ORGANIC
LETTERS

2008
Vol. 10, No. 17
3793−3796

Sonogashira Couplings of Aryl Bromides: Room Temperature, Water Only, No Copper

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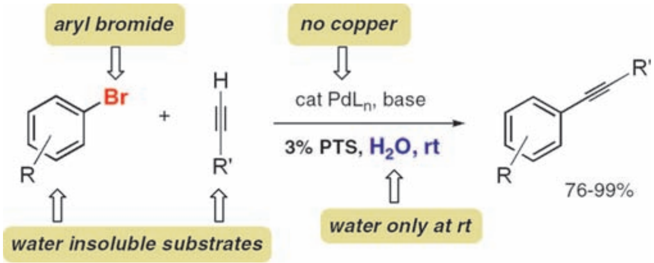
Received June 29, 2008

ABSTRACT



Cross-coupling reactions between lipophilic terminal alkynes and aryl bromides can be catalyzed by ligated Pd, in the absence of copper, in pure water at ambient temperatures. Small amounts of the nonionic amphiphile PTS assist by virtue of nanometer micelles formed spontaneously in an aqueous medium.

Among the leading "name" reactions in organic synthesis,[1] Sonogashira couplings[2] rank especially high given the intrinsic value and flexibility of a newly introduced acetylenic moiety.[3] Traditionally, these cross-couplings rely on the presence of both palladium and copper to contribute to catalysis,[4] although much effort of late has gone into effecting such C−C bond constructions in the absence of one[5] or the other metal[6] or by virtue of alternative methodologies that accomplish the same net aryl−alkyne bond.[7] Aryl iodides are frequently used in organic media, usually at elevated temperatures.[8] The corresponding bromides and especially chlorides are less prone to participate, requiring more forcing conditions,[9] the extent to which depends upon levels of halide activation and specifics of ligand choice.[10] While Sonogashira couplings under mixed organic/aqueous conditions are common, reactions in water alone place significant demands on substrates and catalyst solubilities

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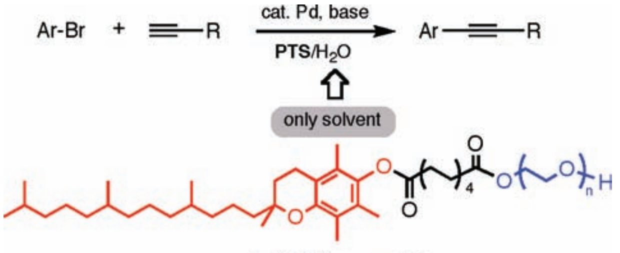
10.1021/ol801471f CCC: $40.75

and, hence, are rare.[11] Indeed, an aryl bromide-terminal acetylene cross-coupling in water at ambient temperatures is unprecedented to our knowledge. In this paper, we describe a new method that, for the first time, allows Sonogashira couplings to occur in the absence of both copper and organic solvents and at room temperature using commercially available reagents.

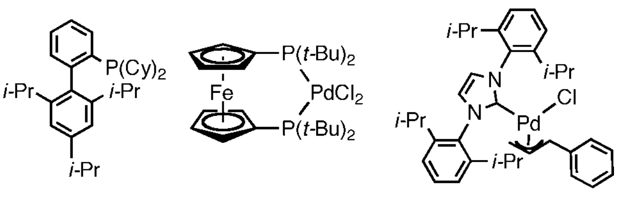
The key to success was anticipated to derive from micellar catalysis[12] using the lipophilic vitamin E core (in red) of the nanomicelle-forming amphiphile PTS (**1**; Scheme 1),[13] in effect, as solvent. As recently shown in related Pd-catalyzed Heck[14] and Suzuki[15] couplings, otherwise water-insoluble substrates and catalysts out of the bottle react in commercially available PTS/H_2O[16] to afford the desired products in high isolated yields. Variables such as the ligand on palladium and the choice/amount of base play crucial roles, requiring that conditions be "matched" not only to the educts but to the micellar environment.

Scheme 1. Overall Conversion in Water Using PTS



1, **PTS** (n = *ca.* 13)

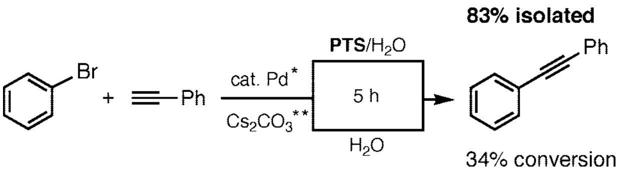
Aromatic acetylenes could be constructed from aryl bromides and 1-alkynes at room temperature using a 3% (by weight) PTS/H_2O solution, excess Cs_2CO_3 as base, and X-Phos[17] (**2**; Figure 1) as ligand in the presence of catalytic $PdCl_2(CH_3CN)_2$. The H_2O used as solvent is briefly degassed prior to mixing with PTS to prevent ligand oxidation. Reactions, therefore, are best run under inert atmosphere. A model system composed of bromobenzene and phenylacetylene led to the desired product diarylacetylene in good isolated yield (100% conversion; 83% isolated yield; Scheme 2), while the corresponding reaction "on water"[18] (i.e., without PTS) gave noticeably inferior results (34% conversion) within the same time frame (5 h). Inclusion of copper salts proved to be unnecessary. Other catalysts were screened early in this study [including dppf analogue **3**,[19] Umicore's CX-31 (**4**),[20] and $PdCl_2(Ph_3P_2)$] with the Pd(II)/X-Phos complex found to be the most effective.



2; X-Phos **3**; Pd(dtbpf)Cl_2 **4**; Neolyst™ CX31

Figure 1. Ligand/catalysts examined in this study.

Scheme 2. Impact of Amphiphile PTS on a Model Cross-Coupling



*1% $PdCl_2(CH_3CN)_2$, 2.5% ligand **2**; ** 3.5 equiv

Significant sensitivity to base was also noted. Among heterogeneous bases, Cs_2CO_3 gave excellent results (Table 1). Several soluble amine bases under otherwise identical conditions led to considerable variation in levels of conversion and isolated yields. Ultimately, Et_3N emerged as the base of choice (e.g., see entries 1b, 2b, 3, and 4) relative to pyrrolidine, *i*-Pr_2NEt, and DBU. Cross-coupling of hindered bromides such as educt **5** with enyne **6** was also achieved using Et_3N as base, although in this case pyrrolidine worked equally well. Deactivated substrate **7** reacted readily with phenylacetylene (entry 2a) but was slow to couple with an alkyl-substituted acetylene **8** (entry 2b). Activated bromides (entries 4 and 5) coupled smoothly in high yields. Both 2-bromonaphthalene (entry 6) and 9-bromophenanthrene (entry 7) gave the corresponding unsymmetrical internal alkynes. Unexpectedly, neither *n*-Bu_3N nor (*n*-octyl)$_3$N led

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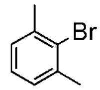
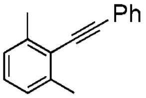
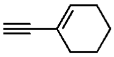
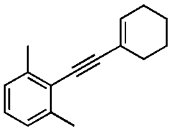
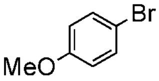
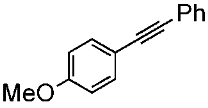
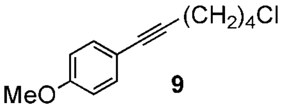
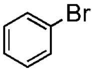
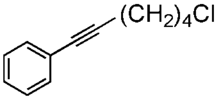
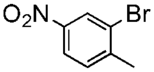
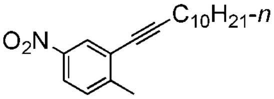
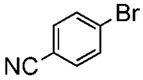
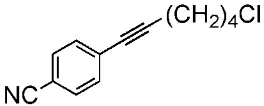
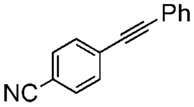
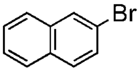
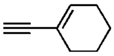
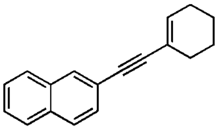
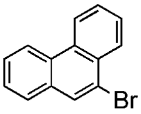
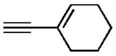
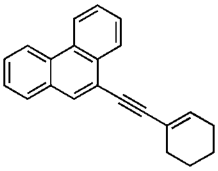
Table 1. Sonogashira Couplings of Aryl Bromides Using $PdCl_2(CH_3CN)_2$ + Ligand **2** in 3% PTS/H_2O at rt

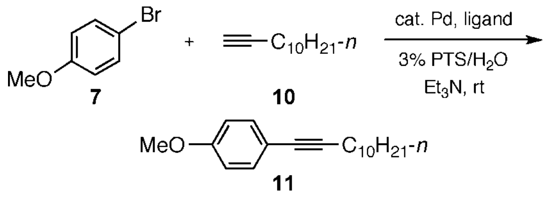
entry	Ar-Br	alkyne	base	time (h)	product[a]	yield (%)[b]
1	 **5**	(a) ≡—Ph	Cs_2CO_3	20		99
		(b)  **6**	Cs_2CO_3	29		75
			K_3PO_4	24		66
			pyrrolidine	22		quant
			Et_3N	23		quant
2	 **7**	(a) ≡—Ph	Cs_2CO_3	20		89
		(b) ≡—$(CH_2)_4Cl$ **8**	Cs_2CO_3	4 d	 **9**	26
			Et_3N	25		55
			$(n\text{-Bu})_3N$[c]	23		0
			$(n\text{-Oct})_3N$[c]	23		0
3		≡—$(CH_2)_4Cl$	Cs_2CO_3	26		83
			Et_3N	20		82
			DBU	25		<30
4		≡—$C_{10}H_{21}$-*n*	Cs_2CO_3	47		58
			Et_3N	18		99
5		(a) ≡—$(CH_2)_4Cl$	Cs_2CO_3	6		93
		(b) ≡—Ph	Cs_2CO_3	4		97
6			Et_3N	21		84
7			Et_3N	21		98

[a] Isolated; fully characterized. [b] Isolated, chromatographically purified material. [c] Used as received from vendor.

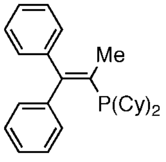
to any product **9** (entry 2b), although the acetylenic partner **8** was consumed by formation of polymeric materials, as seen previously by others in related reactions in the presence of copper.[17] Thus, increased hydrophobicity of the base (and hence, assumed greater solubility within the micelle) is not commensurate in this case with an increase in the desired reaction pathway.

Three additional monophosphine ligands, **12**−**14**, were studied (Table 2) in an effort to find conditions that lead to more rapid conversions, especially involving electron-rich aryl bromides (e.g., **7**; Table 1, entry 2). Coupling *p*-bromoanisole (**7**) with alkyne **10** in the presence of catalytic Pd (1%), X-Phos (**2**; 2.5%), and base (Et_3N; 3 equiv) did progress essentially to completion over the course of 3 days.

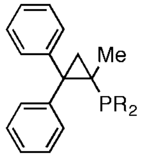
Table 2. Additional Ligand Study in Sonogashira Couplings



Pd source	ligand	time	results
$PdCl_2(CH_3CN)_2$	**2**	3 d	92% conversion
$Pd(OAc)_2$	**12**	20 h	95% conversion
$Pd(OAc)_2$	**13**	10 h	75% isolated
$Pd(OAc)_2$	**14**	**10 h**	**96% isolated**



12 (Cy-vBRIDP)



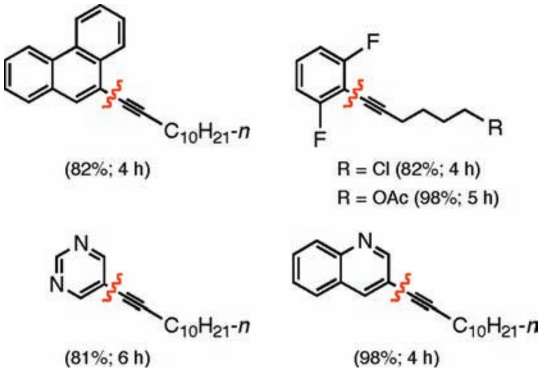
13: R = Cy (Cy-cBRIDP)
14: R = *t*-Bu (cBRIDP)

The combination of $Pd(OAc)_2$ with the recently introduced monodentate cyclopropylphosphine **14** from Takasago,[21] on the other hand, led to >99% conversion in ≤10 h and, ultimately, 96% isolated yield of product **11**. Identical results were obtained using either degassed, or nondegassed, PTS/H_2O. Related ligands **12** and **13** were also quite effective, although coupling in the presence of **14** was cleaner. Several additional examples using ligand **14**, as illustrated in Scheme 3, document the remarkable effectiveness and generality of this catalyst/amphiphile combination.

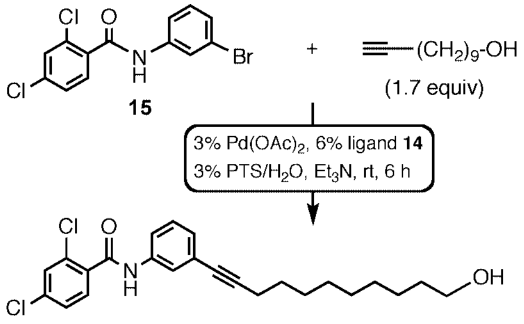
One further application of ligand **14** to a more highly functionalized aryl bromide (**15**) was investigated (Scheme 4). Coupling of **15** with undecynol in PTS/H_2O at rt led to alkyne **16** in good isolated yield.

In summary, new technology based on micellar catalysis using the "designer surfactant" PTS has been developed. Sonogashira couplings can now be run with lipophilic partners and commercial catalysts in water at ambient temperature. Minimizing reliance on organic solvents as reaction media in metal-based catalysis is a worthy goal in green chemistry; PTS may help along the way.[22]

Scheme 3. Additional Couplings Using Ligand **14** in PTS/H_2O



Scheme 4. Cross-Coupling Using Ligand **14** at rt in Water



16 (78% isolated yield)

Acknowledgment. We warmly thank Zymes, LLC for continued support of our programs in green chemistry. We are indebted to Johnson Matthey for supplying ligand **3**, Umicore for their gift of ligand **4**, and Takasago for a generous supply of their newly disclosed vinyl- and cyclopropylmonophosphines **12**−**14**.

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

OL801471F

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