Pd-Catalyzed Intramolecular Oxyalkynylation of Alkenes with Hypervalent Iodine
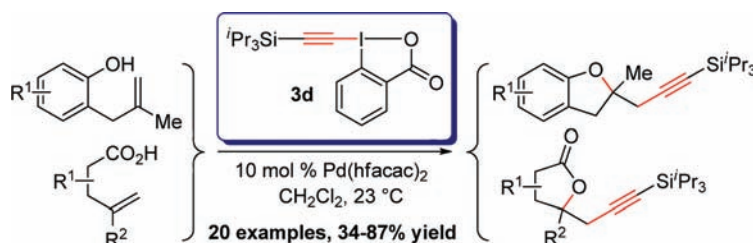
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ABSTRACT

The first example of intramolecular oxyalkynylation of nonactivated alkenes using oxidative Pd chemistry is reported. Both phenol and aromatic or aliphatic acid derivatives could be used under operator-friendly conditions (room temperature, technical solvents, under air). The discovery of the superiority of benziodoxolone-derived hypervalent iodine reagent 3d as an alkyne transfer reagent further expands the rapidly increasing utility of hypervalent iodine reagents in catalysis and is expected to have important implications for other similar processes.

Cyclic structures are ubiquitous in natural products and other bioactive substances.[1] Consequently, the efficient synthesis of carbo- and heterocycles is an important field of research in organic chemistry. Metal-catalyzed cyclization reactions, especially when involving multiple C−C or C−X bond formations, constitute an efficient pathway to heterocycles.[2] One such method is the Wacker cyclization, which is the Pd-catalyzed cyclization of nucleophiles on double bonds (Scheme 1, A).[2c,3] In place of β-hydride elimination, further C−C,[2c,4] C−O,[5] C−N,[6] and C−Cl[7] bond formation together with cyclization have been reported.[8]

In particular, C−O and C−N bond formations have profited tremendously from the use of hypervalent iodine reagents as oxidants.[5,6] In contrast, C−C bond formation has been limited to SP[2] hybridized vinyl, carbonyl, and aryl groups; none of these methods reported the use of hypervalent iodine reagents.[2c,4] It was recently demonstrated that oxidation of Pd(II) intermediates with aryliodonium salts was much slower than with PhI(OAc)$_2$, which would make C−C

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Scheme 1. Wacker Cyclization and Alkoxyalkynylation Reaction
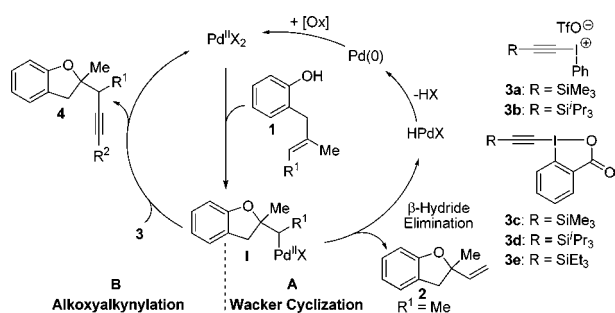
bond formation unable to compete with other side reactions.[8b] Herein, we report a Pd-catalyzed Wacker cyclization–alkynylation domino process using a benziodoxolone-derived reagent **3d** (Scheme 1, B).

Acetylenes have broad utility in organic chemistry, biological chemistry, and material sciences.[9] Furthermore, the direct addition of acetylenes to nonactivated olefins is challenging and has been successful only for strained olefins[10] or using radical methods.[11] The Pd-catalyzed C–C bond formation between a SP^3 and a SP center is also a difficult process, which was successful only in rare cases.[12] Our report constitutes the first example of intramolecular oxyalkynylation of nonactivated alkenes, which represents an important breakthrough in the area of oxidative Pd chemistry. The discovery of the unique superiority of benziodoxolone derived reagents **3c**−**3e** for alkynyl transfer when compared with established alkynyliodonium salts (**3a**, **3b**) constitutes an important advance in the burgeoning field of hypervalent iodine chemistry[13] and opens new perspective for the development of more efficient reagents in Pd-

Table 1. Optimization of the Alkoxyalkynylation Reaction

entry	catalyst	reagent	solvent/additive	yield[a]
1	PdCl$_2$(CH$_3$CN)$_2$	**3a**	Toluene, base[b]	6% (<20%)
2	PdCl$_2$(CH$_3$CN)$_2$	**3c**	Toluene, base[b]	traces (<20%)
3	Pd(TFA)$_2$	**3d**	Toluene, base[b]	19% (73%)
4	Pd(TFA)$_2$	**3d**	CH$_2$Cl$_2$	17% (100%)
5	PdCl$_2$(CH$_3$CN)$_2$	**3d**	CH$_2$Cl$_2$	40% (93%)
6	Pd(hfacac)$_2$	**3d**	CH$_2$Cl$_2$	73% (100%)
7	Pd(hfacac)$_2$	**3c**	CH$_2$Cl$_2$	20% (84%)
8	Pd(hfacac)$_2$	**3e**	CH$_2$Cl$_2$	43%[c] (>90%)
9	Pd(hfacac)$_2$	**3d**	CH$_2$Cl$_2$	71%[c]
10	Pd(hfacac)$_2$	**3d**	CH$_2$Cl$_2$	73%[c,d]

[a] Reaction conditions: 0.069 mmol **1a**, 0.014 mmol catalyst, 0.083 mmol reagent in 5 mL dry solvent under N$_2$ at 23 °C for 12−16 h. Yield was determined via GC-MS. Conversion is given in parentheses. [b] K$_2$CO$_3$ (2 equiv) and 0.20 equiv pyridine were used as base. [c] Isolated yield using 0.40 mmol **1a**, 0.48 mmol **3d** and 0.040 mmol catalyst in 10 mL CH$_2$Cl$_2$. [d] As Entry 9, but using technical solvent under air.

mediated C–C bond formation and other acetylene transfer processes. Indeed, we recently discovered in our group that benziodoxolone derivatives were also unique acetylene-transfer reagents in a completely different process, namely the Au-catalyzed alkynylation of heterocycles.[14]

Alkynyliodonium salts are known as oxidative/electrophilic alkynylation reagents,[13c−f] but they have been used only rarely for the metal-mediated introduction of acetylene groups.[15] Preliminary results using Stoltz' conditions[3g] with phenol **1a** and alkynyliodonium salts **3a** were disappointing, leading mostly to acetylene dimerization and low conversion (Table 1, Entry 1). However, using neutral benziodoxolone reagents **3c** and **3d**, which have been largely ignored as acetylene transfer reagents, a 19% yield of the desired product was obtained with **3d** (Entries 2−3).[16] Bases were not required and CH$_2$Cl$_2$ was the best solvent (Entry 4).[17] At this point, full conversion was obtained, but a nonidentified decomposition pathway consumed the starting material.[18] A catalyst screen (Entries 4−6) identified Pd(hfacac)$_2$[19] as the most efficient Pd source for preventing the decomposition of the substrates (73% yield, Entry 6). To the best of our knowledge, the use of this complex has not been reported yet for oxidative Pd catalysis.

A sterically hindered silyl group is important to obtain good yields, (Entries 6−8), but it is the benziodoxolone

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structure that is essential for success, as the use of alkynyli-odonium salts **3a** or **3b** or simple iodoacetylenes under the optimized conditions were not successful (results not shown). On a 0.40 mmol scale with 10 mol % catalyst, 71% of **4b** was isolated after purification (Entry 9). Using technical grade CH_2Cl_2 in a flask open to air, 73% of product was obtained, demonstrating the tolerance of the reaction to air and moisture (Entry 10). On a 2.4 mmol scale, 68% of product was isolated and 65% of 2-iodobenzoic acid was recovered through basic extraction. This acid can then be recycled to prepare reagent **3d** in 2 steps and 76% overall yield.

The scope of the reaction with phenols was examined next (Table 2, Entries 1−10). A 4-methyl group led to a lower yield (Entry 2) and more electron-rich derivatives could not be used.[20] Apart from this limitation, the reaction displayed good functional group tolerance, including bromo, cyano, nitro and ketone groups (Entries 3−6). The bromo tolerance makes the method orthogonal to Pd(0) chemistry. The reaction was also successful for 5-Br and 6-Br substituted substrates (Entries 7 and 8). Promising preliminary results were obtained for allyl phenol **1i** (Entry 9) and for the formation of 6-membered rings (Entry 10). The former result demonstrates that alkynylation can be efficient even in the presence of a β-hydrogen atom. Although full conversion was observed, no compound was isolated in significant amount beside the desired product and optimization of the reaction conditions was not successful to improve the yield.

As we hypothesized, the limitation of the scope observed with phenols was due to the sensibility of the substrate under oxidative conditions, we thus decided to examine benzoic acid derivatives next (Table 1, Entries 11−15).

Indeed, excellent results were obtained and an electron-donating group on the benzene ring (Entry 12) or a diaryl olefin (Entry 13) were now tolerated in the reaction. Even a trisubstituted olefin could be used (Entry 14). In this case the 1,3 addition product was obtained, probably via isomer-ization of the formed Pd-alkyl intermediate. Formation of a 6-membered ring was also possible in 80% yield (Entry 15). A single example of nitrogen nucleophile gave a useful amount of product, but further control of the chemoselectivity will be needed (Entry 16).

Although aliphatic alcohols could not be used (not shown), aliphatic acids worked well in the reaction and full conver-sion and good yields were obtained after 3 h (Entries 17−20). In this case, the presence of β-hydrogen on the double bond was not deleterious to the yield (Entries 19−20) and even simple commercially available 4-pentenoic acid could be

(17) See Supporting Information for a complete list of tested reaction conditions and catalysts.

(18) Beside the desired product, no low-molecular weight compound was isolated from the reaction mixture. That would indicate that the main pathway for decomposition is polymerization, either via the alkene, or via the aromatic nucleus, for example through hypervalent iodine mediated oxidation.

(19) hfacac = hexafluoroacetonate.

(20) Excepted when stated otherwise, full conversion was observed for all substrates in Table 2. In the case of electron-rich substrates, decomposi-tion was observed and no defined low-molecular weight product could be isolated. We speculate that this class of substrates is not compatible with the oxidative conditions of the reaction.

Table 2. Scope of the Oxyalkynylation Reaction

entry	substrate	product	isolated yield[a]
1	**1a**: R=H	**4b**	71%
2	**1b**: R=4-Me	**4d**	34%
3	**1c**: R=4-Br	**4e**	68%
4	**1d**: R=4-CN	**4f**	76%
5	**1e**: R=4-NO₂	**4g**	72%
6	**1f**: R=4-Ac	**4h**	87%
7	**1g**: R=5-Br	**4i**	66%
8	**1h**: R=6-Br	**4j**	52%
9	**1i**	**4k**	43%[b]
10	**1j**	**4l**	46%[c]
11	**5a**	**6a**	83%
12	**5b**	**6b**	80%
13	**5c**	**6c**	70%
14	**5d**	**6d**	56%
15	**5e**	**6e**	80%
16	**7a**	**8a**: X = NOBn, Y = O / **8b**: X = O, Y = NOBn	69% **8a:8b** = 1.5:1
17	**9a**	**10a**	70%[d]
18	**9b**	**10b**	72%[d]
19	**9c**	**10c**	76%[d]
20	**9d**	**10d**	82%[d]

[a] Reaction conditions: 0.40 mmol substrate, 0.48 mmol reagent and 0.040 mmol Pd(hfacac)₂ in 10 mL CH_2Cl_2 at 23 °C for 12 h. [b] In 10 mL CHCl₃. [c] No full conversion was observed. [d] Reaction time was 3 h.

cyclized in good yield (Entry 20). The obtained γ-lactones bearing an acetylene group are important building blocks for the synthesis of bioactive compounds.[21]

As the oxyalkynylation process involves several bond forming steps, understanding the mechanism is challenging. Nucleophilic attack on alkynyliodonium salts proceeds via β-addition followed by 1,2 shift.[13d] However, when a ^{13}C-label was introduced next to Si in **3d**, no shift was observed (eq 1), eliminating the possibility of this pathway. At least two mechanisms could still be envisaged (Scheme 2): (1) oxidative addition of **3d** to Pd^{II} to form a Pd^{IV} intermediate **II**,[22] followed by oxy-palladation to form **V** and reductive elimination to give **4a** or (2) initial oxy-palladation to give **IV**, either via phenolate complex **III** or directly from **1a**; oxidative reaction with **3d** to form **V** and reductive elimination. Currently, we tend to favor the latter, as oxidation to form a Pd^{IV} from Pd^{II}-alkyl intermediate should be easier, electron-deficient catalysts worked best and the intramolecular oxy-palladation of olefins with Pd^{II} catalysts is well-precedented.[3g] Furthermore, a fast reaction was not observed when mixing the reagent and the catalyst.


(1)
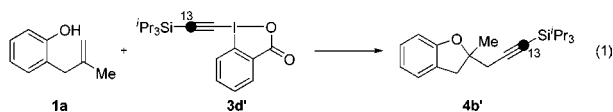
Finally, we think that the basicity of the 2-iodo benzoate formed in the reaction could be important to promote reaction turnover by accelerating proton transfer from **1a** in the oxy-palladation step (conversion of **VI** to **III** or **IV** in Scheme 2). The generation of a basic carboxylate upon reaction is again specific to the benziodoxolone derivative **3d**, and could further contribute to the exceptional performance of this reagent when compared with more often used alkynyliodonium salts.

In summary, we have reported a novel oxyalkynylation reaction of olefins. Our work represents the first example of

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(22) See reference 15d for an example of a Pd^{IV}−acetylene complex.

Scheme 2. Speculative Mechanism
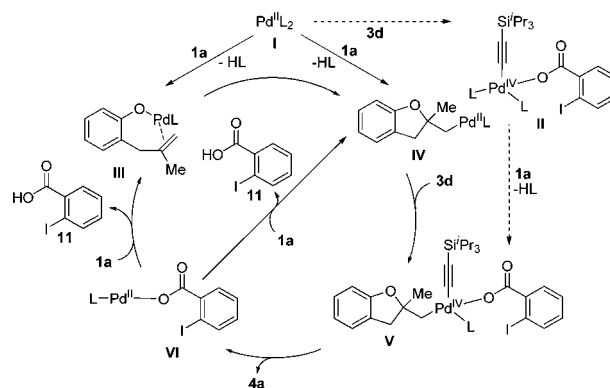
acetylene incorporation to olefins using oxidative Pd chemistry. It is operatively simple and was successful both in the case of phenol and acid derivatives. With phenols, good yields were obtained only for substrates with a geminally disubstituted double bond and electron-donating groups on the benzene ring were not tolerated. With acids, the scope was more general, and good yields were obtained, even for the monosubstituted double bond and in the case of aliphatic substrates. The unprecedented use of benziodoxolone-derived hypervalent iodine was essential for success. Further work on the reaction mechanism, an asymmetric method and the use of hypervalent iodine reagents in other catalytic alkynylation reactions is currently ongoing in our group.

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

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