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Copper-Free Oxime-Palladacycle-Catalyzed Sonogashira Alkynylation of Deactivated Aryl Bromides and Chlorides in Water under Microwave Irradiation

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Palladium-catalyzed Heck alkynylation cross-coupling reactions between terminal alkynes and deactivated aryl chlorides and aryl bromides can be performed in the absence of copper cocatalyst with water as solvent at 130 °C under microwave irradiation. An oxime-derived chloro-bridged palladacycle is an efficient precatalyst for this transformation

Introduction

Palladium-catalyzed reactions for carbon-carbon and carbon-heteroatom bond formations have gained a predominant place in the arsenal of synthetic chemists.^[1] In organic synthesis, among the leading "named" Pd-catalyzed reactions, the Sonogashira-Hagihara coupling^[2] is one of the most important and widely used methods for the preparation of aryl- and alkylacetylenes as well as conjugated enynes, which are precursors for natural products, pharmaceuticals, and optical and electronic materials.^[2,3] Given the relevance of the Sonogashira reaction, the design of sustainable protocols for green aqueous couplings^[4] is nowadays considered of high practical value, especially when deactivated electrophiles such as aryl chlorides^[5] and hydroxyarene derivatives^[6] are involved in the process. The use of water as a solvent in Pd-catalyzed reactions has gained increasing attention during recent years^[7] owing to the environmental and economic benefits of replacing organic solvents by water as well as its interesting chemical properties, including high polarity and strong hydrogen-bonding ability, among others. However, with water as solvent, mostly aryl iodides^[8] and bromides^[9] have been used as coupling partners and only a few reports can be found on the successful coupling of activated aryl chlorides.^[5,10] In recent years, we have demonstrated the high activity of oxime pal-

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with 2-dicyclohexylphosphanyl-2',4',6'-triisopropylbiphenyl (XPhos) as ancillary ligand, pyrrolidine as base, and SBDS as surfactant. All of the reactions can be performed under air and with reagent-grade chemicals under low loading conditions (0.1–1 mol-% Pd).

ladacycles^[11] (1, Figure 1) in a wide variety of cross-coupling reactions with organic and aqueous solvents.^[12] Particularly interesting results are those couplings performed with neat water as solvent and deactivated electrophiles, such as aryl chlorides (Suzuki reaction)^[13] and aryl imidazolylsulfonates (Suzuki^[14] and Sonogashira reactions),^[6] in the presence of surfactants.^[7h,71] In continuation of our exploration on the application of oxime palladacycles under green conditions, we herein describe the Sonogashira coupling reaction of deactivated aryl bromides and chlorides in water under microwave (MW) irradiation.



Figure 1. Oxime palladacycle catalysts.

Results and Discussion

Deactivated aryl chlorides are good indicators of optimal catalyst performance. Thus, we initially investigated the microwave-promoted Sonogashira coupling of phenylacetylene (2a, 1.2 equiv.) with 4-chlorotoluene (3a, 1 equiv.) in water in the presence of hexadecyltrimethylammonium bromide (CTAB, 0.4 equiv.) as additive and triethylamine (TEA, 2 equiv.) as base (Table 1). With an initial microwave irradiation of 40 W, the reaction temperature was main-tained at 130 °C for 30 min. As catalyst, oxime palladacycle **1b** (1 mol-% Pd) in the presence of 2-dicyclohexylphosphanyl-2',6'-dimethoxybiphenyl (SPhos, 2 mol-%) was se-



lected owing to the high activity of this catalytic system for the alkynylation of aryl imidazolylsulfonates in water.^[6,15] Unfortunately, under these conditions (Table 1, Entry 1), the reaction afforded 1-methyl-4-(phenylethynyl)benzene (4a) in only 14% isolated yield together with the envne (E)but-1-en-3-yne-1,4-diyldibenzene (5a) in 7% yield. The formation of 5a has been previously detected in Heck alkynylations of deactivated aryl chlorides and it is postulated to occur by a Pd-catalyzed head-to-head dimerization of

Table 1. Sonogashira alkynylation of 4-chlorotoluene with phenylacetylene. Optimization of reaction conditions.



6	1a	XPhos	CTAB(1)	pyrrolidine	90 (60)
7	1a	XPhos	PTS (1)	pyrrolidine	95 (40)
8	1a	XPhos	Brij 35 (1)	pyrrolidine	> 95 (73)
9	1a	XPhos	Brij C10 (1)	pyrrolidine	> 95 (73)
10	1a	XPhos	SDBS (1)	pyrrolidine	> 95 (76)
11	1a	XPhos	TBAB (1)	pyrrolidine	65
12	1a	XPhos	SDBS (1)	TEA	54
13	1a	XPhos	SDBS (1)	<i>i</i> pr ₂ EtN	50
14	1a	XPhos	SDBS (1)	Cy ₂ NH	87 (54)
15	1a	XPhos	SDBS (1)	piperidine	89 (63)
16	1a	XPhos	SDBS (1)	K_2CO_3	90 (63)
17	1b	XPhos	SDBS (1)	pyrrolidine	> 95 (24)
18	[e]	XPhos	SDBS (1)	pyrrolidine	80 (40)
19	[f]	XPhos	SDBS (1)	pyrrolidine	90 (68)
20	1a	XPhos	SDBS (1)	pyrrolidine	(24) ^[g]
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[a] XPhos: 2-dicyclohexylphosphanyl-2',4',6'-triisopropylbiphenyl; SPhos: 2-dicyclohexylphosphanyl-2',6'-dimethoxybiphenyl. [b] CTAB: hexadecyltrimethylammonium bromide; PTS: polyoxyethanyl-a-tocopheryl sebacate; Brij 35: polyoxyethylene lauryl ether, Brij C10: polyethylene glycol hexadecyl ether; SDBS: sodium dodecyl benzene sulfonate; TBAB: tetrabutylammonium bromide. [c] Conversion determined by GC analysis. In parenthesis, isolated yield after preparative thin layer chromatography. [d] A 7% yield of (E)-but-1-en-3-yne-1,4-divldibenzene (5a) was also obtained. [e] Pd₂(dba)₃ (1 mol-% Pd) was used as catalyst. [f] Pd(OAc)₂ (1 mol-% Pd) was used as catalyst. [g] Isolated yield when the reaction was performed under conventional thermal conditions (130 °C, 24 h).

phenylacetylene.^[16] Indeed, the formation of linear enynes from terminal alkynes, that is, head-to-head coupled products, has been previously achieved by employing a range of metal catalysts.^[17] An optimization of the reaction conditions was then performed to improve the yield and especially the selectivity of the process (Table 1). When the reaction was performed under the same reaction conditions, but with oxime catalyst 1a (1 mol-% Pd), negligible amounts of 5a were observed in the crude reaction mixture, but a low reaction conversion to 4a (21%) was still detected (Table 1, Entry 2). A conversion of 77% was obtained when pyrrolidine was used as base regardless of the amount of surfactant used (Table 1, Entries 3 and 4).

Then, a ligand study was performed with the most chemoselective catalyst and base, namely, 1a and pyrrolidine, (see Supporting Information), which showed that 2dicyclohexylphosphanyl-2',4',6'-triisopropylbiphenyl

(XPhos) was the most effective ligand; compound 4a was obtained in a 60% isolated yield when 1 equiv. of CTAB was used (Table 1, Entry 6). Lisphutz has shown that XPhos is the most effective ligand for the palladium-catalyzed Sonogashira coupling of aryl bromides in water at room temperature with polyoxyethanyl-α-tocopheryl sebacate (PTS) as surfactant.^[9c] The effect of the surfactant on the activity of the catalytic system was then studied (Table 1, Entries 7-11). Nonionic surfactants, such as the polyethers polyoxyethylene lauryl ether (Brij35) and polyethylene glycol hexadecyl ether (BrijC10) as well as the anionic sodium dodecyl benzene sulfonate (SDBS), afforded good yields of 4a; the latter afforded the highest yield (76%, Table 1, Entry 10).

Significant sensitivity to base was also noted (Table 1, Entries 12-16). Thus, good isolated yields were obtained with other organic (dicyclohexylamine and piperidine) and inorganic bases (K_2CO_3), though these experiments did not improve the ability of pyrrolidine in this process.^[18]

Regarding the catalyst, a 24% yield of 4a was obtained under the optimized reaction conditions when oxime-derived palladacycle 1b (1 mol-% Pd) was employed as catalyst (Table 1, Entry 17). Other Pd sources such as Pd₂- $(dba)_3$ (dba = dibenzylideneacetone) and Pd(OAc)₂ were also less effective than 1a and afforded lower yields of 4a (Table 1, Entries 18 and 19).

Finally, the efficiency of the microwave irradiation was demonstrated as only a 24% reaction yield was obtained when the reaction was performed under conventional thermal conditions (130 °C, 24 h; Table 1, Entry 20).

To test the effectiveness of the optimized catalytic system in the Pd-catalyzed Sonogashira coupling in water, a range of aryl- and alkyl-substituted terminal alkynes were examined in the reaction with different aryl chlorides (Table 2). As previously described for 4-chlorotoluene, deactivated 4chloroanisole was coupled with phenylacetylene to afford 4-methoxytolane in 80% yield (Table 2, Entry 2). The coupling of these two deactivated aryl chlorides with electronrich terminal alkynes, such as (4-methoxyphenyl)acetylene, (4-methyphenyl)acetylene, and (2-aminophenyl)acetylene, led to the corresponding 1,2-diarylalkynes 4c and 4d in

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moderate-to-good yields (47–63%; Table 1, Entries 3–5). A 40% yield of the donor–acceptor tolane derivative **4e** with potential optoelectronic properties^[19] was obtained when 4-chlorotoluene was coupled with the electron-poor 4-(tri-fluoromethyl)phenylacetylene, a result that is in accordance with the low reactivity of alkynes bearing electron-with-drawing groups (Table 2, Entry 6) in Sonogashira reactions. The scope of this coupling was extended to other alkynes such as *N*,*N*-dimethyl-2-propynylamine, cyclohexylacetylene, and 1-dodecyne, which after coupling with 4-chloroanisole and 4-chlorotoluene afforded disubstituted alkynes **4f**, **4g**, and **4h** in 50, 20, and 20% yield, respectively (Table 2, Entries 7–9). Hindered 2-chloro-1,3-dimethylbenzene

underwent coupling with phenylacetylene to produce the desired alkyne **4i** in a 63% isolated yield (Table 2, Entry 10). The coupling of heterocyclic 2-chloropyridine and 2-chlorothiophene with phenylacetylene afforded the Sonogashira derivatives **4j** and **4k** in 87 and 53% yield, respectively (Table 2, Entries 11 and 12). Finally, the reactions of activated 4-acetylchlorobenzene and 4-(trifluoromethyl)benzene with phenylacetylene afforded **4l** and **4m** in a 84 and 80% isolated yield, respectively (Table 2, Entries 13 and 14).

Under the optimized reaction conditions for the Sonogashira coupling of aryl chlorides, we also evaluated the alkynylation of aryl bromides in water (Table 3). After a catalyst, temperature, and catalyst loading study (see Support-

Table 2. Sonogashira alkynylation of aryl chlorides.



[a] Isolated yield after preparative thin layer chromatography.



ing Information), we demonstrated that oxime palladacycle **1a** was the most active palladium source for these more active electrophiles and that the palladium loading could be reduced to 0.1 mol-%. As expected, 4-bromotoluene and 4bromoanisole afforded the desired products in high isolated yields after reaction with phenylacetylene and electron-rich alkynes such as (4-methoxyphenyl)acetylene and 4-tolylacetylene respectively (Table 3, Entries 1–2 and 4–5). Lower yields were observed for electron-poor nucleophiles, as found in the reaction between 4-chloroanisole and (4-trifluoromethylphenyl)acetylene, which led to the tolane derivative **4e** in 51% isolated yield (Table 3, Entry 6). A terminal alkyne with an alkene functionality, such as 1-ethynylcyclohexene, underwent Sonogashira coupling with 4-bromoanisole to afford the conjugated enyne 4n in 49% yield (Table 3, Entry 7). In a similar fashion, we next examined aliphatic alkynes as coupling partners with 4-bromotoluene and 4-bromoanisole. Again, we observed that, in general, aliphatic alkynes showed lower reactivities than arylalkynes. The coupling reaction of 4-bromotoluene and 4-bromoanisole with cyclohexylacetylene afforded disubstituted alkynes 4g and 4o in 40 and 37% yield, respectively (Table 3, Entries 3 and 9). A 61% yield of the semicarbazide-sensitive amine oxidase (SSAO) inhibitor^[20] 4f was obtained when 4-

Table 3. Sonogashira alkynylation of aryl bromides.



[a] Isolated yield after preparative thin-layer chromatography.

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Scheme 1. Sonogashira coupling with 1-phenyl-2-(trimethylsilyl)acetylene.

bromoanisole reacted with N,N-dimethyl-2-propynylamine under the optimized conditions (Table 3, Entry 8). A low 30% yield of alkyne **4h** was obtained by reaction of 4bromoanisole with 1-dodecyne (Table 3, Entry 10). The alkynylation of the sterically hindered 2-bromo-1,3-dimethylbenzene with phenylacetylene and 4-tolylacetylene afforded **4i** and **4p** in 69 and 61% yield, respectively (Table 3, Entries 11 and 12). Good isolated yields were also obtained for the coupling of 2-bromopyridine and 2-bromothiophene with phenylacetylene, which led to the Sonogashira coupling products **4j** and **4k** in 91 and 63% yield, respectively (Table 3, Entries 13 and 14). Finally, the reaction between activated 4-acetylbromobenzene and phenylacetylene afforded **4l** in 87% isolated yield (Table 3, Entry 15).

We then decided to investigate the catalytic activity of **1a** in the cross-coupling reaction between deactivated aryl bromides and chlorides and other alkynes. Firstly, we studied the coupling with silylated alkynes. As depicted in Scheme 1, the reactions of 4-chloro- and 4-bromoanisole with 1-phenyl-2-(trimethylsilyl)acetylene afforded 4-methoxytolane (**4b**) in 51 and 70% yield, respectively, under the optimized reaction conditions through a desilylation/cross-coupling sequence.^[21]



Scheme 2. Sonogashira coupling with 2-methylbut-3-yn-2-ol.

On the other hand, the reaction of 4-chloro- and 4bromoanisole with 2-methylbut-3-yn-2-ol afforded a mixture of 4q and 6, as a consequence of the mono- or double alkynylation reaction with the acetylenic nucleophile (Scheme 2).

Finally, we also studied the reactivity of deactivated aryl iodides in the Sonogashira reaction in water under the optimized reaction conditions. With the catalyst loading employed for aryl bromides, good isolated yields were obtained for the coupling of 4-iodotoluene and 4-iodoanisole with phenylacetylene, as depicted in Scheme 3.



Scheme 3. Sonogashira coupling of deactivated aryl iodides in water.

Conclusions

We have disclosed a copper-free oxime palladacycle-catalyzed Sonogashira cross-coupling reaction of deactivated aryl chlorides and aryl bromides with aryl- and alkyl-substituted terminal alkynes with water as solvent under microwave irradiation. This reaction is performed in the presence of XPhos as ligand (0.2–2 mol-%), SDBS as surfactant, and the bench-stable oxime palladacycle **1a** as precatalyst under low loading conditions (0.1–1 mol-% Pd).

Experimental Section

Typical Procedure for the Sonogashira Coupling Under MW Irradiation Conditions: A 10 mL MW vessel was charged with 4-chlorotoluene (0.038 g, 0.3 mmol, 1 equiv.), phenylacetylene (0.040 mL, 0.36 mmol, 1.2 equiv.), pyrrolidine (0.050 mL, 0.6 mmol, 2 equiv.), sodium dodecylbenzenesulfonate (0.1045 g, 0.3 mmol, 100 mol-%), catalyst **1a** (0.0012 g, 1 mol-% Pd), XPhos (0.0029 g, 2 mol-%), and H_2O (1.5 mL). The vessel was sealed with a pressure lock, and the mixture was heated at 130 °C for 30 min with the aid of an initial 40 W MW irradiation in a CEM Discover MW reactor. After this time, the reaction mixture was extracted with EtOAc (3 × 10 mL), and the organic layers were washed with H_2O (3 × 10 mL), dried with MgSO₄, filtered through Celite, and concentrated under reduced pressure. The crude residue was purified by preparative thin layer chromatography (hexane) to obtain the corresponding pure coupling compound (0.044 g, 76% yield).

Supporting Information (see footnote on the first page of this article): Experimental procedures for the cross-coupling reactions as well as spectroscopic data for all synthesized products.

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