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Tandem Chloropalladation/Cyclization and Dearomative Cyclization toward Functionalized Tricyclic Bridged [3.2.1] Skeleton Compounds

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Supporting Information

ABSTRACT: A palladium-catalyzed tandem reaction is reported that involves chloropalladation/cyclization and dearomative cyclization to construct a tricyclic bridged [3.2.1] carbocyclic-skeleton and oxa- and aza-skeletons. In this domino process, a level of ring strain and other competitive reactions, i.e., protonolysis, β-hydride elimination, and chlorination of the C−Pd bond, were suppressed to the lowest level under mild reaction conditions.

A practical and efficient strategy for construction of bridged skeletons plays an important role in the synthesis of numerous families of natural products and biological molecules that possess a broad range of significant biological activities and potential medicinal prospects.[1] Molecules containing a bridged [3.2.1] carbocyclic skeleton are particularly interesting because of their anti-inflammatory,[2] anticancer,[3] anticonvulsant,[4] antibiotic,[5] and other bioactivities (Figure 1).[6] Recent research has

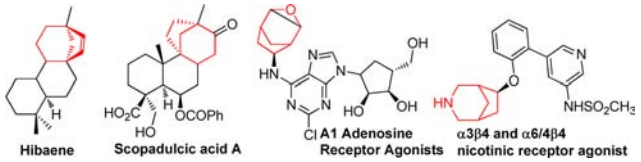
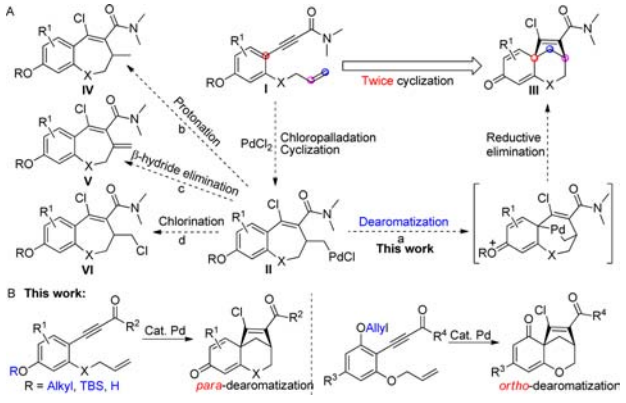


Figure 1. Selected natural products and biological molecules incorporating a bridged [3.2.1] skeleton moiety.

shown that some new bridged [3.2.1] oxa- and aza-skeleton compounds also exhibit interesting biological activities[7] (Figure 1) that justify novel methods to prepare their analogues in recent years.[8] However, because many current synthetic examples often need multiple steps to build bridged [3.2.1] skeletons, a straightforward and economical method is more attractive via tandem cyclizations in one pot from a chain-shaped substrate. Herein, we report a unique method for building a tricyclic bridged [3.2.1] skeleton from an enyne substrate via a Pd-catalyzed tandem chloropalladation/cyclization and dearomative cyclization (Scheme 1B). This method is general for the construction of functionalized tricyclic bridged [3.2.1] carbocyclic skeletons and [3.2.1] oxa- and aza-skeletons with versatile reactivity that may be useful for the synthesis of diverse compounds and for the discovery of new bioactive compounds with valuable impacts.

Scheme 1. Pd-Catalyzed Tandem Dearomative Cyclization and Its Challenges



As an efficient and important synthetic approach in organic synthesis, halopalladation has frequently been used in coupling reactions to form carbon−halogen bonds that facilitate further diverse functionalization,[9] and dearomative cyclization facilitates the synthesis of spirocyclic skeleton compounds.[10] With our continued interest in Pd-catalyzed tandem reactions,[11] we proposed that a functionalized tricyclic bridged [3.2.1] skeleton could be constructed by using an enyne (**I**) via a Pd-catalyzed tandem process[12] involving chloropalladation[13] /cyclization and dearomative cyclization (Scheme 1A(a)). As depicted in Scheme 1A, traditional chloropalladation of alkyne following the intramolecular coupling of C=C double bond would afford cyclized intermediate **II**, which might be quenched by protonolysis of the C−Pd bond to give compound **IV** (path

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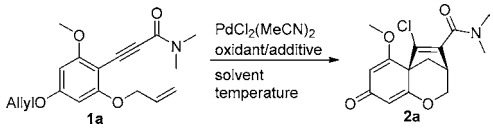
b).[14] In addition, intermediate **II** would also readily undergo β-hydride elimination directly to afford diene **V** through a $Pd^{II/0}$ catalytic cycle[15] (path c) and undergo chlorination to yield chloride **VI** through a $Pd^{IV/II}$ catalytic cycle[13c,f] (path d). If intermediate **II** was to undergo dearomative cyclization to afford bridged [3.2.1] skeleton compound **III** (path a), a level of ring strain and other competitive reactions (path b, c, and d) would be suppressed. Therefore, it is challenging work to build a bridged [3.2.1] skeleton via this synthetic strategy (Scheme 1A(a)) under Pd-catalyzed conditions.

Initial investigation showed that the phenolic hydroxyl group (Scheme 1B) protected by an allyl group was essential for selective *ortho*- or *para*-dearomation, and catalyst screening showed that $PdCl_2(MeCN)_2$ was the optimal catalyst for this Pd-catalyzed tandem dearomative cyclization (see Supporting Information). Therefore, the enyne (**1a**, Table 1) was chosen as a representative substrate for a systematic investigation of this Pd-catalyzed tandem dearomative cyclization by testing various oxidants, solvents, and temperatures in the presence of $PdCl_2(MeCN)_2$.

Table 1. Optimization of Tandem Dearomative Cyclization Oriented by Allyl Group[a]



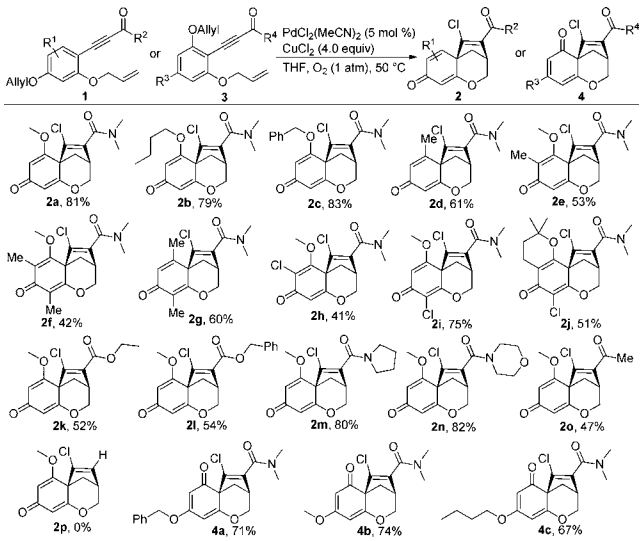
entry	oxidant	solvent	yield (%)[b]
1[c,f]	$CuCl_2$	MeCN	0
2[c,f]	$CuCl_2$	DCM	41
3[c,f]	$CuCl_2$	toluene	26
4[c,f]	$CuCl_2$	THF	54
5[c,e,f]	$PhI(OAc)_2$	THF	0
6[c,e,f]	BQ	THF	0
7[c,e,f]	Oxane	THF	0
8[c,e,f]	O_2	THF	0
9[c,f]	$CuCl_2$	THF	60
10[d,g]	$CuCl_2$	THF	72
11[d,g]	3.0 equiv of $CuCl_2$	THF	77
12[d,g]	4.0 equiv of $CuCl_2$	THF	81
13[d,g]	6.0 equiv of $CuCl_2$	THF	74

[a]**1a** (0.3 mmol), $PdCl_2(MeCN)_2$ (5 mol %), oxidant (2.0 equiv), solvent (5 mL). [b]Isolated yield. [c]1 atm of air. [d]1 atm of O_2. [e]4.0 equiv of LiCl were used. [f]rt. [g]50 °C. rt = room temperature. BQ = 1,4-benzoquinone.

When the reaction was carried out in MeCN with 2.0 equiv of $CuCl_2$ as an oxidant at room temperature, no desired tricyclic compound **2a** was gained (Table 1, entry 1). Further solvent screening at room temperature showed that the reaction occurred more effectively in THF than in dichloromethane and toluene, with a 54% yield of desired product **2a** (entries 2−4). Oxidants were then examined resulting in the conclusion $CuCl_2$ was effective but not $PhI(OAc)_2$, BQ, Oxane, or O_2 alone (entries 5−8). Raising the temperature to 50 °C slightly increased the yield of **2a** (60%, entry 9); However, 2.0 equiv of $CuCl_2$ at 1 atm of O_2 resulted in a 72% yield, implying that $CuCl_2$ activity was improved when assisted by O_2 (entry 10). By increasing the amount of $CuCl_2$ to 4.0 equiv, the yield of **2a** was further improved to 81% (entry 12, optimal condition). Further increasing the amount of $CuCl_2$ to 6.0 equiv decreased the yield of **2a** to 74% (entry 13), and the amount of corresponding chloridized product **VI** (Scheme 1A) was increased noticeably according to UPLC-MS monitoring.

The scopes of this tandem dearomative cyclization were then investigated under the optimal conditions (Scheme 2). For the *ortho*-electron-donating group (R^1), substituted aryl alkynamide derivatives were effective for this reaction, and the corresponding bridged [3.2.1] oxa-skeleton compounds were obtained in moderate to good yields (**2a**−**2d**). This catalytic system was also efficient for multisubstituted substrates to generate the desired compounds (**2e**−**2j**). It was notable that a bicyclic substrate (**1j**) could be successfully converted into the corresponding product **2j** in 51% yield. Other alkynamides were also applicable to synthesize the anticipated compounds with good yields (**2m** and **2n**). It was further revealed that the alkynoates and alkynone gave the corresponding products, respectively (**2k**, **2l**, and **2o**), but that a terminal alkyne did not (**2p**). In fact, the heavily functionalized structure has somewhat limited the application scopes of this tandem reaction. When an allyl group was introduced on the *ortho* hydroxyl group, this Pd-catalyzed tandem dearomative cyclization proceeded successfully to give alternatively 6-carbonyl bridged [3.2.1] oxa-skeleton compounds with good yields when the *para* hydroxyl group was protected by a benzyl, butyl, or methyl group (**4a**−**4c**).

Scheme 2. Palladium-Catalyzed *Para*- and *Ortho*-dearomatization To Build 8- or 6-Carbonyl Bridged [3.2.1] Oxa-skeleton[a]



[a]**1** or **3** (0.3 mmol), $PdCl_2(MeCN)_2$ (5 mol %), $CuCl_2$ (4.0 equiv), THF (5 mL), 50 °C, 1 atm of O_2. Isolated yield.

Other protecting groups on the hydroxyl were investigated as well, and the results are summarized in Scheme 3. Hydroxyl on the *para*-position of the alkynyl protected by methyl, ethyl, benzyl, *tert*-butyldimethylsilyl (TBS), or H instead of an allyl group could also give corresponding *para*-dearomative products (**2a**, **2q**, **2c**, and **2d**) in moderate to good yields. In particular, when the *ortho*- and *para*-positions of an alkynamide included the same alkoxyl group, only *para*-dearomatization was favored (**2a**, **2c**, **2q**, and **2r**). The structure of the corresponding product **2c** was confirmed by X-ray crystal structure analysis. Increasing the spatial hindrance of the carbon−carbon double bond resulted in a significantly reduced yield (**2s** and **2t**).

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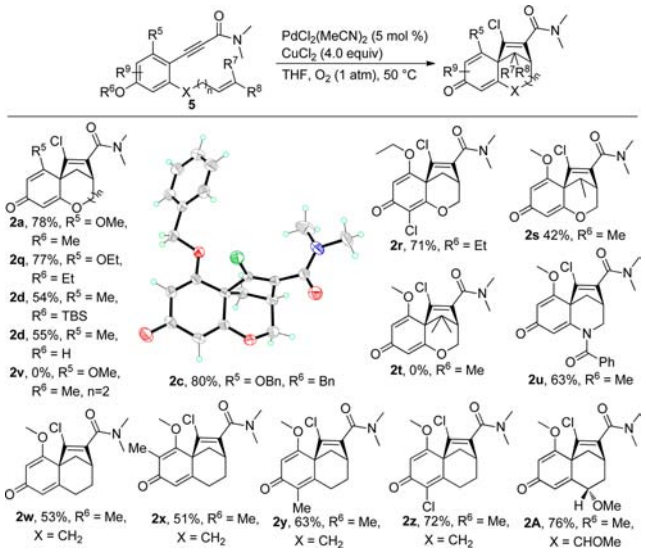
Scheme 3. Investigation on Protecting Group of Hydroxyl and Construction of [3.2.1] Aza- and Carbocyclic Skeletons[a]

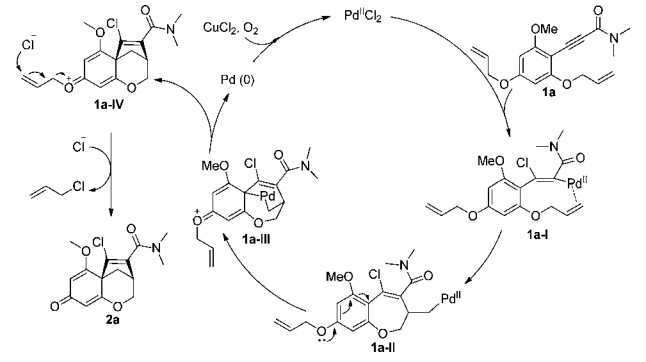


[a]**5** (0.3 mmol), $PdCl_2(MeCN)_2$ (5 mol %), $CuCl_2$ (4.0 equiv), THF (5 mL), 50 °C, 1 atm of O_2. Isolated yield. TBS = *tert*-butyldimethylsilyl.

Unfortunately, this method was not adaptive for further construction of tricyclic bridged [4.2.1] oxa-skeletons (**2v**). To extend the scope of this reaction, an 8-carbonyl bridged [3.2.1] aza-skeleton compound and carbocyclic skeleton compounds were investigated. Aza-skeleton (**2u**) and carbocyclic skeleton compounds (**2w**–**2z** and **2A**) were obtained from corresponding enyne substrates,[16] respectively, via this Pd-catalyzed tandem dearomative cyclization.

A proposed mechanism of the Pd-catalyzed tandem dearomative cyclization is depicted in Scheme 4. *Trans*-

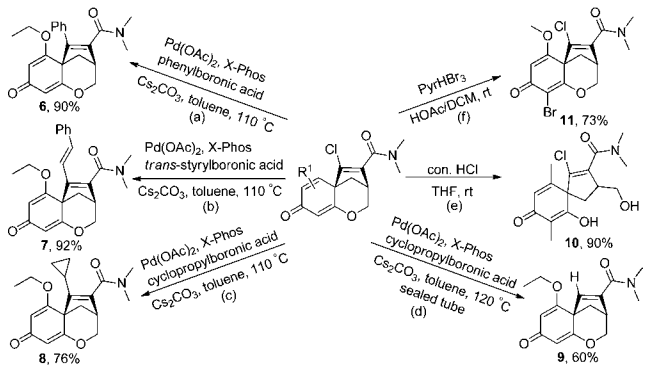
Scheme 4. Proposed Mechanism of the Tandem Chloropalladation/Cyclization and Dearomative Cyclization



chloropalladation of a carbon–carbon triple bond (**1a**) results in vinylpalladium species **1a-I**, which subsequently undergoes intramolecular conjugation with a carbon–carbon double bond to yield intermediate **1a-II**. Then dearomatization occurs to generate intermediate **1a-III** which further undergoes a reductive elimination to give the bridged [3.2.1] oxa-skeleton intermediate **1a-IV** and Pd(0) simultaneously. Pd(0) is oxidized by $CuCl_2$ with the assistance of O_2 to regenerate Pd(II) for the next cycle. Assisted by a chloride anion, the allyl group was removed to generate the desired bridged [3.2.1] oxa-skeleton compound **2a** and a side product allyl chloride which was proven by observation of benzyl chloride when substrate **5c** (Scheme 3, R^5 = OBn, R^6 = Bn) was used for this Pd-catalyzed tandem dearomative cyclization.[17]

Functionalized bridged [3.2.1] skeletons are useful building blocks for the synthesis of natural products, and their versatile applications make them useful in organic synthesis. In this paper, we conducted several reactions with chlorosubstituted bridged [3.2.1] oxa-skeleton compounds (Scheme 5). Aryl- and

Scheme 5. Transformation of Functionalized Bridged [3.2.1] Skeleton Compounds



vinyl-substituted **6** and **7** were obtained via the Suzuki cross-coupling reaction in excellent yields (Scheme 5a, b). When **2q** (Scheme 3) was treated with cyclopropylboronic acid in the presence of $Pd(OAc)_2$, X-Phos, and Cs_2CO_3 under an Ar atmosphere at 110 °C, the corresponding cyclopropyl substituted compound **8** was prepared in 76% yield, and a 20% yield of chloro removal compound **9** was gained (Scheme 5c). Interestingly, when this reaction was carried out in a sealed tube at 120 °C, compound **9** was obtained in 60% yield (Scheme 5d). Bromination of **2a** (Scheme 2) occurred smoothly to afford product **11** as a major product, which could easily make further derivatives under transition-metal-catalyzed conditions (Scheme 5f). When treated with a concentrated HCl aqueous solution in THF, the bridged [3.2.1] oxa-skeleton compound **2g** (Scheme 2) was translated to the spirocyclic compound **10** in 90% yield (Scheme 5e).

In summary, a unique synthetic method to construct a 6-carbonyl or 8-carbonyl bridged [3.2.1] skeleton has been developed. This novel method is attractive because of its mild reaction conditions and universal application for building bridged [3.2.1] carbocyclic, oxa- and aza-skeletons. This Pd-catalyzed tandem dearomative cyclization proceeds smoothly even under some adverse conditions, e.g., spatial hindrance, ring strain, and other competitive reactions including protonolysis, *β*-hydride elimination, and chlorination. As a temporary protecting group, an allyl protective group on the *para*- or *ortho*-positions of an alkynamide selectively resulted in 8- or 6-carbonyl bridged [3.2.1] oxa-skeleton compounds, providing an excellent orientation function for dearomatization.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02076.

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Experimental procedures and spectral data for intermediates, substrates, and final products (^{1}H NMR, ^{13}C NMR, HRMS) (PDF)

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Notes

The authors declare no competing financial interest.

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(16) Structure of **2A** was confirmed by ^{1}HNMR, ^{13}CNMR, HSQC, and NOE. See Supporting Information.

(17) For details, see Supporting Information.

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