6			97
7			90

[a]Reaction conditions: substrate (1 mmol), PdI_2 (2 mol %), Cytop 292 (4.5 mol %), ^{i}Pr$_2$NEt (1.5 mmol), toluene (5 mL), CO (15 psi), 80 °C, 20 h. [b]Isolated yield.

(Table 1, entry 6). Thus PdI_2 was chosen as the metal catalyst for further investigations. When PdI_2 was used as the catalyst and PPh_3 was used as the ligand instead of Cytop 292, the yield decreased from 99% to 75% (Table 1, entry 7). Using dppb as the ligand afforded only trace amounts of the product (Table 1, entry 8). Running the reaction using DBU as the base instead of $^{i}Pr_2NEt$ afforded the product in 78% isolated yield (Table 1, entry 9). When the reaction was carried out in THF with other reaction conditions unchanged, the isolated yield decreased from 99% to 84% (Table 1, entry 10). If the CO pressure was reduced from 100 psi to 15 psi keeping other reaction conditions unchanged, there was no impact on the isolated yield of the product (Table 1, entry 11). Reducing the catalyst loading from 5 to 1 mol % resulted in much lower yield, and some of the substrate still remained after the reaction (Table 1, entry 12). The efficiency of the reaction was improved when the catalyst loading was increased to 2 mol % and the product was obtained in 99% isolated yield.

The intramolecular carbonylation of several other substituted 2-(2-iodophenoxy)anilines was effected to form substituted dibenzo[*b*,*f*][1,4]oxazepin-11(10*H*)-ones under the optimized conditions, and the results are presented in Table 2.

The results in Table 2 show that by the use of PdI_2 as the catalyst and bulky Cytop 292 as the ligand, $^{i}Pr_2NEt$ as the base, and toluene as the solvent, the intramolecular cyclocarbonylation of substituted 2-(2-iodophenoxy)anilines proceeded very smoothly irrespective of the electronic nature of the substituents on the aromatic rings, affording the desired products in good yields comparable to our previous results.[8] Thus, the iodinated arylamines containing either electron-withdrawing or electron-donating substituents could efficiently be converted to the corresponding dibenzoxazepinones in 90−99% yields. Three new substrates were prepared and subjected to the optimized reaction conditions, giving products in 90−97% isolated yields (Table 2, entries 5, 6, and 7). This method can be considered as a valuable alternative to that previously reported,[8] as it uses a simple catalytic system, and mild reaction conditions.

The bulky Cytop 292 ligand shows distinct advantages over some other commonly applied phosphanes for the intramolecular cyclocarbonylation of substituted 2-(2-iodophenoxy)anilines in terms of the reaction efficiency. With simple PdI_2/Cytop 292 as the catalytic system, a series of substituted dibenzo[*b*,*f*][1,4]oxazepin-11(10*H*)-ones were prepared in good yields.

Experimental Section

General Procedure for the Intramolecular Cyclocarbonylation Reaction of Substituted 2-(2-Iodophenoxy)anilines. A mixture of substituted 2-(2-iodophenoxy)aniline (1.0 mmol), PdI_2 (0.02 mmol), Cytop 292 (0.045 mmol), $^{i}Pr_2NEt$ (1.5 mmol), and toluene (5 mL) was placed in a 45 mL autoclave with a magnetic stirring bar. The autoclave was flushed three times with CO and pressurized with CO to 15 psi at room temperature. The autoclave was then immersed in an oil bath preheated at 80 °C for 20 h. Excess CO was discharged at room temperature. The reaction mixture was purified by flash chromatography on silica gel with hexane/EtOAc (v/v, 10:1 to 8:1) as the eluant to give the corresponding dibenzo[*b*,*f*][1,4]oxazepin-11(10*H*)-ones in 90−99% yields.

2-*tert*-Butyl-dibenzo[*b*,*f*][1,4]oxazepin-11(10*H*)-one (14). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.26 (s, 1H), 7.98 (d, 1H, J = 2.4 Hz), 7.54 (dd, 1H, J = 8.4 and 2.4 Hz), 7.29 −7.25 (m, 2H), 7.20 (d, 1H, J = 8.4 Hz), 7.17−7.07 (m, 2H), 1.31 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.7, 157.5, 151.1, 148.0, 131.6, 130.9, 128.3, 125.7, 125.5, 124.4, 121.6, 121.3, 120.2, 34.4, 31.2.; HRMS (EI) m/z: calcd for $C_{17}H_{17}NO_2$ (M^+) 267.1259, found 267.1262.

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