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Microwave-assisted palladium-catalyzed highly regio- and stereoselective head to head dimerization of terminal aryl alkynes in water†

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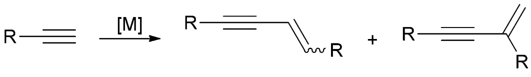
A highly regio- and stereoselective oxime palladacycle/imidazolinium-catalyzed head to head dimerization of terminal aryl alkynes in water is presented. The reaction, which is carried out at 130 °C under microwave irradiation in the presence of 1,3-bis-(2,6-diisopropylphenyl) imidazolinium chloride as ligand, triethylamine as base, and TBAB as surfactant, allows the synthesis of (*E*)-1,4-enynes as single stereoisomers in good isolated yields.

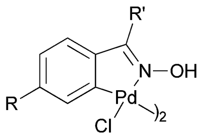
The transition-metal catalyzed dimerization of terminal alkynes[1] is a straightforward and atom-economical approach for the preparation of conjugated enynes, which are important motifs in organic synthesis as well as versatile precursors for natural products, pharmaceuticals, and optical and electronic materials.[2] Different transition-metal complexes and rare earth complexes[3] efficiently catalyze alkyne dimerization reactions to provide enynes. However, a limited number of those allow good selectivities in the process due to the competitive formation of undesired regio- (head to head *vs.* head to tail) and stereoisomeric derivatives (Scheme 1). On the other hand, the use of water as solvent in the transition-metal catalyzed dimerization of terminal alkynes would represent an improvement of the sustainability of this *per se* green process. However, to our knowledge, only two examples have been reported to date using water as solvent and Ru catalysis.[4]



Scheme 1 Metal-catalyzed dimerization of terminal alkynes.

Since 1999, our lab has been involved in the development and use of oxime palladacycles[5] as highly active precatalysts for different cross-coupling reactions using organic and aqueous solvents.[6] Specifically, oxime palladacycles derived from 4,4′-dichlorobenzophenone **1a** and 4-hydroxyacetophenone **1b** have been shown to be very active precatalysts in the copper-free Sonogashira–Hagihara coupling of deactivated aryl bromides and chlorides[7] as well as aryl imidazolylsulfonates[8] with terminal alkynes in water under microwave irradiation (Fig. 1). In continuation of our research on the application of oxime palladacycles in C–C coupling reactions under green conditions, herein we describe the stereo- and regioselective synthesis of (*E*)-head to head 1,4-diaryl-1,3-enynes *via* Pd-catalyzed dimerization of aryl alkynes in water assisted by microwave irradiation.

In the course of our investigation about the **1a**-catalyzed Sonogashira coupling of deactivated aryl chlorides with alkynes in water,[7] we observed the formation of significant amounts of 1,3-enynes as reaction byproducts when using imidazolinium derivatives as auxiliary ligands.[9] Thus, our study commenced with the **1a**-catalyzed (1 mol% Pd) dimerization of phenylacetylene using different imidazolinium ligands (Fig. 2, 2 mol%), hexadecyltrimethylammonium bromide (CTAB, 40 mol%) as surfactant and pyrrolidine as base in water at 130 °C under a 40 W initial microwave irradiation for 30 min (Table 1). When the dimerization was carried out in the presence of the



1a, R = Cl, R′ = 4-ClC$_6$H$_4$
1b, R = OH, R′ = Me

Fig. 1 Oxime palladacycle precatalysts.

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† Electronic supplementary information (ESI) available: Typical experimental procedures and physical and spectroscopic data for all the synthesized compounds are available. See DOI: 10.1039/c4ra08287g

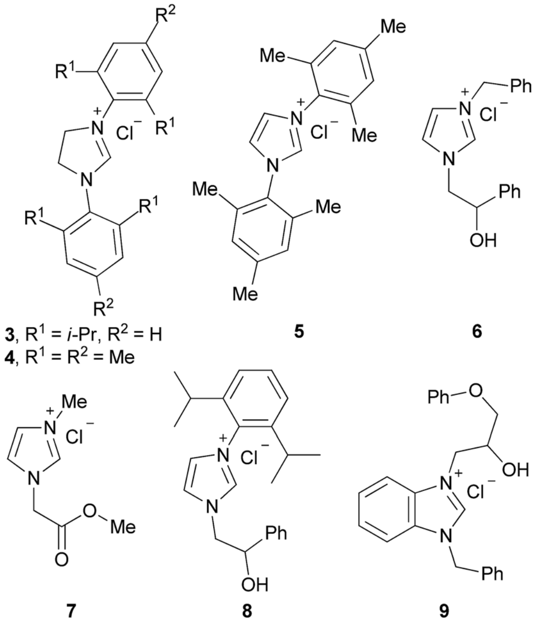


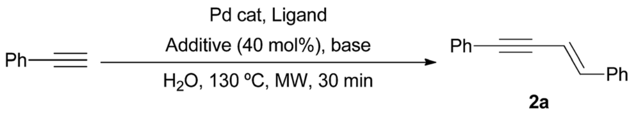
Fig. 2 Ligands tested in the dimerization reaction.

sterically demanding and electron rich ligand 1,3-bis-(2,6-diisopropylphenyl)imidazolinium chloride (**3**, Fig. 2), a 73% reaction conversion was observed being (*E*)-but-1-en-3-yne-1,4-diyldibenzene (**2a**) isolated in a 41% yield (Table 1, entry 1).

Other related ligands, such as 1,3-bis(2,4,6-trimethylphenyl) imidazolinium chloride (**4**, Fig. 2) and 1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride (**5**, Fig. 2) afforded lower conversions than **3** in the process (Table 1, entries 2 and 3). We also tried in the dimerization ligands **6–9** (Fig. 2) which have been successfully used in the Matsuda–Heck[10a] and Hiyama[10b,c] couplings, but all of them led to unacceptable conversions and high levels of alkyne polymerization (entries 4–7). From these results it is clear the importance of the use of sterically hindered and electron-rich ligands for catalyst performance generating coordinatively unsaturated palladium species electron-rich enough to facilitate the oxidative addition to the alkyne C–H bond and the reductive elimination steps.[3e] In fact, not only is the best yield obtained with ligand **3**, but also among the more flexible and therefore less bulky ligands **6–9**, the best result is observed with the imidazolinium derivative **8**, which contains a 2,6-diisopropylphenyl moiety on its structure (Table 1, entry 6).

With respect to the surfactant, increasing the amount to 100 mol% did not improve the yield of the reaction (entry 8). The study with other additives (Table 1, entries 9–12) with similar (tetrabutylammonium bromide, TBAB, cationic) or different (sodium dodecylbenzenesulfonate, SDBS, anionic; polyoxyethanyl-α-tocopheryl sebacate, PTS, non-ionic and polyoxyethylene lauryl ether, Brij 35, non-ionic) ionic character, showed TBAB as the best surfactant affording compound **2a** in a 69% isolated yield (entry 9).

Table 1 Optimization of the dimerization of phenylacetylene[a]



Entry	Pd cat. (mol% Pd)	Ligand (mol%)	Additive	Base	Yield[b] (%)
1	**1a** (1)	**3** (2)	CTAB	Pyrrolidine	73 (41)
2	**1a** (1)	**4** (2)	CTAB	Pyrrolidine	45
3	**1a** (1)	**5** (2)	CTAB	Pyrrolidine	61
4	**1a** (1)	**6** (2)	CTAB	Pyrrolidine	14
5	**1a** (1)	**7** (2)	CTAB	Pyrrolidine	24
6	**1a** (1)	**8** (2)	CTAB	Pyrrolidine	30
7	**1a** (1)	**9** (2)	CTAB	Pyrrolidine	12
8	**1a** (1)	**3** (2)	CTAB[c]	Pyrrolidine	68 (35)
9	**1a** (1)	**3** (2)	TBAB	Pyrrolidine	84 (69)
10	**1a** (1)	**3** (2)	SDBS	Pyrrolidine	78 (33)
11	**1a** (1)	**3** (2)	PTS	Pyrrolidine	83 (24)
12	**1a** (1)	**3** (2)	Brij 35	Pyrrolidine	93 (35)
13	**1a** (1)	**3** (2)	TBAB	TEA	99 (82)[d]
14	**1a** (1)	**3** (2)	TBAB	TEA	<5[e]
15	**1a** (1)	**3** (2)	—	TEA	99 (78)
16	**1a** (1)	—	TBAB	TEA	<5
17	**1a** (1)	**3** (1)	TBAB	TEA	(61)
18	**1b** (1)	**3** (2)	TBAB	TEA	99 (72)
19	$Pd_2(dba)_3$ (1)	**3** (2)	TBAB	TEA	99 (70)
20	$Pd(OAc)_2$ (1)	**3** (2)	TBAB	TEA	99 (55)
21	**1a** (0.1)	**3** (0.2)	TBAB	TEA	63

[a] Reaction conditions: phenylacetylene (0.5 mmol), **1a** (2 mg, 1 mol% Pd), **3** (4.3 mg, 2 mol%), TBAB (64 mg, 40 mol%), TEA (101 mg, 1 mmol), H_2O (1 mL). 130 °C, 40 W, 30 min. [b] Reaction conversion. In parenthesis isolated yield after preparative thin layer chromatography. [c] 1 equiv. of CTAB was used. [d] A 75% isolated yield of **2a** was obtained when the reaction was scaled up to 2 mmol of phenylacetylene. [e] Reaction performed under conventional heating (130 °C, 18 h).

A subsequent base study (see ESI† for the complete study), under the optimized reaction conditions obtained so far, revealed triethylamine (TEA) as the best choice being **2a** isolated in a 82% yield (Table 1, entry 13). Furthermore, a 75% yield of **2a** was obtained when the reaction was scaled up to 2 mmol of phenylacetylene. Also, we could demonstrate the efficiency of the microwave irradiation since **2a** formation was not detected when the reaction was performed under conventional thermal conditions (130 °C, 18 h, entry 14). Interestingly, a good yield (78%) was also obtained for **2a** when no surfactant was added to the dimerization reaction in water (Table 1, entry 15).

In relation with the Pd/ligand ratio, the reaction failed in the absence of ancillary ligand (Table 1, entry 16). Also, a lower 61% isolated yield of **2a** was obtained when used a Pd/**3** ratio of 1/1 (entry 17).

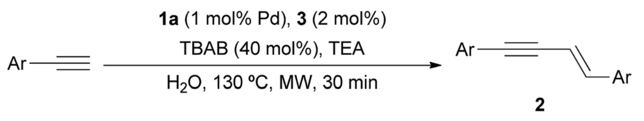
We also studied other different Pd(0) and Pd(II) precatalysts. For instance, **2a** was isolated in a 72% yield when 4-hydroxyacetophenone oxime palladacycle **1b** (1 mol% Pd) was used as catalyst (Table 1, entry 18). Other Pd sources such as $Pd(OAc)_2$ and $Pd_2(dba)_3$ were also less effective than **1a** affording lower yields of **2a** as shown in entries 19 and 20. Finally, a 63% reaction conversion was observed when the **1a** loading was reduced to 0.1 mol% of Pd (Table 1, entry 21).

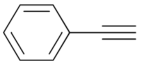
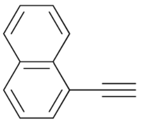
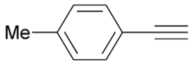
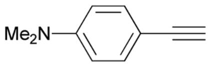
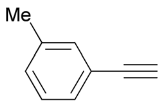
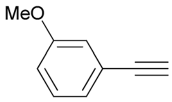
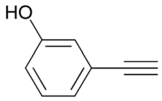
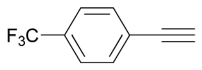
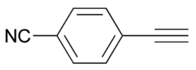
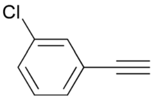
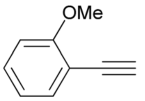
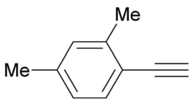
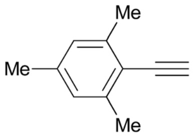
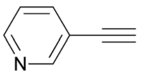
The optimized reaction conditions (Table 1, entry 13) were tested for the dimerization reaction of different terminal aryl alkynes. It was found that most of the studied aryl acetylenes underwent the dimerization reaction in water to produce the head to head dimers in good to high yields with very high regio- and stereocontrol (Table 2).[11]

As previously described for phenylacetylene (Table 2, entry 1), 1-ethynylnaphthalene afforded enyne **2b** in a 70% isolated yield (Table 2, entry 2). The palladium-catalyzed hydroalkynylation of the electron-rich 4-ethynyltoluene, 4-ethynylanisole, 4-ethynyl-*N*,*N*-dimethylaniline, 3-ethynyltoluene, 3-ethynylanisole, and 3-ethynylphenol led to the corresponding (*E*)-1,3-enynes **2c–2h**, in good isolated yields (55–79%, Table 2, entries 3–8).[12] The catalytic system was also effective for the head to head dimerization of activated 1-ethynyl-4-(trifluoromethyl)benzene, 4-ethynylbenzonitrile, and 3-ethynylchlorobenzene, alkynes that afforded dimers **2i**, **2j**, and **2k** in a 62, 68, and 54% isolated yield, respectively (Table 2, entries 9–11).

Electron-rich and hindered 1-ethynyl-2-methoxybenzene and 1-ethynyl-2,4-dimethylbenzene underwent the dimerization to produce the desired enynes **2l** and **2m** in a 47% and 80% yield (entries 12 and 13). Interestingly, 2-ethynyl-1,3,5-trimethylbenzene afforded (*E*)-2,2′-(but-1-en-3-yne-1,4-diyl)bis(1,3,5-trimethylbenzene) (**2n**) as a single regio and stereoisomer in a 51% yield (Table 2, entry 14). On the other hand, the coupling of the heterocyclic 3-ethynylpyridine afforded compound **2o** in an 80% yield (Table 2, entry 15). Finally, since the isolated yield for compound **2a** was very similar regardless of the presence or absence of TBAB as surfactant in the model reaction (Table 2, entry 1), compounds **2e**, **2f**, **2i**, **2k**, and **2o** were prepared without adding the surfactant. As depicted in Table 2, entries 5, 6, 9, 11, and 15, all the isolated yields were always lower in the absence of TBAB, the use of this additive was essential to obtain good yields of the corresponding dimers. The results obtained with

Table 2 Head to head dimerization of terminal alkynes



Entry	ArC≡CH	2	Yield[a] (%)
1		**2a**	82 (78)
2		**2b**	70
3		**2c**	79
4		**2d**	67
5		**2e**	58 (22)
6		**2f**	71 (57)
7		**2g**	62
8		**2h**	55
9		**2i**	62 (33)
10		**2j**	68
11		**2k**	54 (46)
12		**2l**	47
13		**2m**	80
14		**2n**	51
15		**2o**	80 (41)

[a] Isolated yield after preparative thin layer chromatography. In parenthesis, isolated yield when the reaction was performed in the absence of TBAB.

terminal aryl acetylenes possessing one or even two substituents at the *ortho* position of the aromatic ring (Table 2, entries 12–14) clearly indicate that the **1a**/**3**-catalyzed dimerization in water does not involve agostic interactions between the Pd centre and the *ortho* protons of the aromatic ring of the alkyne.[3b] Therefore, as recently proposed by Gevorgyan,[3e] under the optimized reaction conditions, the dimerization should occur *via* a hydropalladation pathway (Scheme 2).

With respect to the active species involved in the catalytic cycle, palladacycles have been proposed as a source of highly active palladium nanoparticles. However, a mercury poisoning experiment performed on the model reaction (see ESI† for experimental details), pointed to the participation of other different catalytically active palladium species, whose identification is currently performed in our lab.

Conclusions

In conclusion, we have optimized a palladium-derived catalytic system that efficiently mediates the dimerization of functionalized aromatic alkynes in a highly regio- and stereoselective manner to afford (*E*)-1,3-enynes with good yields in water as solvent being microwave irradiation crucial for this process to succeed.

Acknowledgements

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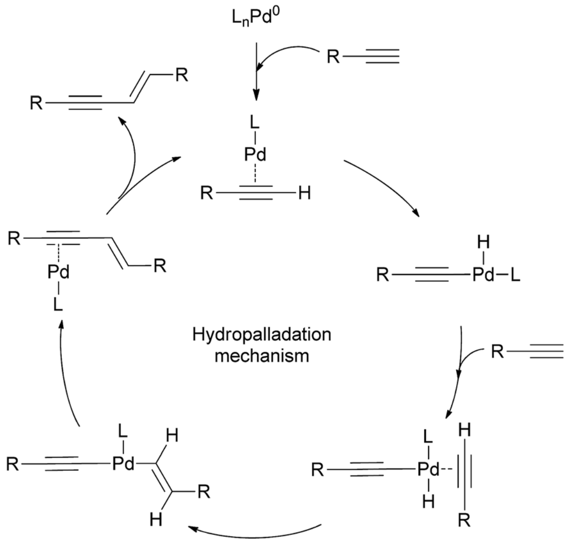

Scheme 2 Hydropalladation mechanism for alkyne dimerization.[3e]

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