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Highly Stereoselective Generation of Complex *Oxy*-Bicyclic Scaffolds *via* an Atom-Economic Pd(II)-Catalyzed Hydroalkynylation, Isomerization and Diels–Alder Cycloaddition Sequence

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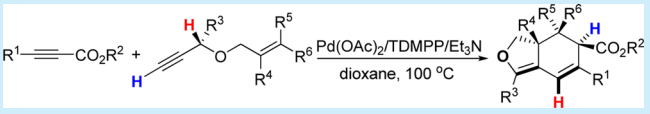
Supporting Information

ABSTRACT: An atom-economic tandem Pd(II)-catalyzed hydroalkynylation, alkyne-allene isomerization, and Diels–Alder cycloaddition is reported. The reaction employs readily available starting substrates, proceeds in a highly ordered fashion, features high regio- and stereoselectivity, and tolerates a wide range of functionality and structural motifs, thus offering an attractive strategy for producing new molecular complexity and diversity from easily available starting materials. A mechanistic study with density functional theoretical calculations was conducted to rationalize the observed stereoselectivity.



The fast and concise creation of molecular complexity and diversity from simple and readily available starting materials is inarguably of central importance in organic synthesis.[1] In this regard, the transition metal catalyzed tandem or domino reaction continues to play important roles due to its powerful capacity to execute multiple bond- and stereocenter-forming events in a single synthetic operation.[2,3] Recently, the Pd-catalyzed tandem coupling–isomerization reaction (CIR, Figure 1a)[4] has emerged as a powerful method for producing complex and diversified carbo- and heterocycles, as well as for finding novel lead structures with applications in medicinal chemistry and material science.[4−7] Mechanistically, these reactions rely on the formation of an allene intermediate from a Pd(0)-catalyzed Sonogashira coupling with an unexpected yet very facile propargyl-allenyl isomerization. This allene intermediate,[8] as demonstrated by Müller and us, is of unique reactivity and capable of participating in a wide range of complexity-generating transformations including [4 + 2] cycloaddition,[5a−c,6a−d] [3 + 2] azide–olefin cycloaddition,[6e] Alder-ene reaction,[6f] Claisen rearrangement,[5d,e,6g] and Schmittel cyclization.[6h] Interception by these transformations thus led to the establishment of an array of efficient domino reactions. While the methodology has proven successful to access a diversity of valuable molecular skeletons not easily fabricated by other methods, there still exist some inherent defects and limitations which restrict further applications. For example, the reactions are generally not atom economical from a modern synthetic perspective, and tedious procedures are often required for the preparation or prefunctionalization of the starting substrates for a successful cascade. In particular, the stereo-defined vinyl halides are still difficult to access.[9]

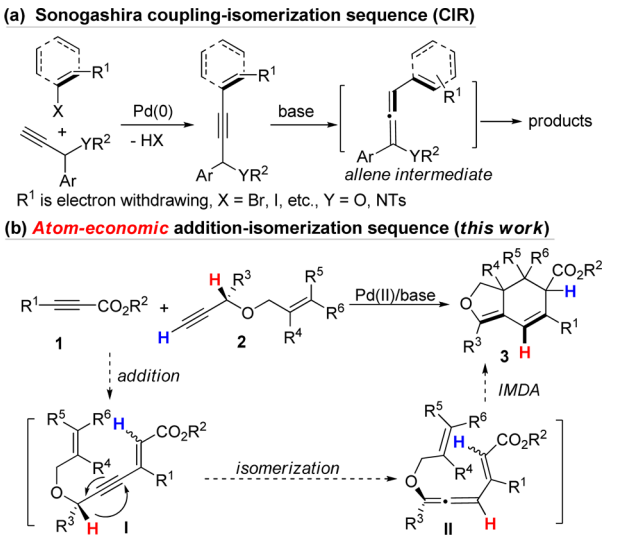


Figure 1. Sonogashira coupling–isomerization sequence vs an atom-economic addition–isomerization sequence.

Herein we propose a new paradigm of a tandem reaction sequence as an evolution of CIR toward an atom-economic method via the combination of the Trost's hydroalkynylation with the alkyne–allene isomerization (Figure 1). Thus, the Pd(II)-catalyzed cross addition of a terminal alkyne to an internal C–C triple bond, discovered by Trost in the late 1980s,[10a] represents one basic, highly effective, and atom-economic way to access molecules with a conjugated enyne unit.[10] It has been applied to the total synthesis of bryostatin 16[11] and several members of naturally occurring polyenynes.[10b,c] Furthermore, the reaction has also been utilized in tandem reaction design to build more complex structures.[12] For example, a new strategy based on this addition with sequential

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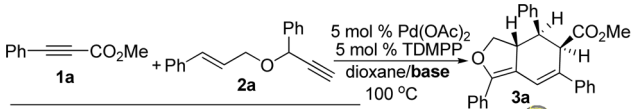
Pd(II)-catalyzed heterocyclization has been realized recently for pyrrole and related heterocycle synthesis.[12] The versatility of this reaction led us to hypothesize that the Pd(II)-catalyzed hydroalkynylation should also be an ideal reaction for the generation of an enyne-ene **I** from a simple ynoate **1** and an alkyne **2**, provided that the Pd(II) catalyst would not negatively interfere with the following steps. Isomerization of **I** upon mutually compatible reaction conditions followed by an intramolecular Diels–Alder reaction (IMDA) may give the fused 1,6,7,7a-tetrahydroisobenzofuran **3**, a structural motif occurring in many biologically active compounds (Figure 1b).[13]

While such a strategy would enable two linear starting materials, which by themselves are very easily accessible, to be directly converted to two annulated cycles without loss of any atom, we also anticipated that a high degree of stereoselectivity could be achieved considering the unusual facilitation of cycloaddition and unique geometry of the allene intermediate.[9] Furthermore, due to the easy availability of the starting substrates **1** and **2** from a pool of alcohols, propiolic acids, and allylic compounds, we further anticipated that this methodology could serve as a promising strategy for generating new molecular complexity and diversity, which is fundamental for modern drug discovery and chemical genetics technology.[14]

We initially chose methyl 3-phenyl propiolate (**1a**) and (*E*)-3-phenylallyl 1′-phenylprop-2′-ynyl ether (**2a**) as model substrates to probe the hypothesis. Optimization experiments demonstrated that the use of $Pd(OAc)_2$ as the catalyst, tris(2,6-dimethoxyphenyl)phosphine (TDMPP) as the ligand, Et_3N as a base, and dioxane as the solvent is optimal for the reaction, yielding the targeted product **3a** in 68% yield at 100 °C in 1 h (Table 1, entry 1). The reaction at rt led to a long reaction time

Table 1. Compatibility of Bases with the Pd Catalyst To Produce 3a[a]

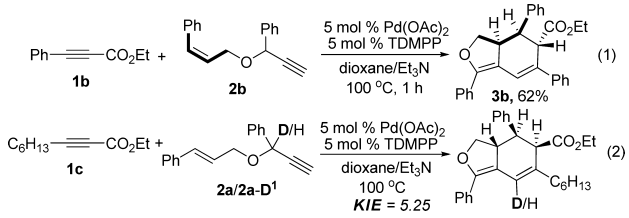


entry	base	time (h)	yield (%)[b]
1	Et_3N	1	68
2	*i*-Pr_2NEt	2	66
3	DABCO[c]	3	60
4	NMM	2	63
5	DBU[c]	2	68
6	no base	1	0
7	Inorganic base[d]	1	0
8	*t*-BuOK	1	0

[a]Reaction conditions: **1** (0.2 mmol), **2** (0.25 mmol), $Pd(OAc)_2$ (5 mol %), TDMPP (5 mol %) and base (0.2 mL), dioxane (0.8 mL). [b]Isolated yields. [c]1.0 equiv. [d]Cs_2CO_3 or K_2CO_3 or K_3PO_4, 4 equiv.

and lower yield. Performing the reaction in the absence of a base did not result in the formation of **3a**. Investigation into the compatibility of bases with the Pd catalysts revealed that organic bases such as $^iPr_2NEt$, 1,4-diazabicyclo[2.2.2]octane (DABCO), and *N*-methylmorpholine(NMM) were also competent in promoting the reaction (entries 2–4). A clean reaction was also observed when 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was employed, indicative of the compatibility of this base with the current Pd catalyst (entry 5). However, inorganic bases Cs_2CO_3, K_2CO_3, and K_3PO_4 were incapable of promoting the tandem process despite the high temperature employed (entry 7), and *t*-BuOK was incompatible as the reaction resulted in a mixture of unidentifiable products (entry 8).

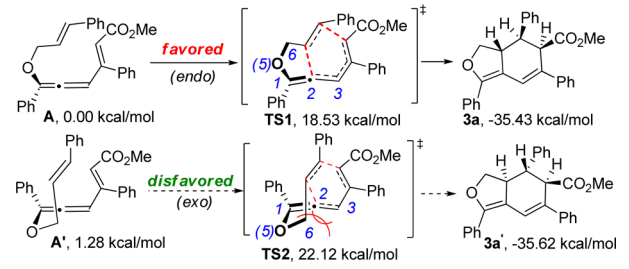
Noteworthy, although there were three stereogenic centers generated in the reaction, we note that **3a** was obtained as a single diastereoisomer as identified from ^1H and ^{13}C NMR spectra, indicative of the high stereoselectivity in the reaction. This remarkable feature was also observed from the reaction of **1b** with (*Z*)-3-phenylallyl 1′-phenylprop-2′-ynyl ether (**2b**) bearing a *cis*-double bond, which furnished **3b** in a 62% yield (eq 1). Recrystallization of **3a** from hexane and CH_2Cl_2 yielded



crystals suitable for X-ray crystallographic analysis, which unambiguously confirmed the structure and revealed that the adjacent carboxyl, phenyl groups and hydrogen atom are in a *cis*-configured fashion.

As to the observed stereoselectivity, we reasoned that the *in situ* generated ene-vinylallene **A** from a *cis*-addition and a kinetically slow isomerization (K_H/K_D = 5.25, eq 2; for a detailed study, see Supporting Information) may favor an *anti-endo* transition state **TS1** over an *anti-exo* **TS2** to undergo the IMDA reaction (Scheme 1). We surmised that the nonbonding

Scheme 1. Mechanistic Rationale for the Stereochemistry



interactions which influence the relative energies of the competing transition states may account for the selectivity. **TS1** is lower in energy because of the absence of the nonbonding interactions between C2–C6, which exist in the transition state **TS2**. Further information to support the speculation was obtained from a computational study. Thus, density functional theoretical (DFT) calculations indicate that the formation of **3a**/**3a**′ is exothermic almost equally by ca. 35 kcal/mol whereas the barrier height of the two optimized transition states corresponds to a 3.6 kcal/mol difference in favor of **TS1**, implying a kinetic preference for the formation of **3a** (Scheme 1). As shown in Figure 2, the bond-forming bond lengths are 2.08 and 2.82 Å in **TS1** and 2.05 and 3.05 Å in **TS2**. Particularly, the atoms C2–C1–O5–C6 in **TS2** are much more planar with a dihedral angel of −5.1° (23.3° for **TS1**). The bond angles of C2–C1–O5 and C1–O5–C6 are 116.5° and 109.3° respectively (119.4° and 110.5° for **TS1**). Such geometry may cause considerable repulsive interactions between C2–C6 thus elevating the energy of **TS2**. In addition, the more bent bond angle of the allene moiety (C1–C2–C3) in **TS2** should also contribute to the higher energy (138.6° vs

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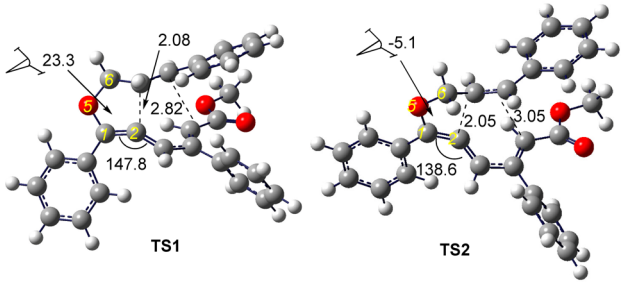


Figure 2. Calculated transition state structures of **TS1** and **TS2**. Bond lengths are in Å. Bond and dihedral angles are in degree.

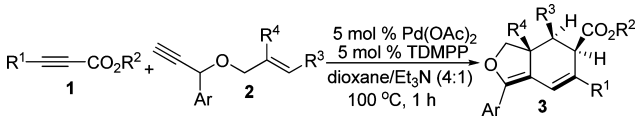
147.8°). Notably, this *endo*-selectivity is different from a previous observation.[5a]

The results compiled in Table 2 show that this operationally simple tandem reaction indeed represents an efficient and straightforward method to access fused bicyclic compounds from simple linear starting materials. Phenylpropiolic acid esters derived from ethanol, isopropanol, and 1-naphthalenylmethanol all can be applied. Particularly, the expected product **3g** was also obtained in 68% yield when but-3-enyl 3-phenylpropiolate was used (entry 5), indicating the tolerance of the double bond appended in ynoate. In addition to phenylpropionic acid esters, alkylpropionic acid esters ethyl but-2-ynoate and ethyl non-2-ynoate can also be used, affording the desired products highly stereoselectively albeit in relatively low yields (entries 10−12 and 15). As to allyl propargyl ethers, Ar could be an *orth*-, *meta*-, and *para*-substituted phenyl group with either an electron-donating or -withdrawing group (entries 6−9). Thus, the reaction of **1a** with allyl 1-(3-chlorophenyl)-prop-2-ynyl ether (entry 6) and allyl 1-(4-*tert*-butylphenyl)-prop-2-ynyl ether (entry 8), for example, proceeded smoothly to afford **3h** and **3j** in 65% and 68% yield. Furthermore, bromide functionality on the aromatic ring is also compatible with the current Pd catalysts (entry 7). In the case of using a substrate bearing a methyl group (R^4 = Me) in the olefin moiety, an all-carbon quaternary center could be incorporated into the product (entries 12 and 13).

Further investigation into the reaction scope demonstrated that the use of 3-alkyl substituted allyl propargyl ethers also led to clean reactions to produce the corresponding bicyclic compounds (Scheme 2). Thus, the reaction of **1b** and **2c** which bears an *n*-butyl group at the 3-position of the olefin moiety gave **4a** in 61% yield as the only product. The exclusive formation of **4b** was also observed from the reaction of **1c** and **2c**. Furthermore, this tandem reaction is also effective with substrates **2** that contain heteroatom groups (Scheme 2). Substrate **2d** bearing a free hydroxyl group reacted smoothly with **1c** to give **4c** in 69% yield in 1 h. Prolonging the reaction time did not result in a further lactonization product. Other substrates bearing alkoxyl, amino (a morpholine motif), and phthalimido groups also participated effectively and efficiently in producing the products, except for the reaction of a bis(2-hydroxyethyl)amino-attached substrate **2h** which required a longer time to deliver the desired product **4g** in an acceptable yield, and a thiocyanate substrate unfortunately failed to give the expected product probably due to the sulfur poisoning of the Pd catalyst.

In a synthetic application of the present reaction to generate new molecular complexity and diversity, we finally examined several naturally occurring alcohol derived ynoates **5a**−**5e** to produce complex natural-product-like molecules. As demonstrated in Figure 3, despite the structural complexity, **5a**−**5e** all could be used to produce the corresponding products in good yields. The reaction of a (−)-menthol derived ynoate **5a** with **2a**, for example, gave the expected product **6a** in 61% yield. Similarly, the use of (−)- nopol derivative **5d** gave **6d** and **6e** in 68% and 64% yields. While the diastereoselectivities obtained from **5a**−**5d** were generally low, interestingly, the use of the cholesterol derivative **5e** afforded the sterol derivatives **6f** and **6g** with excellent diastereoselectivity as identified from ^{1}H, ^{13}C NMR and DEPT spectra. The net result of the asymmetric induction effect in the reaction is intriguing, considering its potential use for the synthesis of optically active compounds.

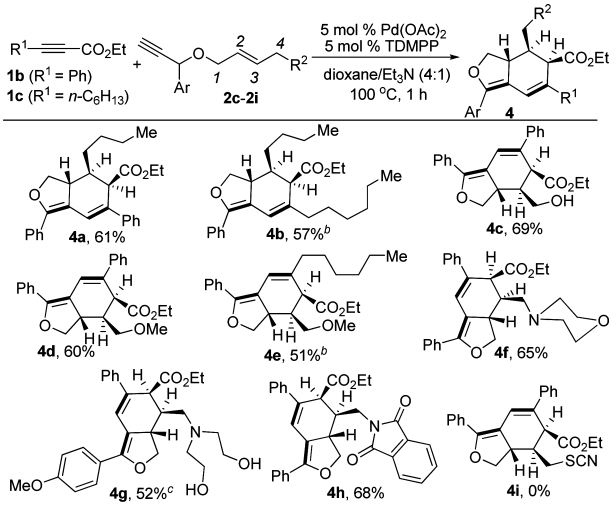
Table 2. Efficient Formation of 5,6-Bicycles 3[a]



	1		2			
entry	R^1	R^2	R^3	R^4	Ar	3 yield (%)[b]
1	Ph	Et	Ph	H	Ph	**3c**, 69
2	Ph	Et	H	H	Ph	**3d**, 70
3	Ph	*i*-Pr	H	H	Ph	**3e**, 68
4	Ph	1-napCH$_2$	H	H	Ph	**3f**, 71
5	Ph	homoallyl	H	H	Ph	**3g**, 68
6	Ph	Me	H	H	*m*-ClC$_6$H$_4$	**3h**, 65
7	Ph	Me	H	H	*o*-BrC$_6$H$_4$	**3i**, 56
8	Ph	Me	H	H	*p*-*t*-BuC$_6$H$_4$	**3j**, 68
9	Ph	Et	H	H	*p*-MeOC$_6$H$_4$	**3k**, 65
10	*n*-C$_6$H$_{13}$	Et	H	H	Ph	**3l**, 56[c]
11	Me	Et	H	H	Ph	**3m**, 41[c]
12	Me	Et	H	Me	Ph	**3n**, 53[c]
13	Ph	Me	H	Me	Ph	**3o**, 69
14	Ph	*i*-Pr	Ph	H	Ph	**3p**, 67
15	*n*-C$_6$H$_{13}$	Et	Ph	H	Ph	**3q**, 47[c]

[a]Reactions were carried out on a 0.2 mmol scale following a standard procedure. [b]Isolated yields. [c]1.5 h.

Scheme 2. Efficient Formation of Fused 5,6-Bicycles 4[a]



[a]Reactions were conducted on a 0.2 mmol scale following a standard procedure in 1 h unless otherwise noted. [b] 1.5 h. [c] 8 h.

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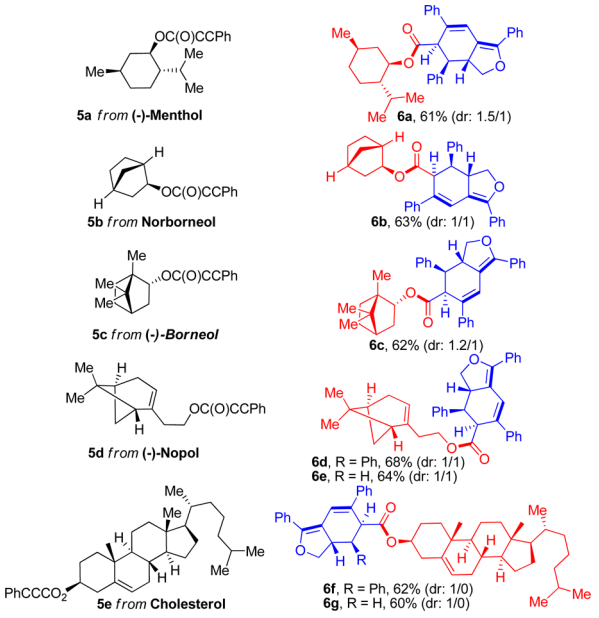

Figure 3. Utility of naturally occurring alcohols derived ynoates for generation of natural-product-like molecules.

The development of asymmetric variants of the reaction with such a strategy is underway and will be reported in due course.

In summary, we have realized an atom-economic Pd(II)-catalyzed addition/alkyne−allene isomerization/IMDA reaction, providing a highly efficient synthesis of complex oxygen bicycles with diversified functional groups and structural motifs. The reaction is regio- and stereoselective, proceeds in a highly ordered fashion, and employs readily available substrates. Due to the unique reactivity of allene intermediates, we believe that this conceptually intriguing addition−isomerization sequence will open up new opportunities to access valuable compounds.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, DFT calculation data, characterization of the products, CIF file. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

R.S. would like to dedicate this paper to the memory of his mentor, Prof. Xian Huang, on the occasion of his 80th birthday.

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