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Ligand-, Copper-, and Amine-Free Sonogashira Reaction of Aryl Iodides and Bromides with Terminal Alkynes

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Abstract: Conditions for an efficient ligand-, copper-, and amine-free palladium-catalyzed Sonogashira reaction of aryl iodides and bromides with terminal alkynes have been developed. Critical to the success of this new protocol is the use of tetrabutylammonium acetate as the base. Noteworthy features of this method are room-temperature conditions and the tolerance of a broad range of functional groups in both reaction partners.

The palladium-catalyzed reaction of aryl halides with terminal alkynes, known as the Sonogashira reaction, constitutes an important facet of alkyne as well as of organopalladium chemistry.[1,2] This reaction is generally cocatalyzed by Cu(I), and an amine as a base and a phosphine as a ligand for palladium are also typically included.[3] An important side reaction encountered with the presence of a Cu(I) cocatalyst is the Glaser-type oxidative dimerization of the alkyne.[4] To address this issue, several reports have described copper-free Sonogashira reactions, but none of them are free of an amine and a ligand simultaneously, while also operating at room temperature.[5] For example, in 1986, Cacchi et al. reported the coupling of enol triflates with terminal alkynes under copper-free conditions, but a phosphine-ligated palladium precursor and a temperature of 60 °C were employed.[6] In 1993, Linstrumelle published a paper on the Pd-catalyzed coupling of aryl or vinyl halides (I, Br, OTf) with terminal alkynes.[7] In this report, only one example of a phosphine- and copper-free (but not amine-free) Sonogashira coupling of a vinyl iodide with a terminal alkyne was described, and the coupling proceeded in only moderate yield (57%). For an aryl iodide (only iodobenzene was used), a phosphine-ligated palladium source was included under copper-free conditions. In both cases, 5 mol % palladium catalyst was employed. Herrmann reported a procedure for the Sonogashira reaction of aryl bromides, but it was necessary to use air-sensitive and pyrophoric P(*t*-Bu)$_3$ as a ligand, although the coupling did proceed with only 0.5 mol % of palladium and ligand.[8] It is worthy of note that P(*t*-Bu)$_3$ can be replaced with the air-stable [(*t*-Bu)$_3$PH]BF$_4$ in Sonogashira couplings.[9] Ryu described a Sonogashira method for coupling aryl iodides in ionic liquids, but it required an elevated temperature (60 °C) as well as the use of a phosphine ligand.[10] Recently, Nájera has disclosed a palladacycle catalyst for the cross-coupling of aryl iodides and terminal alkynes.[11] However, this methodology requires relatively harsh conditions (110 °C) and a multistep synthesis of the catalyst. TBAF, TBAOH, and Ag_2O were used by Mori as activators for the Sonogashira coupling of aryl iodides, but an elevated temperature (60 °C) and a phosphine-based palladium catalyst were needed in all three cases.[12] Moreover, use of a silver catalyst not only would add cost to the catalyst but also to expense of metal waste disposal/recovery. Astruc described the use of a preformed Pd(II)−phosphine catalyst for a Sonogashira coupling of aryl halides in neat Et_3N.[13] Leadbeater has reported a copper-free Sonogashira methodology for aryl iodides and activated aryl bromides with the traditional palladium catalyst Pd(PPh$_3$)$_2$Cl$_2$ (4 mol %) at 70 °C in neat piperidine.[14] Interestingly, however, the observation was made that under phosphine- and copper-free conditions, neither palladium acetate nor palladium on charcoal catalyzed the aforementioned reaction. More recently, a report by Buchwald has appeared describing the coupling of aryl chlorides and aryl tosylates with terminal alkynes, utilizing a bulky biphenylphosphine ligand under copper- and amine-free conditions.[15]

From an industrial as well as an economic standpoint, a ligandless and copper-free process would provide much needed impetus to the development of improved catalyst systems for Sonogashira couplings. Further, such a process would be advantageous for synthetic chemists who would generally prefer not to use expensive and sensitive ligands. In addition, the elimination of amines (generally used in large excess) would be welcome because industrial wastes containing them would require treatment for environmental purposes.

Our continuing interest in palladium-catalyzed organic transformations[16−18] prompted us to extend our attention

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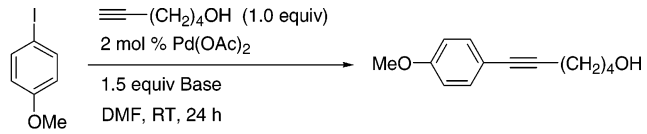
TABLE 1. Screening of Bases for Sonogashira Coupling of 4-Iodoanisole and 5-Hexyn-1-ol



1.0 equiv

entry	base	yield[a] (%)
1	Bu_4NOAc	93[b]
2	Cs_2CO_3	69
3	Et_3N	5
4	DBU	8
5	*i*-Pr_2NEt	5
6	piperidine	5
7	*i*-Pr_2NH	10
8	Na_2CO_3	30
9	NaO-*t*-Bu	0
10	NaOAc	25

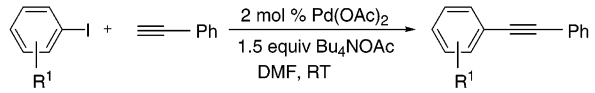
[a] Isolated yields (average of two runs). [b] Reaction time was 6 h.

to the Sonogashira reaction. Herein we report for the first time a room-temperature, general, and efficient procedure for a ligand-, copper-, and amine-free Sonogashira reaction of aryl iodides and bromides with terminal alkynes using $Pd(OAc)_2$ or $Pd_2(dba)_3$ as the catalyst and tetrabutylammonium acetate as the base.

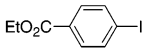
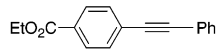
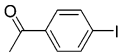
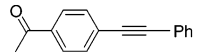
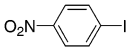
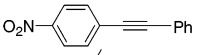
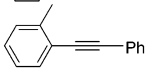
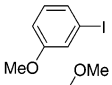
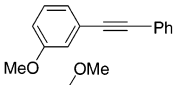
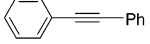
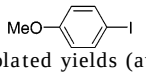
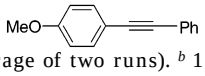
For preliminary optimization of the reaction conditions, we studied the reaction of electron-rich 4-iodoanisole and 5-hexyn-1-ol in the presence of 2 mol % of $Pd(OAc)_2$ in DMF at room temperature (Table 1). An important initial goal was to find a suitable base that would effect the desired reaction. Surprisingly, commonly used secondary and tertiary amine bases such as triethylamine, DBU (diazabicyclo[5.4.0]undec-7-ene), *N*-ethyldiisopropylamine (*i*-Pr_2NEt), piperidine, and diisopropylamine (*i*-Pr_2NH) as well as Na_2CO_3, NaO-*t*-Bu, and NaOAc gave inferior results. Gratifyingly, however, both Cs_2CO_3 and Bu_4NOAc were effective as bases, with Bu_4NOAc being the more reactive, allowing the reaction to be completed in 6 h. Among the solvents screened (THF, toluene, dioxane, CH_3CN, and DMF), DMF proved to be the most efficient. Other palladium sources such as $PdCl_2$, $Pd_2(dba)_3$, and $[(\pi\text{-allyl})PdCl]_2$ were also effective catalysts for the aforementioned reaction.

Using equimolar reagent concentrations, 2 mol % $Pd(OAc)_2$, 1.5 equiv of Bu_4NOAc, and DMF as the solvent at room temperature, reactions of a series of substituted aryl iodides were carried out via the palladium-catalyzed Sonogashira reaction with phenylacetylene (Table 2). Good to excellent yields were generally obtained under these *ligandless, copper- and amine-free* conditions. Functional groups such as carboxyethyl, keto, and nitro were well tolerated (Table 1, entries 1−3). Aryl iodides with electron-withdrawing groups gave higher yields than those with electron-neutral or electron-rich groups, and the coupling proceeded with substantially lower palladium catalyst loading. The cross-coupling of sterically hindered aryl iodides (2-iodotoluene and 2-iododanisole) also proceeded quite well (Table 1, entries 4 and 6). As expected, no homocoupling product was detected by GC under these conditions. It may be noted that while the reactions of aryl iodides possessing electron-withdrawing groups were completed in 3 h the electron−neutral and electron-rich aryl iodides reacted in 6 h.

TABLE 2. Ligand-, Copper-, and Amine-Free Sonogashira Couplings of Aryl Iodides with Phenylacetylene



1.0 equiv 1.0 equiv

entry	aryl iodide	product	time (h)	yield (%)[a]
1			3	96[b]
2			3	97[b]
3			3	97[b]
4			6	68
5			6	73 (80)[c]
6			6	74 (79)[c]
7			6	77 (86)[c]

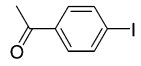
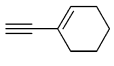
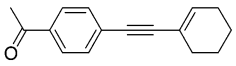
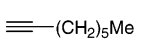
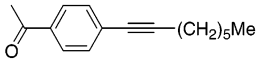
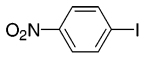
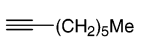
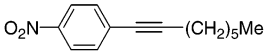
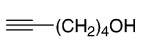
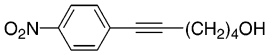
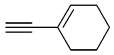
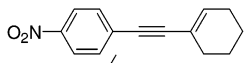
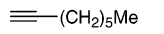
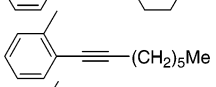
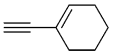
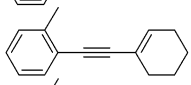
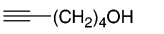
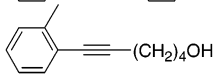
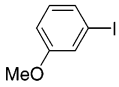
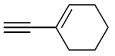
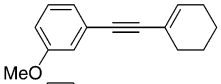
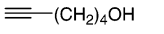
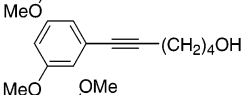
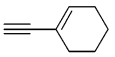
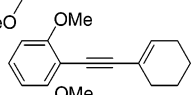
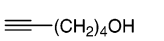
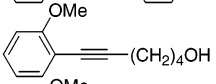
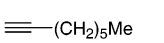
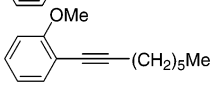
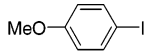
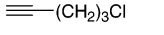
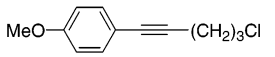
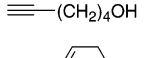
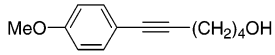
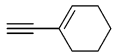
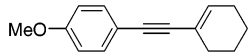
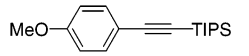
[a] Isolated yields (average of two runs). [b] 1 mol % of $Pd(OAc)_2$ was employed. [c] Parenthesized yields were obtained with 3 mol % of $Pd(OAc)_2$.

In an effort to further expand the scope of our ligand-, copper-, and amine-free Sonogashira reaction, we next investigated the reaction of substituted aryl iodides with a series of aliphatic terminal alkynes as summarized in Table 3. The yields were generally higher than those obtained when phenylacetylene was used as the reaction partner. Unfunctionalized alkynes, for example, 1-octyne in Table 3 (entries 2, 3, 6, and 13) as well as functionalized alkynes bearing a hydroxy group (entries 4, 8, 10, 12, and 15), a chloride group (entry 14), a cyano group (entry 18), or a TIPS group (entry 17) reacted efficiently with various aryl iodides to afford the corresponding aryl alkynes in excellent yields. Even a terminal alkyne with an alkene functionality underwent Sonogashira coupling in good yields (entries 1, 5, 7, 9, 11, and 16).

The efficiency of aryl bromides as a coupling partner under *ligandless, copper- and amine-free* conditions was also studied (Table 4). Although $Pd_2(dba)_3$ was employed as the catalyst in these reactions, $Pd(OAc)_2$ was also found to be a suitable palladium precursor. However, this method was effective only for electron-deficient aryl bromides and it required a slightly higher catalyst loading (4 mol % Pd) to provide good to excellent yields of the desired product. Thus, aryl bromides with nitro (entries 1−3), keto (entry 4), and cyano (entries 5−7) functional groups were smoothly coupled with a variety of terminal alkynes. Unfortunately, the Sonogashira couplings of electron-rich aryl bromides were sluggish under these conditions.

Presently, the beneficial effect of Bu_4NOAc in these reactions is not clear. Undoubtedly, Bu_4NOAc acts as a mild base to deprotonate the most acidic hydrogen in the

TABLE 3. Ligand-, Copper-, and Amine-Free Sonogashira Couplings of Aryl Iodides with Aliphatic Terminal Alkynes[a]

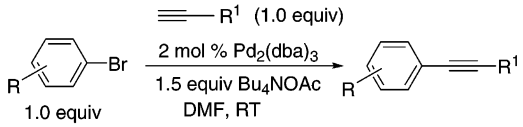
entry	aryl iodide	alkyne	product	time (h)	yield (%)[b]
1				3	90[c]
2				3	94[c]
3				3	96[c]
4				3	98[c]
5				3	97[c]
6				6	95
7				6	96
8				6	89
9				6	70 (81)[d]
10				6	85
11				6	75 (86)[d]
12				6	77 (86)[d]
13				6	93
14				6	80[e]
15				6	93
16				6	76 (84)[d]
17				6	97
18				6	87[e]

[a] For reaction conditions, see Table 1. [b] Isolated yields (average of two runs). [c] 1 mol % of $Pd(OAc)_2$ was employed. [d] Parenthesized yields were obtained with 3 mol % of $Pd(OAc)_2$. [e] $Pd_2(dba)_3$ was used in place of $Pd(OAc)_2$.

alkyne. In addition, it may facilitate the reduction of $Pd(OAc)_2$ to a catalytically active Pd(0) species. The latter phenomenon has been observed previously by Caló[19] and by Reetz[20] and co-workers, who observed Pd nanoparticle formation, albeit at elevated temperatures. However, we have found that the reaction in Table 1 proceeds in the presence of mercury, thus supporting a homogeneous catalytic pathway.[21] A particular role for the tetrabutylammonium cation seems to be precluded because we found that Me_4NOAc can be substituted for Bu_4NOAc. On the other hand as expected, the coupling of 4-iodoanisole and 5-hexyn-1-ol did not proceed in the presence of Bu_4NBr (TBAB). These results indicate that the acetate anion in combination with a bulky cation plays a very essential role in promoting such coupling reactions, perhaps by providing a naked more reactive acetate anion. Another possibility is that in the catalytic cycle, the oxidative addition adduct ArPd(II)X, a 12 e^- unstable complex, could be stabilized by tetrabutylammonium acetate to afford a 16 e^- complex $[ArPd(II)X_3]^{2-}\ 2Bu_4N^+$ (X = OAc, and/or I or Br) in which the metal center could be expected to be more stable and more electrophilic thus facilitating its complexation with an alkyne. Deprotonation (by Bu_4NOAc), isomerization, and product-forming

(19) Caló, V.; Nacci, A.; Monopoli, A.; Laera, S.; Cioffi, N. *J. Org. Chem.* **2003**, *68*, 2929.
(20) Reetz, M. T.; Maase, M. *Adv. Mater.* **1999**, *11*, 773.
(21) Widegren, J. A.; Bennett, M. A.; Finke, R. G. *J. Am. Chem. Soc.* **2003**, *125*, 10301.

TABLE 4. Ligand-, Copper-, and Amine-Free Sonogashira Couplings of Aryl Bromides with Terminal Alkynes



entry	aryl bromide	product	time (h)	yield (%)[a]
1	O_2N—Br	O_2N—Ph	5	86
2		O_2N—$(CH_2)_4OH$	5	92
3		O_2N—$(CH_2)_5Me$	5	91
4	O, Br	O, $(CH_2)_5Me$	5	90
5	NC—Br	NC—$(CH_2)_4OH$	8	94
6		NC—TIPS	12	89
7		NC—Ph	24	70

[a] Isolated yields (average of two runs).

reductive elimination would constitute the remaining steps of the catalytic cycle.

In summary, we have established that $Pd(OAc)_2$ or $Pd_2(dba)_3$ catalyzes the Sonogashira reaction of aryl iodides and bromides at room temperature in the absence of ligand, amine, and Cu(I). The choice of tetrabutylammonium acetate as the base is important for obtaining high yields of arylalkynes. The methodology encompasses a wide variety of functional groups, and it is worthwhile noting that our protocol employs a relatively low palladium catalyst loading. To the best of our knowledge, this is the first ligand-, copper-, and amine-free method for the cross-coupling of aryl iodides and bromides with terminal alkynes. These conditions render our protocol potentially attractive for industrial as well as academic applications of Sonogashira couplings.

Experimental Section

General Procedure for the Sonogashira Reaction. An oven-dried Schlenk flask equipped with a magnetic stirring bar was charged with Bu_4NOAc (1.5 mmol) and $Pd(OAc)_2$ (1−3 mol %) or $Pd_2(dba)_3$ (2 mol % for aryl bromides) inside a nitrogen-filled glovebox. The flask was capped with a rubber septum, and then it was removed from the glovebox. An aryl iodide or bromide (1.0 mmol) and DMF (3 mL) were then successively added, and after 5 min of stirring, the alkyne (1.0 mmol) was added. Stirring was continued at room temperature under argon for the corresponding reaction times indicated in the tables, after which time the reaction mixture was diluted with water (10 mL) and extracted with diethyl ether (4 × 10 mL). The combined ether layers were dried over Na_2SO_4, filtered, concentrated, and purified by alumina gel flash chromatography using hexanes or hexanes/ether to elute the desired coupling product.

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Supporting Information Available: Experimental details and complete characterization of compounds prepared. This material is available free of charge via the Internet at http://pubs.acs.org.

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