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Palladium-catalyzed highly diastereoselective cascade dihalogenation of alkyne-tethered cyclohexadienones *via* Umpolung of palladium enolate†

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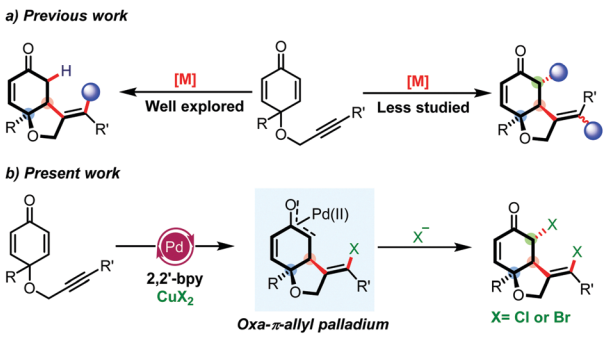
Herein, we report a highly diastereo- and regioselective dihalogenation of alkyne-tethered cyclohexadienones for the synthesis of *cis*-hydrobenzofurans. One carbon–carbon and two carbon–halogen bonds were formed in an efficient manner and three contiguous stereocenters were generated. The reaction proceeds through *cis*-halopalladation, migratory insertion followed by a nucleophilic attack of a halide anion on a palladium enolate.

cis-Hydrobenzofurans belong to a class of privileged structural motifs that are present in various natural products and exhibit a wide range of biological activities including antimicrobial, anti-inflammatory and antiviral activities.[1] Consequently, tremendous efforts have been made for the construction of these motifs in a straightforward and efficient synthetic manner. In this context, functionalization of cyclohexadienones *via* cascade cyclization represents a powerful strategy and has captured a lot of attention in the past few years.[2] In particular, alkyne-tethered cyclohexadienones, which are easily accessible by the oxidative dearomatization of phenols, were utilized in a variety of Rh,[3] Pd,[4] Ni[5] and Cu[6] catalyzed reactions (Scheme 1a). Majority of these reports involve formation of mono-functionalized *cis*-hydrobenzofuran derivatives leaving the cyclohexanone moiety unfunctionalized. In sharp contrast, only a single report exists depicting the synthesis of di-functionalized benzofurans by Sasai and co-workers.[4b] They illustrated a diacetoxylative carbocyclization under Pd(II) catalysis in AcOH. Apart from this elegant work, nucleophilic interception of oxa-π-allyl palladium species is an uncharted territory in spite of its ability to install a variety of functional groups at the α-carbon of the carbonyl group.

Discovery of transition metal catalyzed cross coupling reactions has made alkenyl halide a major workhorse and valuable building block.[7] Therefore, several new strategies have been developed to meet its high demand.[8] Among these transformations, halopalladation of alkynes was found to be rather appealing as it leads to the construction of C–C and C–halogen bonds in a single step, often with high stereo- and regioselectivities.[9] Vinyl-σ-palladium(II) species, formed by the halopalladation of alkynes, can be trapped with a variety of electrophiles and also by nucleophiles under oxidative conditions.[10] Despite the elegant advances in both the Pd-catalyzed cascade cyclizations and halopalladation chemistry, dihalogenation of alkyne-tethered cyclohexadienones still remains unexplored. In view of the wide applicability of vinyl-halides and α-halo-carbonyl derivatives in organic synthesis and our recent studies on cyclohexadienones,[11] we envisioned that the oxa-π-allyl palladium(II) intermediate generated by the cascade halopalladation/alkene insertion could be trapped with a halide anion leading to difunctionalized *cis*-hydrobenzofurans (Scheme 1b). Initial challenges associated with the envisioned protocol include the competing facile β-hydride elimination or protonation of the oxa-π-allyl palladium enolate. An additional challenge would be to control the stereoselectivity at the α-carbonyl centre by suppressing the epimerization of palladium-enolate.



Scheme 1 Overview of the work.

We commenced our investigation of the cascade halopalladation/conjugate addition by choosing **1a** as a model substrate. On treatment of **1a** with 10 mol% of $Pd(OAc)_2$ and 2 equiv. of $CuCl_2$ at 50 °C, dichlorinated product **2a** was observed, albeit in a lower yield of 18% (see the ESI† for the full optimization table).

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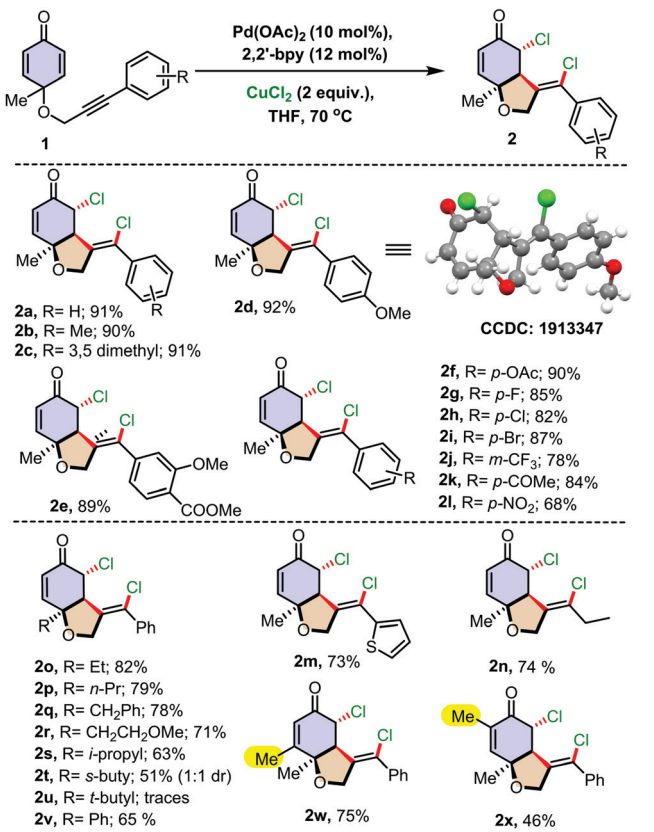
After careful screening of the various reaction parameters like ligands, solvents, temperature and Pd-catalysts, we were delighted to observe the best yield of 93% using 10 mol% of $Pa(OAc)_2$, 12 mol% of 2-2′-bpy along with 2 equiv. of $CuCl_2$, at 70 °C in THF. Nitrogen-containing ligands such as 2,2′-bpy and 1,10-phenanthroline were found to be advantageous for the dichlorination, probably because of their ability to accelerate the intramolecular migratory insertion and at the same time to suppress the undesired β-hydride elimination (see the ESI†). Remarkably, the whole sequence consists of efficient formation of one carbon–carbon and two carbon–halogen bonds with three contiguous stereocenters. Pleasingly, only one diastereomer was observed in the crude ^{1}H NMR spectrum of the reaction mixture. The stereospecific (*E*)-configuration of the exocyclic double bond supports the expected *cis*-chloropalladation. The chloride at the α-carbon of the carbonyl group was found to be *trans* to the fused furan ring.

With the optimized reaction conditions in hand, we started to probe the versatility of the developed protocol against a variety of alkyne-tethered cylcohexadienones **1** (Table 1). We were pleased to find that electron-donating and electron-withdrawing groups, as well as halogen substituents like chloro and bromo, which are sensitive to oxidative addition, were compatible on the aromatic ring of the alkyne, affording the corresponding products in good to excellent yields (**2b-2l**, 68–91%). Heteroaryl- and aliphatic-alkyne-tethered cyclohexadienones were also found to be amenable substrates furnishing the dihalogenated products (**2m** and **2n**, 73 and 74%). The single crystal X-ray diffraction analysis of **2d**, **2f**, **2k** and **2l** unambiguously confirmed the regio- and diastereoselectivity of the dichlorinated products **2**. Next, we screened various substituents at the quaternary center of the cyclohexadienone to understand the steric effect on the cascade dichlorination (**2o-2v**). While primary alky groups gave products **2o-2r** in comparable yields (71–82%), the yields decreased significantly in the case of secondary alkyl groups (**2s** and **2t**, 63 and 51%) and a *tert*-butyl group led to the product only in traces, indicating a prominent steric effect of the substituent on the reactivity. This can be due to the Umpolung attack of chloride ions from the opposite face, on the oxa-π-allyl palladium intermediate and the chloride nucleophile approaches from the same face of the substituent on the quaternary center. Subsequently, 3- and 2-methyl substituted cyclohexadienones **1w** and **1x** were examined to study the regioselectivity of the cascade cyclization and we were pleased to see that the migratory insertion takes place selectively with the less substituted double bond of cyclohexadienones affording **2w** and **2x** as single regioisomers in 75% and 46% respectively. Unfortunately, *N*-tethered cyclohexadienones were not found to be amenable substrates for the transformation.

Table 1 Substrate scope of cascade dichlorination[a]

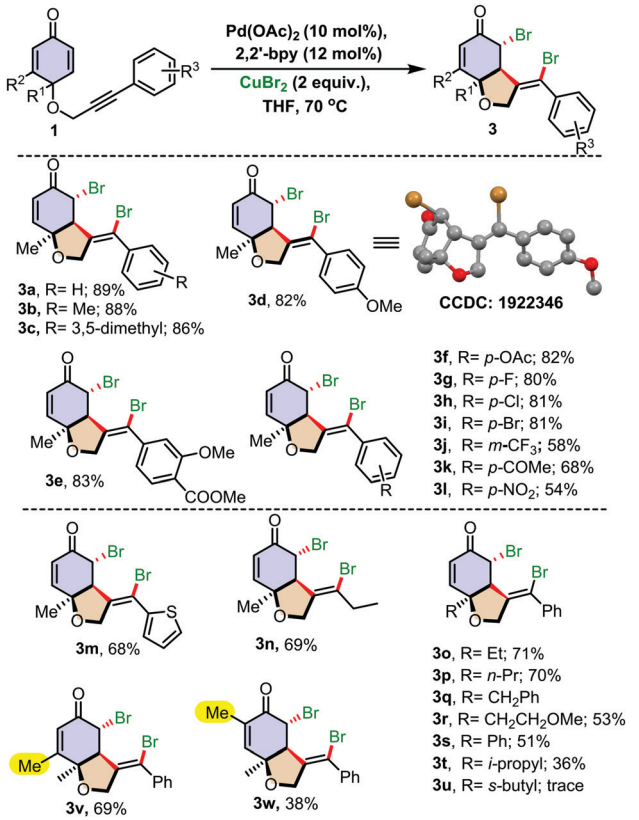


[a] Reaction conditions: **1** (0.2 mmol), $CuCl_2$ (2 equiv.), $Pd(OAc)_2$ (10 mol%), 2,2′-bpy (12 mol%), THF (2 mL). 70 °C, 16 h, under nitrogen.

The superior reactivity of alkenyl bromides in metal-catalyzed cross-coupling reactions due to their facile oxidative addition and the importance of α-bromo carbonyl compounds encouraged us to study the cascade dibromination of alkyne-tethered cyclohexadienones. With this in mind, we investigated the reaction using 2 equiv. of $CuBr_2$ for bromopalladation and also as the bromide nucleophile, and we were delighted that under our standard conditions **1a** afforded the corresponding dibrominated *cis*-hydrobenzofuran **3a** in 89% yield (Table 2). The substrate scope for the dibromination was also found to be wide as different aryl-, thiophenyl- and aliphatic-alkyne tethered cyclohexadienones **1** reacted smoothly to form the corresponding dibromo-hydrobenzofurans **3b-3n** in good to excellent yields (54–89%). The structure and regio- and diastereoselectivity of the dibrominated products were also similar to that of dichlorinated products as confirmed by the single-crystal X-ray diffraction analysis of **3b**, **3d** and **3f** (see the ESI†). Of particular note is the effect of substituents at the quaternary center on the dibromination. Primary alkyl and phenyl substituents led to the corresponding products **3o-3s** in 51–71%. However, in the case of the i-propyl group, the reaction did not go to completion even after prolonged reaction time (**3t**, 45%). Furthermore, *sec*-butyl derived alkyne **1t**, which gave the dichlorination product **2t** in 51% yield, failed to give any dibromination. This could be due to the increased steric hindrance in the case of bulky bromide, exerted by the substituent at the quaternary center. Similar to dichlorination, dibromination also was highly regio-selective in the case of unsymmetrical cyclohexadienones (**3v** and **3w** in 69% and 38%).

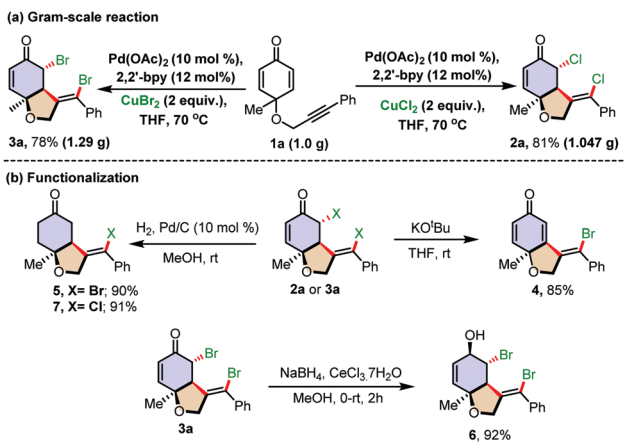
Next, we carried out gram scale reactions of **1a** under the optimized reaction conditions to isolate 1.05 g (81%) of **2a** and 1.29 g (78%) of **3a** (Scheme 2a). The synthetic utility of the dihalogenation products was illustrated by converting them into other useful products. Upon treatment of **3a** with a strong

Table 2 Substrate scope of cascade dibromination[a]



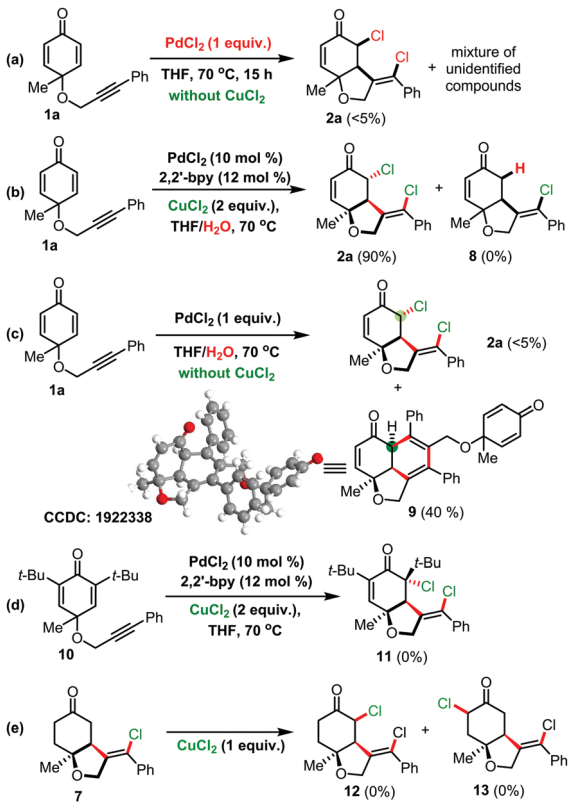
[a] Reaction conditions: 1 (0.2 mmol), $CuBr_2$ (2 equiv.), $Pd(OAc)_2$ (10 mol%), 2,2′-bpy (12 mol%), THF (2 mL). 70 °C, 16 h, under nitrogen.

base like KO*t*Bu at room temperature cyclohexadienone-fused hydro-furan **4** was isolated in 85% (Scheme 2b). Interestingly, under catalytic hydrogenation conditions, both the cyclohexenone double bond and α-halogen were selectively reduced leaving the *exo*-olefin untouched furnishing **5** and **7** in excellent yields. Selective reduction of the carbonyl group under Luche reaction conditions ($NaBH_4$, $CeCl_3{\cdot}7H_2O$ in MeOH at rt) resulted in alcohol **6** as a single diastereomer in 92%.

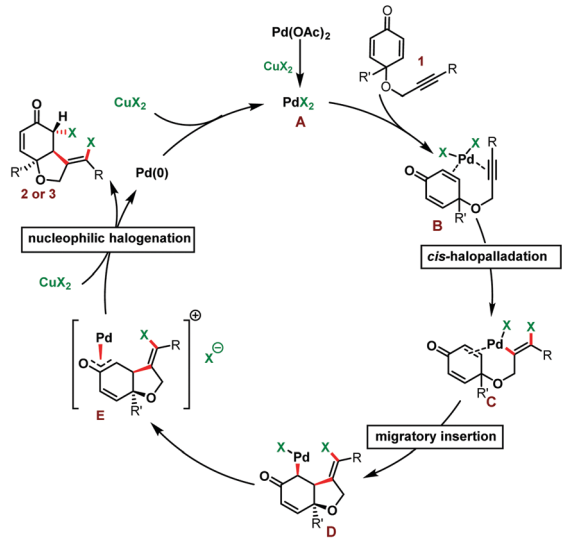


Scheme 2 Gram-scale synthesis and functionalization.

The (*E*)-geometry of the *exo*-olefin and the stereochemistry at the α-position of the carbonyl group provided crucial information about the *cis*-halopalladation pathway. In order to gain more insights into the reaction mechanism, control studies were carried out. Reaction of **1a** with stoichiometric amounts of $PdCl_2$ in the absence of $CuCl_2$ led to a complex mixture and **2a** was observed in <5%, indicating the essential role of $CuCl_2$ as the chloride source (Scheme 3a). This also sheds light on the operative mechanism and a Pd(II)/Pd(0) mechanism involving reductive elimination can be ruled out. Furthermore, to understand the nature of the oxa-π-allyl palladium species, the reaction was carried out in the presence of 8 equiv. H_2O. Remarkably, **2a** was formed exclusively and no protonation was observed, illustrating the Umpolung behavior of the palladium enolate (Scheme 3b). When the stoichiometric control experiment was done in a 7 : 1 THF/H_2O mixture, interestingly a fused tricycle **9** was isolated in 40% (Scheme 3c). Notably, the stereochemistry at the α-carbon of **9** was opposite (*cis* to the fused furan ring) to that of dihalogenation products **2** (*trans* to the furan ring). Sluggish reactivity of cyclohexadienone **10** having bulky *t*-butyl substituents at the 2,6-positions also supports the back face attack of a halide nucleophile on the palladium enolate, similar to the Tsuji–Trost reaction (Scheme 3d).[12] To exclude the possibility of α-chlorination directly with $CuCl_2$ as the Cl_2 source, **7** was treated with 1 equiv. of $CuCl_2$ and no reaction was observed (Scheme 3e, see the ESI† for more details).[13] Finally, addition of a radical scavenger such as (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) did not hamper the reaction, suggesting the absence of radical intermediates.



Scheme 3 Mechanistic studies.



Scheme 4 Proposed mechanism.

On the basis of our mechanistic studies, a plausible mechanism for the Pd-catalyzed dihalogenation of cyclohexadienones is depicted (Scheme 4). Initial coordination of Pd(II)-salt with the alkyne and alkene units of **1** forms intermediate B. Regioselective *cis*-halopalladation of the alkyne would lead to the formation of vinylpalladium(II) species C. Intramolecular *syn*-migratory insertion with the less-substituted double bond would form the palladium-enolate D. Nucleophilic attack of a halide ion on rather electrophilic oxa-π-allyl intermediate E from the back side affords **2** and Pd(0). Re-oxidation of Pd(0) with $CuCl_2$ generates Pd(II)-salt and completes the catalytic cycle.

In conclusion, we have developed a widely applicable Pd-catalyzed cascade dihalogenation of alkyne-tethered cyclohexadienones using CuX_2 as the halide source. The protocol was highly regio- and diastereoselective affording densely functionalized *cis*-hydrobenzofuranone derivatives with three stereocenters. Key control experiments and mechanistic studies revealed the involvement of an unusual electrophilic palladium enolate illustrating Umpolung behaviour. The practical utility of cascade cyclization has been further demonstrated with the gram scale reaction and further functionalization of these derivatives into other useful compounds.

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Conflicts of interest

There are no conflicts to declare.

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