Synthetic Methods

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Palladium Enolate Umpolung: Cyclative Diacetoxylation of Alkynyl Cyclohexadienones Promoted by a Pd/SPRIX Catalyst**

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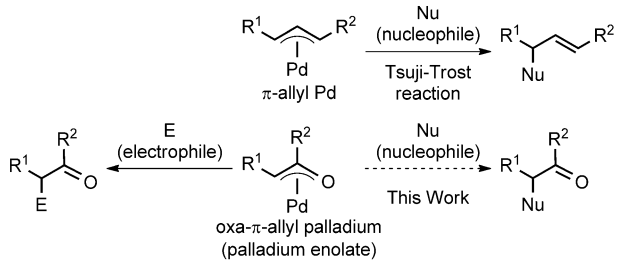
Abstract: *A novel palladium-catalyzed reaction involving an unusual nucleophilic attack on a palladium enolate was developed using a spiro-bis(isoxazoline) (SPRIX) ligand. Treatment of alkynyl cyclohexadienone substrates with a Pd/SPRIX catalyst in acetic acid under an oxygen atmosphere furnished diacetoxylated benzofuranone derivatives in good yields. This cyclative diacetoxylation proceeded enantioselectively in the presence of an optically pure SPRIX ligand.*

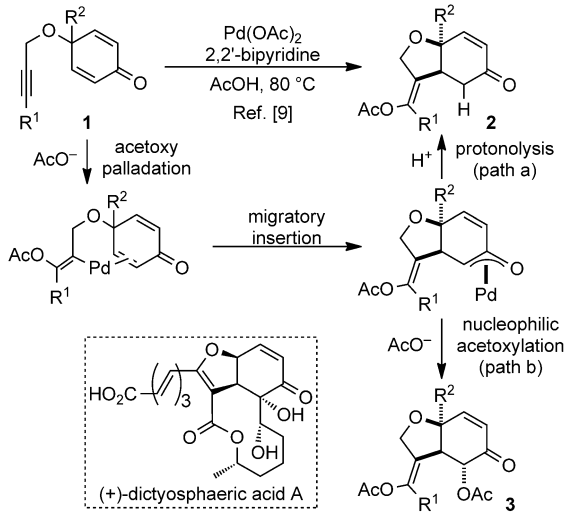
The π-allyl palladium complex is known to react with a wide range of nucleophiles, which is a key step in the palladium-catalyzed allylic substitution referred to as the Tsuji–Trost reaction (Scheme 1).[1] A great number of successful examples



Scheme 1. General reactivity of π-allyl palladium complexes and oxa-π-allyl palladium complexes (palladium enolates).

of the asymmetric Tsuji–Trost reaction have been reported and are extensively applied in organic synthesis.[2] In contrast, palladium enolates, an analogue of π-allyl palladium complexes wherein one carbon atom of the π-allyl ligand is replaced by an oxygen atom, do not exhibit any reactivity toward a nucleophile. Such oxa-π-allyl palladium species commonly react with electrophiles, for example, aldehydes, imines, and enones.[3–6] Nucleophilic interception of the palladium enolate is however promising as a powerful synthetic method of functionalized carbonyl compounds.

So far, we have succeeded in the development of a unique ligand, spiro-bis(isoxazoline), abbreviated as SPRIX, which possesses isoxazoline coordination sites on a rigid spirobackbone.[7] SPRIX has proven to be highly effective in various palladium-catalyzed asymmetric cyclizations, wherein the low σ-donor ability of SPRIX contributes to their promotion.[8] To explore a new enantioselective reaction catalyzed by Pd/SPRIX, we focused on cyclization of the alkynyl cyclohexadienones **1** reported by Harned and co-workers (Scheme 2).[9a,b] This reaction produces benzofuranone derivatives



Scheme 2. Cyclative diacetoxylation of the alkynyl cyclohexadienones **1**.

(**2**) through an initial acetoxypalladation of the alkyne component, a subsequent migratory insertion, and a final protonolysis of the resultant palladium enolate (Scheme 2, path a).[10,11] During the course of the development of its asymmetric version,[9c] we found a substantial amount of the α-acetoxy ketone products **3**. The formation of **3** implied that nucleophilic acetoxylation of the palladium enolate intermediate proceeded instead of the protonolysis (Scheme 2, path b). This sequential reaction would potentially become a useful transformation because the α-oxy benzofuranone core is a ubiquitous structural motif in natural products,[12] for example, (+)-dictyosphaeric acid A.[12a] Herein we disclose cyclative diacetoxylation of **1** by utilizing a Pd/SPRIX catalyst, and the reaciton involves, to our knowledge, the first example of an umpolung nucleophilic attack on a palladium enolate.[13,14]

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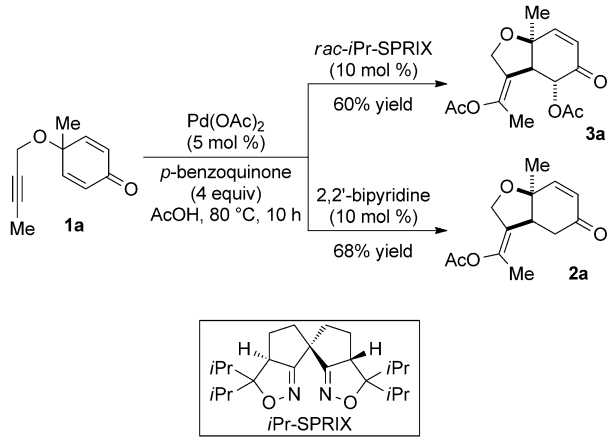


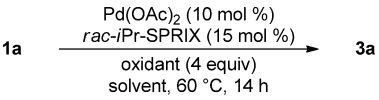
Scheme 3. Initial attempt.

The result of an initial attempt using 4-(but-2-ynyloxy)-4-methylcyclohexa-2,5-dienone (**1a**) in the presence of an oxidant is depicted in Scheme 3. When **1a** was treated with 5 mol% of $Pd(OAc)_2$, 10 mol% of *rac*-*i*Pr-SPRIX, and 4 equivalents of *p*-benzoquinone in AcOH at 80°C for 10 h, **3a** was obtained in 60% yield from the cyclative diacetoxylation. The structure of **3a** was fully characterized by NMR spectroscopy, IR, and HRMS. Upon addition of the 2,2′-bipyridine ligand, employed under Harned's conditions, in place of SPRIX, no umpolung reaction proceeded at all, thus resulting in 68% of protonated product **2a**. SPRIX was found to be essential for this process because no other ligands promoted this unusual nucleophilic acetoxylation of the palladium enolate.[15]

Table 1 shows selected optimization results for the improvement of the chemical yield.[15] Complete consumption of **1a** was observed, even at lower temperature (60°C), to give **3a** in 60% yield (entry 1). The chemical yield was increased to 82% by using a 9:1 mixture of AcOH and toluene as the solvent (entry 2). The ratio of AcOH had an impact on the reaction efficiency. Thus, **3a** was obtained in a somewhat lower 62% yield using a 1:1 mixed solvent, whereas the reaction in a solvent mixture in which toluene was the major component, hardly proceeded (entries 3 and 4). Other oxidants such as $Cu(OAc)_2$, $PhI(OAc)_2$, and $K_2S_2O_8$ were applicable to this cyclative diacetoxylation (entries 5–7). Molecular oxygen and air were also found to serve as the oxidant, albeit sluggishly, to furnish **3a** in 81 and 56% yields, respectively (entries 8 and 9). The reaction under non-oxidative conditions, that is, under an inert atmosphere, produced only 8% of **3a**, and was consistent with a single turnover of the catalyst (entry 10). Based on this result, a Pd^{II} species is believed to be an active catalyst in the present reaction.[16] From an environmental viewpoint, we decided to employ the conditions in entry 8 for further investigation.

Next, the substrate scope of this cyclative diacetoxylation was examined with a variety of alkynyl cyclohexadienones (**1**; Table 2). The substrate **1b**, having a hexynyl chain, showed a high reactivity, similar to that of **1a**, to give **3b** in 74% yield (entry 2). Although a slight deleterious effect was detected for a bulky substituent at the alkyne, **3c** with an *i*Pr group and **3d** with a *t*Bu group were isolated in 68 and 64% yields, respectively (entries 3 and 4). Aryl acetylene was also tolerant to this reaction, thus leading to 72% of **3e** (entry 5). The substrate **1f**, bearing a benzyl-protected hydroxymethyl group at the alkyne terminus, was converted into the

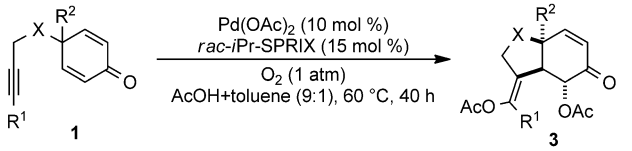
Table 1: Optimization of reaction conditions.[a]



Entry	Solvent	Oxidant	Yield [%][b]
1	AcOH	*p*-benzoquinone	60
2	AcOH + toluene (9:1)	*p*-benzoquinone	82
3	AcOH + toluene (1:1)	*p*-benzoquinone	62
4	AcOH + toluene (1:9)	*p*-benzoquinone	trace
5	AcOH + toluene (9:1)	$Cu(OAc)_2$	35
6	AcOH + toluene (9:1)	$PhI(OAc)_2$	40
7	AcOH + toluene (9:1)	$K_2S_2O_8$	80
8	AcOH + toluene (9:1)	O_2[c]	81[d]
9	AcOH + toluene (9:1)	air[e]	56[d]
10	AcOH + toluene (9:1)	none[f]	8[d]

[a] All reactions were carried out in the presence of 10 mol% of $Pd(OAc)_2$, 15 mol% of *rac*-*i*Pr-SPRIX, and 4 equiv of oxidant in solvent (0.1 M) for 14 h under an O_2 atmosphere. [b] Yield of isolated product. [c] Under an O_2 atmosphere. [d] 40 h. [e] In air. [f] Under an N_2 atmosphere.

Table 2: Cyclative diacetoxylation of **1**.[a]

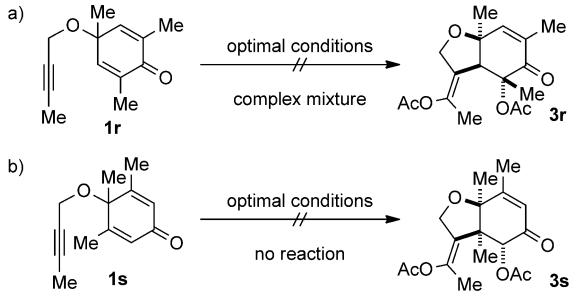


Entry	Substrate	R^1	R^2	X	Product	Yield [%][b]
1	**1a**	Me	Me	O	**3a**	81
2	**1b**	Pr	Me	O	**3b**	74
3	**1c**	*i*Pr	Me	O	**3c**	68
4	**1d**	*t*Bu	Me	O	**3d**	64
5	**1e**	Ph	Me	O	**3e**	72
6	**1f**	$BnOCH_2$	Me	O	**3f**	71
7	**1g**	H	Me	O	**3g**	–[c]
8	**1h**	Me	Et	O	**3h**	75
9	**1i**	Me	*i*Pr	O	**3i**	76
10	**1j**	Me	Ph	O	**3j**	84
11	**1k**	Me	4-BrC_6H_4	O	**3k**	69
12	**1l**	Me	$MeO(CH_2)_2$	O	**3l**	73
13	**1m**	Me	$Br(CH_2)_2$	O	**3m**	67
14	**1n**	Me	$Nphth(CH_2)_2$[d]	O	**3n**	70
15	**1o**	Ph	Ph	O	**3o**	71
16	**1p**	Me	Me	NTs	**3p**	64
17	**1q**	Me	Me	CH_2	**3q**	79[e]
18[f]	**1a**	Me	Me	O	**3a′**[g]	52[h]

[a] All reactions were carried out in the presence of 10 mol% of $Pd(OAc)_2$ and 15 mol% of *i*Pr-SPRIX in AcOH + toluene (9:1, 0.1 M) for 40 h under an O_2 atmosphere. [b] Yield of isolated product. [c] Complex mixture. [d] Nphth is phthalimidyl. [e] Isolated as a 3:1 mixture. See the Supporting Information. [f] $EtCO_2H$ + toluene (9:1) was used. [g] $EtCO_2$ groups were introduced into the product instead of the AcO group. [h] Isolated as a 5:1 mixture. See the Supporting Information.

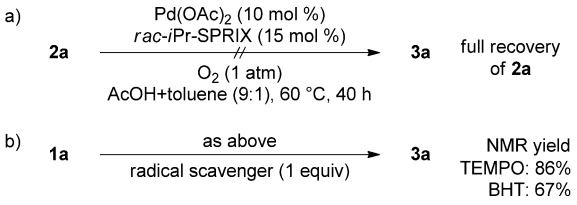
benzofuranone **3f** in 71% yield and no regioisomeric products were observed (entry 6).[9c,11c] However, the terminal alkyne substrate **1g** was presumably too reactive to allow the formation of the desired product (entry 7). When R^2 at the tetrasubstituted carbon atom was changed from Me to Et (**1h**), *i*Pr (**1i**), or Ph (**1j**), the reactions proceeded smoothly to afford the corresponding α-acetoxy ketones in good yields (entries 8–10). The aryl bromide moiety, known to be reactive in palladium-catalyzed cross-couplings, remained intact throughout this catalysis (entry 11). Other functional groups such as methyl ether (**1l**), bromoalkyl (**1m**), and phthalimide (**1n**) did not interfere with the umpolung acetoxylation of the palladium enolate (entries 12–14). The product **3o**, in which a Ph group was introduced at both the alkyne tether and the cyclohexadienone skeleton, was also obtained in 71% yield (entry 15). Single-crystal X-ray analysis of **3o** unambiguously established its structure which consists of a 3-methylene-5-oxo-hexahydrobenzofuran and two AcO groups.[15] The relative configuration and the geometry at the olefinic moiety were in good agreement with those determined spectroscopically. No detrimental effects were observed even upon alteration of the oxygen linker. The products **3p** with a sulfonamide linker and **3q** with a methylene linker were obtained in reasonable yields (entries 16 and 17). When propanoic acid was used in place of AcOH, the propanoate group was incorporated at the α-position of the carbonyl as well as on the exocyclic double bond (entry 18).

In contrast, substituents on the cyclohexadienone core exerted a considerable influence on the process. A complex mixture was generated in the reaction of **1r**, bearing Me groups adjacent to the carbonyl, thus implying instability of the resulting palladium enolate intermediate (Scheme 4a). No reaction took place for the β-methylated **1s**, thus suggesting that the initial chelation step and/or the migratory insertion step were susceptible to steric hindrance (Scheme 4b).



Scheme 4. Effect of substituents on the cyclohexadienone core on the cyclative diacetoxylation.

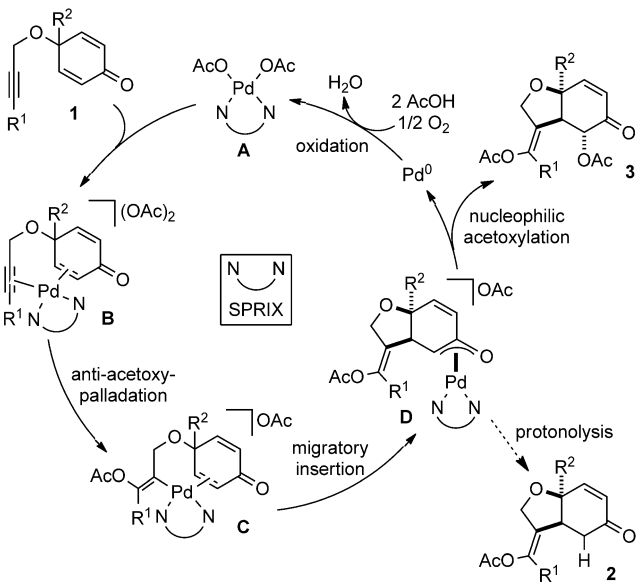
Preliminary mechanistic investigations were then carried out because oxidation of the carbonyl α-carbon atom (Rubottom oxidation) might be regarded as an alternative pathway for the formation of **3**. When **2a** was subjected to the optimum reaction conditions, no conversion was observed and resulted in the full recovery of the substrate (Scheme 5a). Since a radical mechanism was also proposed for the



Scheme 5. Control experiments.

palladium-catalyzed Rubottom oxidation,[17] we evaluated the effect of a radical scavenger on our system. The reaction of **1a** in the presence of 1 equivalent of 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) or 2,6-di-*tert*-butyl-*p*-cresol (BHT) provided **3a** without significant loss of efficiency (Scheme 5b). Furthermore, the groups of El-Qisairi and Ritter independently demonstrated that a bimetallic palladium complex worked as the catalytically active species in the palladium-catalyzed Rubottom oxidation.[18] To gain insight into the active catalyst, we performed kinetic studies on the concentration of the catalyst. The initial reaction rate displayed a linear correlation with the catalyst loading.[15] These results clearly indicate little possibility of the direct oxidation pathway by way of radical intermediates or promotion by a bimetallic palladium complex.

A plausible catalytic cycle is illustrated in Scheme 6. Initially, the coordination of **1** to the Pd/SPRIX catalyst **A** gives the intermediate **B**. The following *anti* acetoxypalladation of the activated carbon–carbon triple bond leads to the vinyl palladium species **C**, which converts into the palladium enolate **D** by migratory insertion of the intramolecular olefin. In the presence of the SPRIX ligand, the nucleophilic acetoxylation of **D** occurs over the protonolysis to afford product **3** and Pd^0, the latter of which is oxidized by the action of O_2 to regenerate **A**. The AcO group at the α-position to the carbonyl is located *trans* to the fused furan ring. We therefore



Scheme 6. Plausible catalytic cycle.

suppose that the acetate anion attacks the enolate from the backside of the palladium in a similar manner to the traditional Tsuji–Trost reaction.

Noteworthy is that this cyclative diacetoxylation turned out to proceed enantioselectively by using optically pure SPRIX. Thus, when reactions of **1a**, **1i**, and **1j** were conducted with (*M*,*S*,*S*)-*i*Pr-SPRIX under otherwise identical reaction conditions, the desired products **3a**, **3i**, and **3j** were obtained with 58, 71, and 82% *ee*, respectively.[19]

In summary, we have developed a palladium-catalyzed cyclative diacetoxylation of alkynyl cyclohexadienones (**1**), which proceeds using O_2 gas as a green oxidant. A sequence of alkyne acetoxylation, intramolecular cyclization, and the umpolung acetoxylation produces the densely functionalized benzofuranone derivatives **3**. The use of a low σ-donor SPRIX ligand is indispensable for the unusual nucleophilic attack on the palladium enolate. Additional investigations into the reaction mechanism and the tolerance of other nucleophiles are now in progress.

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[15] For details, see the Supporting Information.
[16] When **1a** was treated with a stoichiometric amount of a Pd(OAc)$_2$(*i*Pr-SPRIX) complex in the absence of any oxidants, **3a**

was obtained in 72% yield. This result evidently rules out the possibility of the generation of a Pd^{IV} species in the catalytic reaction. Hence, the present cyclative diacetoxylation involves the Pd^{0}/Pd^{II} redox couple.

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[19] A bulky substituent at the alkyne terminal provided a negative effect on the enantioselectivity: Under identical reaction conditions, 13 and 10% *ee* were observed for **3c** and **3d**, respectively.

