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Microwave-Promoted Copper-Free Sonogashira–Hagihara Couplings of Aryl Imidazolylsulfonates in Water

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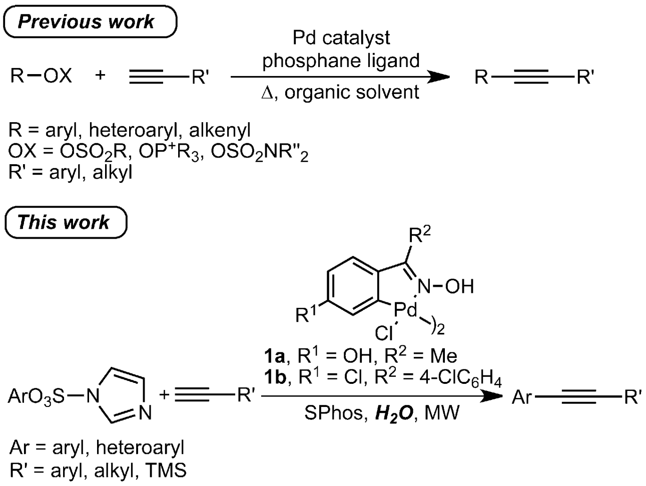
Abstract: Aryl imidazol-1-ylsulfonates have been efficiently cross-coupled with aryl-, alkyl-, and silylacetylenes in neat water under copper-free conditions at 110 °C assisted by microwave irradiation. Using 0.5 mol% of an oxime palladacycle as precatalyst, 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl (SPhos, 2 mol%) as ligand, hexadecyltrimethylammonium bromide (CTAB) as additive, and triethylamine (TEA) as base, a wide array of disubstituted alkynes has been prepared in good to high yields in only 30 min.

Keywords: cross-coupling; microwave chemistry; palladacycles; Sonogashira–Hagihara reaction; water

Introduction

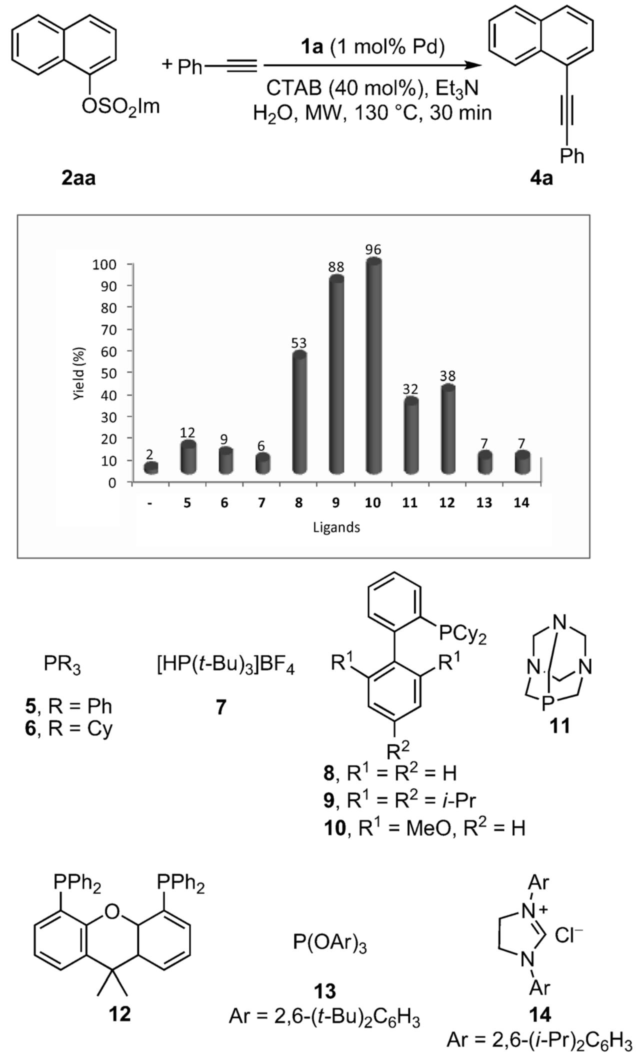
The palladium-catalyzed Sonogashira–Hagihara reaction is one of the most important and widely used methods for preparing aryl- and alkylacetylenes as well as conjugated enynes,[1] which are precursors for natural products, pharmaceuticals, and optical and electronic materials.[1,2] Although aryl and alkenyl halides are most commonly employed as the electrophilic partner in the Sonogashira reaction, considerable efforts have recently been directed to search for alternative electrophiles. O-based electrophiles are particularly attractive partners in cross-coupling reactions due to their high stability and the ubiquitous presence of hydroxylated compounds both in nature and in synthetic systems. Hydroxyarene derivatives offer a valuable alternative given that phenols are typically inexpensive and readily available materials.[3,4] Although triflates have shown high performance as electrophiles in the Pd-catalyzed Sonogashira reaction, their limited stability has focused recent studies on the development of less common but still stable phenol-based electrophiles.[5] Among them, good results have been reported for the palladium-catalyzed coupling of terminal alkynes with aryl mesylates,[6] tosylates,[6,7] phosphonium salts,[8] and imidazolylsulfonates.[9] However, these couplings have all been performed using high catalyst loadings (2–10 mol% Pd), usually in the presence of a copper salt as cocatalyst, and employing organic solvents as reaction medium (Scheme 1). Very recently, we have disclosed a phosphane-free oxime-palladacycle[10,11]-catalyzed Suzuki cross-coupling reaction of aryl imidazol-1-ylsulfonates[12] with arylboronic acids and potassium aryl trifluoroborates in aqueous methanol, a reaction which can be performed using



Scheme 1. Sonogashira coupling of phenol-derived electrophiles.

conventional or microwave heating, under conditions with low catalyst loading (1 mol% Pd).[13] This coupling can be also performed in neat water by using the cationic surfactant[14] hexadecyltrimethylammonium bromide (CTAB) as additive, which has allowed us to cross-couple aryl imidazol-1-ylsulfonates with potassium aryl- and alkenyltrifluoroborates under microwave heating (40 W, 110 °C) using 0.5 mol% of oxime palladacycle **1a**.[15]

To date, no examples have been reported for transition-metal catalyzed Sonogashira cross-coupling of phenol derivatives in neat water (Scheme 1).[16] In this contribution, we present the first Sonogashira coupling of aryl imidazolylsulfonates performed in neat water using oxime palladacycle **1a** as precatalyst under microwave irradiation (Scheme 1).



Scheme 2. Sonogashira coupling in water: ligands study.

Results and Discussion

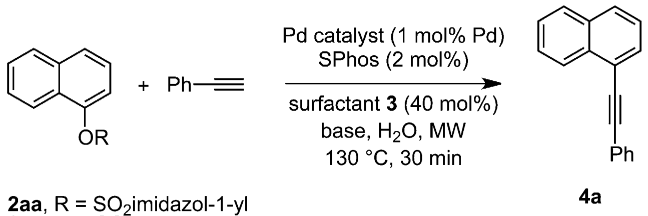
Initially, we investigated the microwave-promoted Sonogashira coupling of naphthalen-1-yl 1*H*-imidazole-1-sulfonate (**2aa**, 1 equiv.) with phenylacetylene (1.5 equiv.) in water in the presence of CTAB (**3a**), which was the best surfactant in the Suzuki reaction,[13] and TEA (2 equiv.) as base (Scheme 2). With an initial microwave irradiation of 40 W, the reaction temperature was maintained at 110 °C for 30 min. As catalyst, oxime palladacycle **1a** (1 mol% Pd) was selected to perform the initial screening due to the high activity of this complex as precatalyst in different cross-coupling and Heck-type reactions in aqueous medium.[11,13,14] Unfortunately, under these conditions, the alkynylation did not take place and starting materials were mostly recovered (Scheme 2). Since we have previously demonstrated the improvement of the activity of oxime palladacycles using phosphanes in the Suzuki arylation[17a] and alkenylation[17b] reactions of the challenging deactivated aryl chlorides, we assembled a small catalyst library prepared *in situ* by mixing **1a** (1 mol% Pd) and different electron-rich and sterically demanding ligands (2 mol%). As depicted in Scheme 2, the most active catalytic system was obtained when using Buchwald's ligands **9** and **10**, especially the tertiary electron-rich and sterically hindered SPhos ligand **10**, which led to an excellent 96% isolated yield for **4a**. Other mono- and bidentate phosphane-derived ligands such as **5**–**12** as well as the sterically hindered phosphate **13** and the imidazolinium NHC ligand **14** always led to lower yields in the process (Scheme 2).

Having identified SPhos as the optimal ligand for the copper-free Sonogashira reaction in water, further optimization of the reaction conditions was carried out in order to improve the efficiency of the catalytic system (Table 1).[18]

Initially, the efficiency of the microwave irradiation was demonstrated since only a 48% yield was obtained for **4a** when the reaction was performed under conventional thermal conditions (130 °C, 24 h, Table 1, entry 1). Regarding the catalyst, a 58% yield of 1-(phenylethynyl)naphthalene was obtained under the optimized reaction conditions when oxime palladacycle **1b** (1 mol% Pd) was employed as catalyst (Table 1, entry 2). This result confirmed the facility of palladacycle **1a** in cross-coupling reactions in aqueous medium. Other Pd sources such as $Pd(OAc)_2$ and $Pd_2(dba)_3$ were also less effective than **1a** affording lower yields of **4a** as shown in entries 3 and 4.

With respect to the base (Table 1, entries 5–9), good isolated yields were obtained with other organic (pyrrolidine, 89%) and inorganic bases (K_2CO_3 and K_3PO_4, 75 and 78%, respectively), although these experiments did not improve the ability of TEA in this process.

Table 1. Sonogashira alkynylation of **2** in water; reaction conditions study.



2aa, R = SO_2imidazol-1-yl
2ab, R = CO_2Bu-*t*
2ac, R = $CONMe_2$
2ad, R = P(O)oxazolidin-3-yl-2-one
2ae, R = $SO_2C_6H_4$-4-CH_3
2af, R = SO_2NMe_2

Entry	2	Surfactant[a]	Pd catalyst	Base	Yield [%][b]
1	**2aa**	CTAB (**3a**)	**1a**	TEA	96 (48)[c]
2	**2aa**	CTAB (**3a**)	**1b**	TEA	58
3	**2aa**	CTAB (**3a**)	$Pd(OAc)_2$	TEA	75
4	**2aa**	CTAB (**3a**)	$Pd_2(dba)_3$	TEA	24
5	**2aa**	CTAB (**3a**)	**1a**	pyrrolidine	89
6	**2aa**	CTAB (**3a**)	**1a**	K_2CO_3	75
7	**2aa**	CTAB (**3a**)	**1a**	KOH	31
8	**2aa**	CTAB (**3a**)	**1a**	CsOH	26
9	**2aa**	CTAB (**3a**)	**1a**	K_3PO_4	78
10	**2aa**	TBAOH (**3b**)	**1a**	TEA	76
11	**2aa**	SDS (**3c**)	**1a**	TEA	85
12	**2aa**	MAXEMUL6112 (**3d**)	**1a**	TEA	91
13	**2aa**	PTS (**3e**)	**1a**	TEA	67
14	**2aa**	SPAN80 (**3f**)	**1a**	TEA	73
15	**2aa**	ZONYL 9361 (**3g**)	**1a**	TEA	86
16	**2aa**	ZONYL FSN (**3h**)	**1a**	TEA	72
17	**2ab**	CTAB (**3a**)	**1a**	TEA	<5
18	**2ac**	CTAB (**3a**)	**1a**	TEA	<5
19	**2ad**	CTAB (**3a**)	**1a**	TEA	<5
20	**2ae**	CTAB (**3a**)	**1a**	TEA	<5
21	**2af**	CTAB (**3a**)	**1a**	TEA	<5

[a] CTAB: hexadecyltrimethylammonium bromide; TBAOH: tetrabutylammonium hydroxide; SDS: sodium dodecyl sulphate; PTS: polyoxyethanyl-α-tocopheryl sebacate; for the rest of surfactant acronyms, see the Supporting Information.

[b] Isolated yield after flash chromatography.

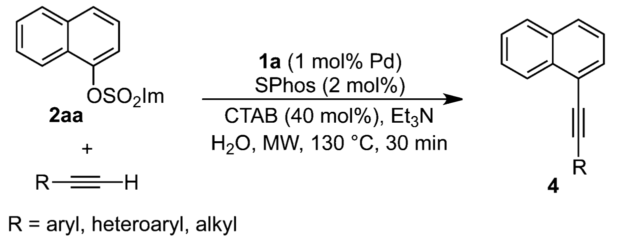
[c] Isolated yield when the reaction was performed under conventional thermal conditions (130 °C, 24 h).

The effect of the surfactant on the activity of the catalytic system was also studied (Table 1, entries 10–16). Regardless of the ionic character of the additive, lower yields were observed for the alkynylation reaction, with the exception of the anionic phosphate ester-derived surfactant MAXEMUL 6112, which afforded **4a** in a 91% isolated yield (Table 1, entry 12).

Finally, we also tested the reactivity of the electrophiles **2ab**–**2af** in the process under the optimized reaction conditions. As depicted in Table 1 (entries 17–21), none of these derivatives showed any reactivity and only starting material was recovered from the crude reaction mixtures.

To test the effectiveness of the catalytic system in the Pd-catalyzed Sonogashira coupling in water, a range of terminal alkynes was examined in the reaction with the imidazol-1-ylsulfonate **2aa** under the optimized reaction conditions (Table 2). Thus, naphthalen-1-yl 1*H*-imidazole-1-sulfonate (**2aa**) was coupled with 4-tolyl- and 4-methoxyphenylacetylenes in excellent 96 and 87% yields, respectively (Table 2, entries 2 and 3). Lower yields were achieved in the coupling with the electron-poor 4-(trifluoromethyl)phenyl-, and 2-pyridylacetylenes (Table 2, entries 4 and 5), results which were also observed for alkyl-substituted acetylenes such as cyclohexylacetylene (63%, entry 6) and 1-butyne (40%, entry 7). In the case of using trimethylsilylacetylene as nucleophile, a double arylation process was observed affording 1,2-di(naphthalen-1-yl)ethyne (**15**) as major product in a 45% isolated yield (Table 2, entry 8). Unfortunately, this yield could not be improved by using two equivalents of

Table 2. Sonogashira cross-coupling reaction: nucleophile scope.



Entry	R	No.	Yield [%][a]
1	Ph	**4a**	96
2	4-MeC_6H_4	**4b**	96
3	4-$MeOC_6H_4$	**4c**	87
4	4-$CF_3C_6H_4$	**4d**	59
5	2-pyridyl	**4e**	52
6	cyclohexyl	**4f**	63
7	C_3H_7	**4g**	40
8	TMS	**15**	45[b,c]
9	CO_2H	**15**	37[b,d]
10	$(CH_3)_2C(OH)$	**4j**	38

[a] Isolated yield after flash chromatography.

[b] Isolated yield for 1,2-di(naphthalen-1-yl)ethyne (**15**).

[c] A 7% yield (GC) of trimethyl(naphthalen-1-ylethynyl)silane (**4h**) was also detected in the crude reaction mixture.

[d] A 7% yield (GC) of 3-(naphthalen-1-yl)propiolic acid (**4i**) was also detected in the crude reaction mixture.

electrophile, conditions which afforded **15** in a poor 15% yield. When **2aa** was allowed to react with propiolic acid, the double coupling process was also observed affording **15** in a 37% yield (Table 2, entry 9). However, the alkynylation of **2aa** with 2-methylbut-3-yn-2-ol, led to the monoarylated compound **4j** in a 38% yield (Table 2, entry 10).

Regarding the electrophilic component, moderate to high yields (45–95%) were obtained in the microwave-assisted **1a**/S-Phos-catalyzed cross-coupling of different terminal acetylenes with neutral, electron-rich, and electron-poor phenylimidazol-1-ylsulfonates (Table 3). Thus, phenyl 1*H*-imidazole-1-sulfonate (**2ba**) as well as the electron-rich 4-methoxyphenyl 1*H*-imidazole-1-sulfonate (**2ca**) and 3,5-dimethylphenyl 1*H*-imidazole-1-sulfonate (**2da**) reacted with phenylacetylene to afford compounds **4k**, **4l**, and **4m** in 89, 78, and 55% yields, respectively (Table 3, entries 1–3). High yields were also observed for the coupling of the activated electrophiles **2ea** and **2fa** with phenylacetylene and 4-tolylacetylene, respectively (Table 3, entries 4 and 5). The process was also effective for the coupling of 2-aryl- and 2-alkylacetylenes with deactivated and sterically hindered electrophiles such as *o*-tolyl 1*H*-imidazole-1-sulfonate (**2ga**) and 2,6-dimethylphenyl 1*H*-imidazole-1-sulfonate (**2ha**), reactions which afforded the corresponding cross-coupled products in yields ranging from 41 to 95% (Table 3, entries 6–10). Finally, the heterocyclic pyridin-2-yl 1*H*-imidazole-1-sulfonate (**2ia**) led to compound **4u** in a modest 45% yield after reaction with phenylacetylene (Table 3, entry 11).

Conclusions

We have disclosed a copper-free oxime palladacycle-catalyzed Sonogashira cross-coupling reaction of electron-rich, electron-poor, and sterically hindered aryl imidazol-1-ylsulfonates with aryl- and alkyl-substituted terminal alkynes using water as solvent under microwave irradiation. This reaction is carried out in the presence of SPhos as ligand (2 mol%), hexadecyltrimethylammonium bromide as additive, and using only 1 mol% Pd of bench stable oxime palladacycle **1a** as precatalyst. Further studies to demonstrate the ability of imidazolylsulfonates as electrophiles in cross-coupling reactions in water are underway in the group.

Experimental Section

Typical Procedure for the Sonogashira Coupling in water under MW Irradiation Conditions

A 10-mL MW vessel was charged with 2-cyanophenyl 1*H*-imidazole-1-sulfonate (0.050 g, 0.2 mmol, 1 equiv.), *p*-tolylacetylene (0.038 mL, 0.3 mmol), Et_3N (0.056 mL, 0.4 mmol), hexadecyltrimethylammonium bromide (0.03 g, 40 mol%), catalyst **1a** (0.6 mg, 1 mol% Pd), H_2O (1.7 mL) and SPhos (0.0017 g, 2 mol%). The vessel was sealed with a pressure lock, and the mixture was heated in air at 130 °C for 30 min with the aid of an initial 40 W MW irradiation in a CEM Discover MW reactor. After cooling to room temperature, the reaction mixture was extracted with EtOAc (3 × 10 mL), and the organic layers were washed with H_2O (3 × 10 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude residue was purified by flash chromatography (hexane) to obtain compound **4o**; yield: 0.040 g (94%).

Acknowledgements

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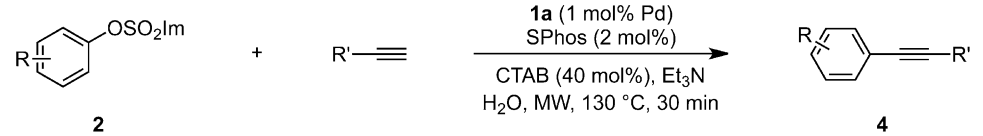
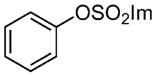
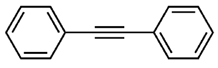
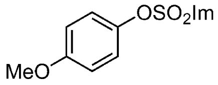
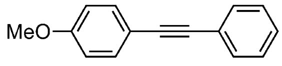
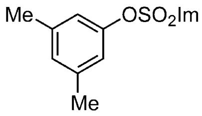
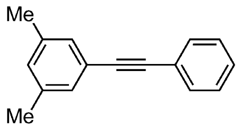
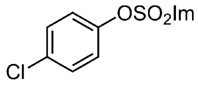
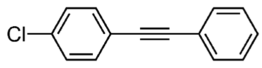
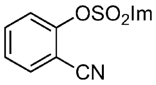
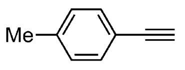
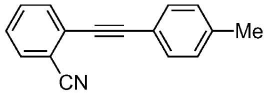
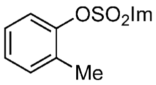
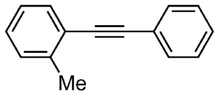
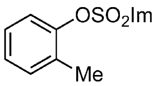
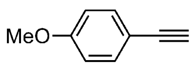
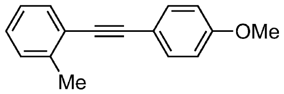
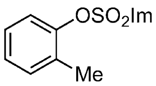
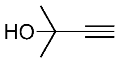
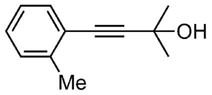
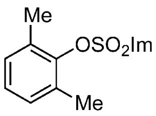
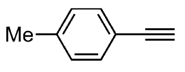
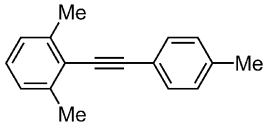
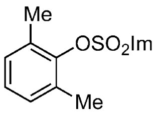
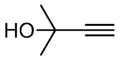
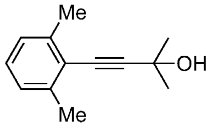
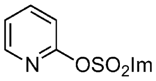
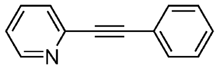
Table 3. Sonogashira cross-coupling reaction: substrate scope.



2 **4**

Entry	ArOSO$_2$Im	No.	R'—≡	Product	No.	Yield [%][a]
1		**2ba**	Ph—≡		**4k**	89
2		**2ca**	Ph—≡		**4l**	78
3		**2da**	Ph—≡		**4m**	55
4		**2ea**	Ph—≡		**4n**	77[b]
5		**2fa**			**4o**	94
6		**2ga**	Ph—≡		**4p**	92
7		**2ga**			**4q**	87
8		**2ga**			**4r**	92[c]
9		**2ha**			**4s**	95
10		**2ha**			**4t**	41[d]
11		**2ia**	Ph—≡		**4u**	45

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[a] Isolated yield after flash chromatography.

[b] A 7% yield (GC) of 1,4-bis(phenylethynyl)benzene (**16**) was also detected in the crude reaction mixture.

[c] A 6% yield (GC) of 1,2-di-o-tolylethyne (**17**) was also detected in the crude reaction mixture.

[d] A 5% yield (GC) of 1,2-bis(2,6-dimethylphenyl)ethyne (**18**) was also detected in the crude reaction mixture.

References

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