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Tetrahedron Letters 45 (2004) 4157–4161

Tetrahedron Letters

Efficient synthesis of trisubstituted alkenes in an aqueous–organic system using a versatile and recyclable Rh/*m*-TPPTC catalyst

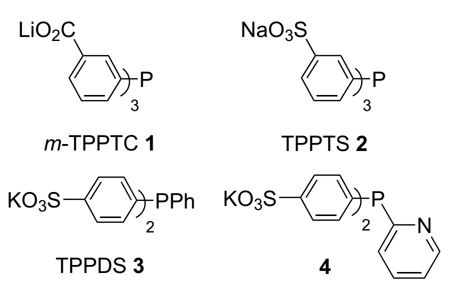
Emilie Genin, Véronique Michelet* and Jean-Pierre Genêt*

Laboratoire de Synthèse Sélective Organique et Produits Naturels, ENSCP, UMR 7573,
11 rue P. et M. Curie, F-75231 Paris Cedex 05, France

Received 25 February 2004; revised 18 March 2004; accepted 22 March 2004

Abstract—We have found that the use of $[Rh(cod)OH]_2$ associated with the water-soluble ligand *m*-TPPTC was highly efficient for the Rh-catalyzed arylation of alkynes. Aryl and alkyl alkynes were transformed to alkenes using 3 mol% rhodium catalyst and 2.5 equiv of boronic acid at 100 °C in a biphasic water/toluene system in 80–99% yield. The reaction was found to be totally regioselective for alkyl arylalkynes and alkyl silylated alkynes. The Rh/*m*-TPPTC system was for the first time recycled with no loss of the activity and with excellent purity of the desired alkene.

Organic synthesis in water has recently received much attention, not only because unique reactivity and selectivity are often exhibited in water but also because it is an economical and environmentally friendly solvent.[1,2] The development of water-soluble organometallic systems has also given the ability to combine the high efficiency of the catalyst with the possible metal recycling and the easy product/catalyst separation.[1,2] As part of an ongoing program devoted to metal-catalyzed reactions in aqueous media,[3] we have recently reported the versatile preparation of the water-soluble ligand *m*-TPPTC **1**, a carboxylated analogue of the sulfonated TPPTS ligand **2** (Scheme 1).[4,5] As recent years witnessed tremendous growth in Rh-catalyzed addition of organoboronic acids to unsaturated compounds,[6] we sought to evaluate the reactivity of the new carboxylated ligand for C–C bond formation.



Scheme 1.

We turned our attention to the Rh-catalyzed addition of boronic acids to alkynes described recently for the first time by Hayashi's group in a dioxane/water mixture.[7] Despite this unique work based on a rhodium/diphenylphosphane[8] system in organoaqueous conditions, there is one system described so far in water.[9] This latter, requiring basic conditions and the presence of a surfactant, is very specific to pyridyl-substituted alkynes as it is inefficient with alkyl or aryl substituted ones. Moreover, the use of the well-known sulfonated ligands TPPTS **2** and TPPDS **3** (Scheme 1) was ineffective and consequently led the authors to synthesize the ligand **4**.[9] Having in hand a novel water-soluble ligand, we wish to report our preliminary results concerning a versatile, highly efficient and for the first time recyclable water-soluble system.

The addition of phenylboronic acid to oct-4-yne **5** was chosen as a standard reaction and some results are summarized in Table 1. We screened different rhodium precursors to find a suitable system to promote the reaction without base or surfactant. For example, the use of $Rh(acac)(C_2H_4)_2$ and $[Rh(C_2H_4)Cl]_2$ gave disappointing results as low yields were obtained (entries 1, 2). Moreover, we observed the formation of a by-product **7a** that was separated from the alkene **6a**

Keywords: Water-soluble ligand; Boronic acids; Alkynes; Recyclable rhodium/*m*-TPPTC system; Biphasic system.

* Corresponding authors. Tel.: +33-1-44-27-67-42; fax: +33-1-44-07-10-62; e-mail addresses: genet@ext.jussieu.fr; michelet@ext.jussieu.fr

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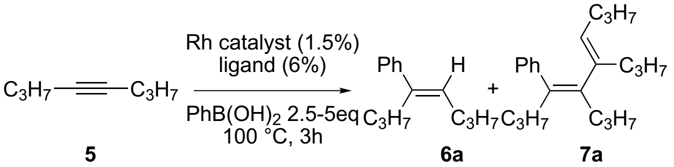
doi:10.1016/j.tetlet.2004.03.136

Table 1. Rh-catalyzed addition of phenylboronic acid to oct-4-yne **5** in water and in biphasic H_2O/toluene media



Entry	Rh catalyst/ligand	Conditions	Yield[a] (%)	**6a/7a** Ratio (%)[b]
1[c]	$Rh(acac)(C_2H_4)_2$/**1**	H_2O	20	70/30
2	$[Rh(C_2H_4)Cl]_2$/**1**	H_2O	22	64/36
3	$[Rh(cod)OH]_2$/**1**	H_2O	95	80/20
4	$[Rh(cod)OH]_2$/**2**	H_2O	63	60/40
5	$[Rh(cod)OH]_2$/**1**	H_2O, Na_2CO_3	99	60/40
6	$[Rh(cod)OH]_2$/**1**	H_2O/toluene 1/1	99	100/0
7[d]	$[Rh(cod)OH]_2$/**1**	H_2O/toluene 1/1	96	98/2
8[d]	$[Rh(cod)OH]_2$/**2**	H_2O/toluene 1/1	89	85/15
9[e]	$[Rh(cod)OH]_2$/**1**	H_2O/toluene 1/1	84	95/5

[a] Isolated yield.

[b] Measured by ^1H NMR and GC.

[c] 3 mol% catalyst.

[d] 2.5 equiv of phenylboronic acid.

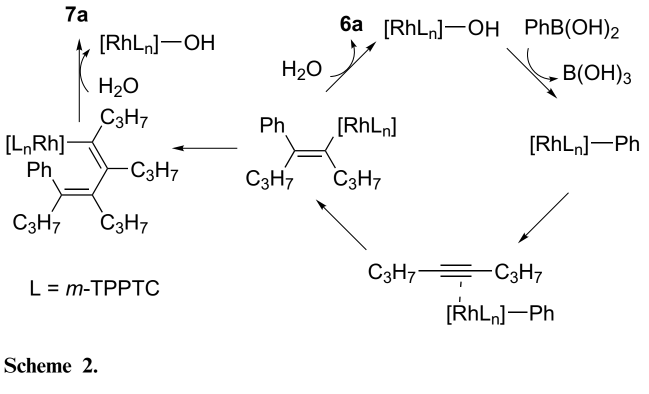
[e] 2.5 equiv of phenylboronic acid, 50 °C, 6.3 h.

and identified as a single diene by spectral ^1H NMR and NOESY effect. No traces of trimer were detected. The formation of such diene is unique during the course of the Rh-catalyzed hydroarylation, since **7a** was only reported with nickel catalyst, as a mixture of stereoisomers though.[10] We prepared the $[Rh(cod)OH]_2$ catalyst according to literature procedure[11] as this precursor seems to be involved in several couplings of boronic acids and other organometallic partners.[6,9,12] We found that under the same reaction conditions, the yield was increased to 95% and the **6a/7a** ratio was still in favor of the desired product (entry 3). The use of the TPPTS ligand **2** gave a 3/2 mixture of compounds **6a/7a** in a moderate 63% yield (entry 4). We also investigated the influence of a base:[4b,9] the addition of a mineral base (Na_2CO_3, 2 equiv) was significant as the **6a/7a** ratio decreased from 80/20 to 60/40 (entry 5).[13] Speculating that the influence of water was also profound on the selectivity of the reaction and more specifically on the formation of **7a**, we studied the hydroarylation under biphasic conditions. We were pleased to find that the use of the biphasic system toluene/water completely suppressed the formation of the diene **7a**. The desired alkene was isolated in 99% yield and 100% selectivity (entry 6). Interestingly, the quantity of boronic acid could then be reduced from 5 to 2.5 equiv (entry 7) with still excellent yield and selectivity.[14] It has to be noticed that the use of the TPPTS ligand **2** afforded a significant amount of the diene **7a** (entry 8) in a lower yield. Lowering the temperature to 50 °C increased the reaction time but still gave **6a** in a good 84% yield (entry 9).

The optimized system therefore consists of 3 mol% of rhodium, 6 mol% of the water-soluble monophosphane **1** and only 2.5 equiv of boronic acid in an essential biphasic water/toluene media. These conditions also provide a facile separation of the resulting alkene from the catalyst system.[14]

The well-accepted catalytic cycle involves a classic transmetallation leading to a $[RhL_n]$-Ph intermediate[6] and then an addition to the alkyne (Scheme 2).[7] Subsequent hydrolysis with water results in the formation of alkene **6a** and regeneration of the catalyst.[15] The formation of the diene **7a**, that may also be related to polymerization reactions,[16] is favored in water. This may be rationalized by the unique structure and properties of water compared to usual solvents. It is now well-known that water has the highest cohesive energy density, a very large surface tension, and a high heat capacity.[1,2] The principal consequence of these effects is the entropy-driven association of apolar solutes in water. The hydrophobic effect, in our case due to the low water-solubility of the alkyl alkyne, may therefore promote a second addition of alkyne, as several alkynes are close to each other. The use of a biphasic system thus controls the concentration[17] of the alkyne in the water phase and therefore influences the selectivity of the reaction in favor of the monoaddition of the alkyne.

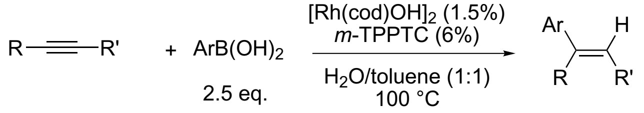
The versatility of the catalyst system and especially the addition of various arylboronic acids to alkyl and aryl substituted alkynes was then examined (Table 2). Other

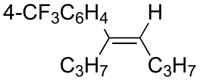
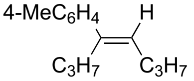
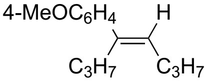
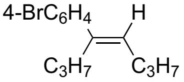
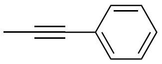
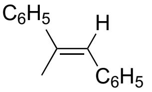
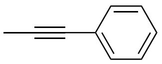
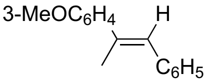
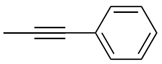
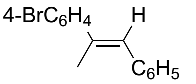
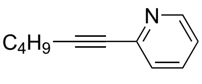
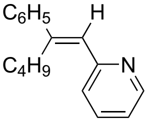
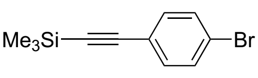
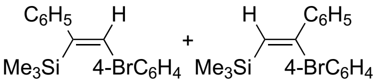
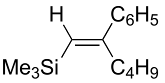


Scheme 2.

boron partners still reacted very smoothly in the standard conditions. Either electro-withdrawing boronic acid (entry 1) or electro-donating boronic acids (entries 2, 3) could react in short reaction time leading to 80–99% isolated alkenes **6b–c**. It has to be noted that no reduction of the boronic acid was observed, especially in the case of the 4-methoxyphenylboronic, on the contrary to the study of Hayashi et al.[7] The reaction was also chemoselective as the bromo-substituted boronic acid (entry 4) was added with an excellent yield. The addition of a bromoaryl group to unsaturated compound was already found to be chemoselective with different Rh systems in water and is of particular interest for further cross-coupling reactions.[4b,18] We decided to study the difficult case of 1-phenylpropyne, for which only a mixture of regioisomers (3:1) could be obtained so far.[7] We observed the formation of the expected alkenes **9a–c** with high yields (entries 5–7). Moreover, the regioselectivity was found to be >95% as no trace of another isomer was detected by NMR or GC. The addition of the aryl groups occurs exclusively at the β-position of the phenyl group. The ability of the catalytic system to perform the hydroarylation in high yield and to induce formation of a unique isomer may be a consequence of the intrinsic properties (steric and electronic) of the phosphane.[4b,19] The system was also compatible with a pyridyl substituted alkyne[9] and an excellent regioselectivity was also observed. The alkene **11** was isolated in 98% yield (entry 8). The influence of a silyl group was then investigated through the reaction of the aryl-substituted alkyne **12**. The reaction was still highly chemoselective. Despite the total conversion of

Table 2. Rh-catalyzed arylation of alkynes in a biphasic H_2O/toluene phase



Entry	Alkyne		Ar	Product		t (h)	Yield[a] (%)
1	$C_3H_7-\equiv-C_3H_7$	**5**	$4\text{-}CF_3C_6H_4$		**6b**	3	99
2	$C_3H_7-\equiv-C_3H_7$	**5**	$4\text{-}MeC_6H_4$		**6c**	3	98
3	$C_3H_7-\equiv-C_3H_7$	**5**	$4\text{-}MeOC_6H_4$		**6d**	3	80
4	$C_3H_7-\equiv-C_3H_7$	**5**	$4\text{-}BrC_6H_4$		**6e**	3	99
5		**8**	C_6H_5		**9a**	2.5	95
6		**8**	$3\text{-}MeOC_6H_4$		**9b**	2.5	96
7		**8**	$4\text{-}BrC_6H_4$		**9c**	2.5	95
8		**10**	C_6H_5		**11**	3	98
9		**12**	C_6H_5		**13**	3	99[b]
10	$Me_3Si-\equiv-C_4H_9$	**14**	C_6H_5		**15**	3	94

[a] Isolated yield.

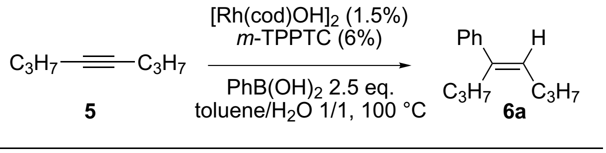
[b] 1/1 mixture determined by ^1H NMR and GC.

the alkyne, we observed the formation of two isomers **13**, which were found to be regioisomers (entry 9).[20] The silyl group may therefore have the same effect as the phenyl group and promotes the addition of the aryl group at the β-position. This could be demonstrated by choosing a substrate bearing an alkyl and a silyl group. The addition of phenylboronic acid to alkyne **14** indeed gave exclusively the isomer **15** in 94% yield (entry 10).

Having found a suitable biphasic system for the arylation of alkynes bearing various groups in water, we then explored the recycling possibility of the catalyst Rh(I)/*m*-TPPTC, which has never been disclosed to our knowledge for this reaction. We have conducted the addition of phenylboronic acid to oct-4-yne **5** using 1.5 mol% $[Rh(cod)OH]_2$, 6 mol% *m*-TPPTC **1** under biphasic conditions. As shown in Table 3, we were pleased to find that the water-soluble ligand **1** preserves successfully the expensive rhodium in water, and allows a catalyst recycling. Indeed, after completion of the reaction, the toluene phase was separated and the water phase was extracted two times with toluene and reloaded with substrates in solution. The reaction time was still very short for each of the four cycles. The alkene **6a** was isolated in 93–98% yield and with excellent purity (98–99%). It is noteworthy that during the continuous recycle experiments, no deposition of rhodium metal on the glass was observed.

In conclusion, the use of $[Rh(cod)OH]_2$ associated with the water-soluble ligand *m*-TPPTC was found to be highly efficient for the Rh-catalyzed arylation of alkynes. The biphasic water/toluene system was found to be crucial for the selectivity of the reaction. Selected alkynes, which were established to be unreactive in water or, which gave mixtures in organoaqueous media, were transformed to alkenes with a total stereo- and regioselectivity. Furthermore, we could perform for the first time the recycling of the catalyst system for this reaction. Other applications of this system implying various organometallic partners are currently studied and will be reported in due course.

Table 3. Recycling of the $[Rh(cod)OH]_2$/*m*-TPPTC system in a H_2O/toluene mixture



Cycle	*t* (h)	Yield (%)[a]	Purity (%)[b]
1	1.5	96	98
2	1.5	93	99
3	1.5	97	98
4	1.5	98	99

[a] Isolated yield.

[b] Measured by GC.

Acknowledgements

E. Genin is grateful to the Ecole Normale Supérieure de Paris for a grant (2003–2004).

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5. Abbreviations: TPPTS = trisodium salt of 3,3′,3″-phosphanetriylbenzenesulfonic acid, TPPTC = trilithium salt of 3,3′,3″-phosphanetriylbenzenecarboxylic acid, TPPDS = dipotassium salt of 3,3′-phosphanediylbenzenesulfonic acid.
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13. No reaction was observed under basic conditions without rhodium catalyst.
14. Typical procedure: To a mixture of degassed $[Rh(cod)OH]_2$ (3.4 mg, 1.5 mol%) and *m*-TPPTC (12.3 mg, 6 mol%) at

room temperature was successively added a water (0.5 mL)/toluene (0.5 mL), phenylboronic acid (152 mg, 1.25 mmol), and oct-4-yne (74 µL, 0.5 mmol). The mixture was heated at 100 °C until completion of the reaction and then cooled to room temperature. The alkene was isolated either through separation and extraction with toluene (2 times) or direct filtration on a short pad of silica gel and evaporation under reduced pressure. 90 mg (96%) of **6a** were obtained as a pale yellow oil. No further purification was necessary. The purity (>95%) was checked by NMR and GC–MS analyses.

15. The involvement of an arylrhodium complex[7] was not considered as 90% of the deuterated alkene was observed in a 1/1 toluene/D_2O mixture.
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19. The *m*-TPPTC ligand displays a higher basicity than the TPPTS phosphane. This study will be published elsewhere.
20. We have conducted a desilylation reaction of the mixture under standard conditions using *n*-Bu_4NF in THF leading to a mixture of *gem*-disubstituted and *trans*-disubstituted alkenes (selected ^1H NMR 400 MHz $\delta = 5.48$, 5.46 ppm $J = 1.1$ Hz and 7.11, 7.04 ppm $J = 16.5$ Hz).