ORGANIC LETTERS

2013
Vol. 15, No. 1
14–17

Palladium-Promoted [2 + 2 + 2] Cocyclization of Arynes and Unsymmetrical Conjugated Dienes: Synthesis of Justicidin B and Retrojusticidin B

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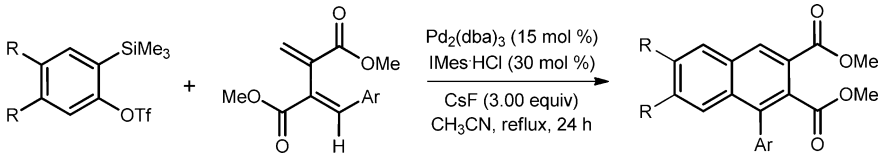
Received October 18, 2012

ABSTRACT



1a: R = methylenedioxy
1b: R = dimethoxy

4a: Ar = phenyl
4b: Ar = 3,4-methylenedioxyphenyl
4c: Ar = 3,4-dimethoxyphenyl

6a–f (58-66%)

A facile synthesis of natural and unnatural arylnaphthalenes has been demonstrated via the unprecedented palladium-promoted [2 + 2 + 2] cocyclization of arynes and unsymmetrical conjugated dienes using the *N*-heterocyclic carbene as a ligand. The unsymmetrical dienes used herein are actually α-coupled acrylate−cinnamate combinations bearing two β-positive carbons and follow the key [2 + 2 + 2] cocyclization pathway.

A transition-metal-catalyzed [2 + 2 + 2] cocyclization of multiple bonds has been an atom economical and useful methodology for the synthesis of an array of polycyclic compounds.[1] The recent development of new methods for generation of arynes under mild conditions has led to the promising exploration of metal-mediated cocyclization reactions of arynes.[2] A large number of nickel-/palladium-catalyzed [2 + 2 + 2] cocyclizations of arynes with several electron-rich substrates such as alkynes, diynes, allyl derivatives, allenes, *ortho*-halobiphenyls, halo-styrenes, and carbon monoxide have been reported in the literature.[3] However, the metal-catalyzed [2 + 2 + 2] cocyclization of arynes with different types of alkenes result in the cotrimerization adducts utilizing the two units of corresponding arynes and/or *ortho*-olefinated biaryls.[4] There have been no reports on metal-catalyzed [2 + 2 + 2] cocyclizations of arynes by using two kinds of alkenes or dienes as an arynophile. Recently, our research group has reported the first S_N2' coupling reaction of Wittig reagents with dimethyl

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10.1021/ol3028658
Published on Web 12/13/2012

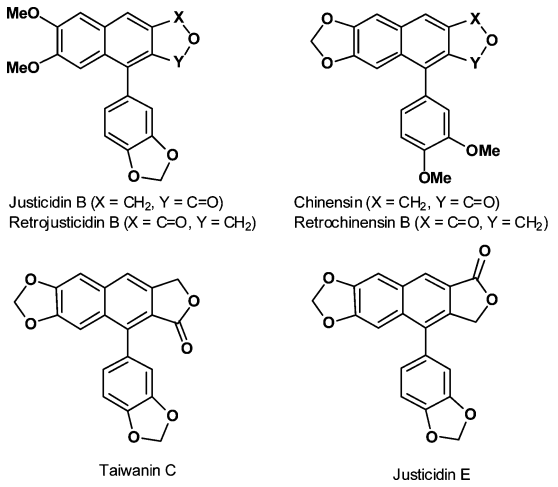
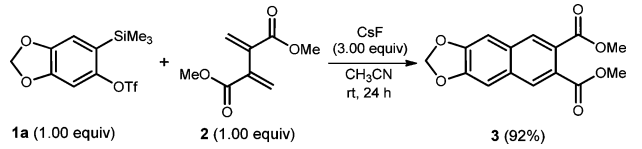


Figure 1. Naturally occurring bioactive arylnaphthalenes.

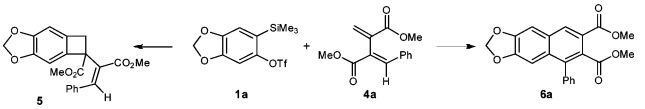
bromomethylfumarate to synthesize various enes/dienes and utilize them to construct a lignan class of natural products.[5,6] We reasoned that these unsymmetrical conjugated dienes are indeed α-coupled to two different dienophiles and their cocyclization reactions with arynes would provide a new approach to regioselectively construct a broad range of an arylnaphthalene class of natural products (Figure 1). In this context, we herein report our results on the synthesis of a variety of natural and unnatural arylnaphthalene architectures (Schemes 1−4 and Table 1).

Scheme 1. [4 + 2] Cycloaddition Reaction of Symmetrical Conjugated Diene **2** with an Aryne



A pilot reaction of aryne and symmetrical conjugated diene **2** in CH_3CN at room temperature directly furnished

Table 1. Optimization of Reaction Conditions for Palladium-Promoted [2 + 2 + 2] Cocyclization of Diene **4a** with an Aryne[a]



entry	reaction conditions[b]	**5**/**6a** (% yield)
1	CsF, CH_3CN, rt, 24 h	**5** (32)
2	CsF, CH_3CN, reflux, 24 h	**5** (11)
3	$Ni(cod)_2$, PPh_3, CsF, CH_3CN, rt, 24 h	NR[c]
4	$Ni(cod)_2$, PPh_3, CsF, CH_3CN, reflux, 24 h	NR[c]
5	$Pd_2(dba)_3$, CsF, CH_3CN, rt, 24 h	NR[c]
6	$Pd_2(dba)_3$, CsF, CH_3CN, reflux, 24 h	**6a** (42)
7	$Pd_2(dba)_3$, PPh_3, CsF, CH_3CN, reflux, 24 h	**6a** (23)
8	$Pd_2(dba)_3$, P(*o*-tol)$_3$, CsF, CH_3CN, reflux, 24 h	**6a** (20)
9	$Pd(PPh_3)_4$, CsF, CH_3CN, reflux, 24 h	**6a** (08)
10	$PdCl_2(PPh_3)_2$, CsF, CH_3CN, reflux, 24 h	NR[c]
11	$Pd_2(dba)_3$, IMes.HCl, CsF, CH_3CN, reflux, 24 h	**6a** (62)

[a] In all the above mentioned reactions in Table 1, formation of a small amount of benzyne trimer, dimer of diene, and polymeric gums were noticed on prolonged stirring at rt or under the reflux conditions. [b] 15 mol % of catalyst, 30 mol % of ligand, 1.50 equiv of diene **4a**, and 3.00 equiv of CsF were used. [c] NR: No reaction.

the corresponding air oxidized [4 + 2] cycloaddition product **3** in 92% yield (Scheme 1). The possible driving force for the present [4 + 2] cycloaddition could be the zero dipole moment at the carbon−carbon single bond in compound **2**. However, the reaction of aryne and β-substituted unsymmetrical conjugated diene **4a** at room temperature under a similar set of reaction conditions followed a different course and formed cyclobutane derivative **5** in 32% yield with the recovery of ∼30% starting diene (Table 1, entry 1). The same reaction in refluxing CH_3CN formed a complex reaction mixture and provided an even lesser amount of dipolar [2 + 2] cycloaddition product **5** (11%), devoid of the formation of even traces of a [4 + 2] cycloaddition product (Table 1, entry 2). The above specified reactions followed an alternate dipolar [2 + 2] cycloaddition route selectively utilizing the less substituted more reactive carbon−carbon double bond from the acrylate part in the unsymmetrical conjugated diene **4a**. The clockwise/anticlockwise electron cascade for the [4 + 2] cycloaddition reaction with unsymmetrical conjugated diene **4a** would be against the thermodynamics due the presence of two different α,β-unsaturated systems (two β-positive carbons). Therefore a systematic study of transition-metal-catalyzed [2 + 2 + 2] cycloaddition reactions of arynes and unsymmetrical conjugated dienes was undertaken to achieve the formation of six-membered cycloadducts to provide a new general approach to an arylnaphthalene structural design.

The reaction of aryne and diene **4a** in CH_3CN using the $Ni(cod)_2$ catalyst and PPh_3 ligand at room temperature or under reflux conditions was futile with the reasonable recovery of starting diene (Table 1, entries 3 and 4). The palladium-promoted [2 + 2 + 2] cocyclization reaction of

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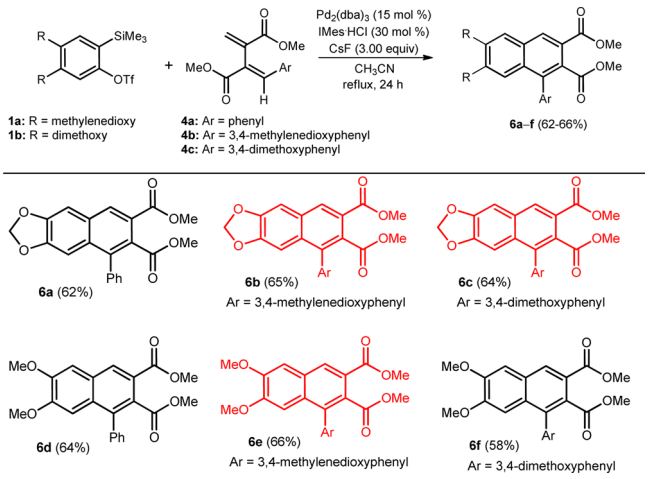
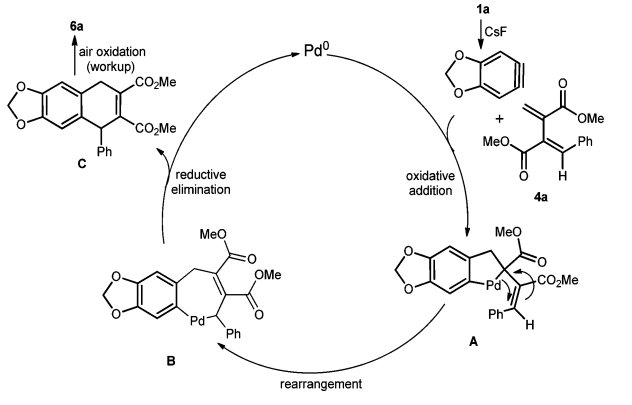
Scheme 2. Generalization of Palladium-Promoted [2 + 2 + 2] Cocyclization of Unsymmetrical Dienes **4a**–**c** with Arynes



aryne and diene **4a** in CH_3CN using the $Pd_2(dba)_3$ catalyst was also unsuccessful at room temperature (Table 1, entry 5). The same reaction under reflux conditions delivered the desired arylnaphthalene product **6a** in 24% yield following the [2 + 2 + 2] cocyclization and postreaction facile air oxidation pathways. All our attempts to isolate the corresponding formed dihydronaphthalene intermediates failed due to the very high air oxidation propensity of these superactivated systems to gain complete aromaticity. On optimization of reaction conditions, the yield of arylnaphthalene **6a** improved only up to 42% (Table 1, entry 6). Attempts to further improve the yield using different ligands such as PPh_3, P(*o*-tol)$_3$, and dppf; various solvents such as toluene or a toluene/CH_3CN mixture; varying molar ratios of reactant/reagents; and different palladium catalysts such as $Pd(PPh_3)_4$, $PdCl_2(PPh_3)_2$, and $Pd(OAc)_2$ were also ineffective (Table 1). Finally, the promising *N*-heterocyclic carbene ligand was used for the further improvement of yield.[7] The use of aryne precursor **1a** (1.00 equiv), diene **4a** (1.50 equiv), the $Pd_2(dba)_3$ catalyst (15 mol %), the 1,3-bis(2,4,6-trimethyl)phenyl imidazolium chloride ligand (IMes·HCl) (30 mol %), and CsF (3.00 equiv) in CH_3CN under reflux conditions furnished the desired product **6a** in 62% yield (Table 1, entry 11). Herein the use of 15 mol % palladium catalyst was essential as the use of catalytic amounts majorly resulted in a mixture of undesired coupling products. In the above-mentioned palladium promoted formation of compound **6a**, we never noticed the generation of compound **5** as the possible intermediate at room temperature/reflux conditions before or after the workup (Table 1, entries 5 and 6). In our hands **5** on exposure to a similar set of palladium-catalyzed cocyclization reaction conditions resulted in the complex mixture. These observations preclude the possibility of **5** being the intermediate in the formation of product **6a**. Finally, the unprecedented palladium-catalyzed [2 + 2 + 2] cocyclization of unsymmetrical conjugated dienes was generalized by using aryne precursors **1a**/**b** and dienes **4a**–**c** to directly obtain the desired arylnaphthalenes **6a**–**f** in 58–66% yields (Scheme 2).

In the above-mentioned reactions, the net [4 + 2] addition products are formed via a [2 + 2 + 2] cocyclization mechanism utilizing the directionally opposite Michael type addition reactions of two different α-coupled dienophiles. A plausible mechanism for the palladium-promoted [2 + 2 + 2] cocyclization of aryne and diene **4a** has been depicted in Scheme 3. The catalytic cycle initiates with the oxidative insertion of Pd^0 to aryne and the less substituted double bond of diene to form a five-membered palladacycle **A**. The formed palladacycle is stabilized by an intramolecular coordination of the carbonyl oxygen atom from an α,β-unsaturated ester moiety with the formation of a five-membered transition state.[8] Subsequent insertion of the more substituted double bond into the Pd–C (alkyl) bond via rearrangement of a five-membered palladacycle **A** to a seven-membered palladacycle forms the intermediate **B**. The reductive removal of zerovalent Pd from intermediate **B** leads to intermediate **C** with the regeneration of the catalyst. The intermediate **C** bears an activated allylic-doubly benzylic reactive carbon atom. Thus the highly oxidation prone intermediate **C** instantaneously oxidizes to arylnaphthalene **6a** during the workup operations of the reaction mixture. The alternate possibility of diene **4a** forming the five-membered palladacycle followed by the reaction with aryne to form the intermediate **B** would also be a stepwise [2 + 2 + 2] cocyclization process due to the presence of two β-positive carbons in the unsymmetrical conjugated diene **4a**.

Scheme 3. Plausible Mechanism for Palladium-Promoted [2 + 2 + 2] Cocyclization of an Unsymmetrical Conjugated Diene with an Aryne



The utility of synthesized imperative advanced intermediates **6b**, **6c**, and **6e** has been previously well demonstrated

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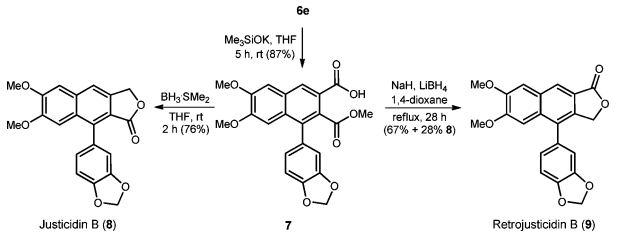
Scheme 4. Concise Synthesis of Justicidin B and Retrojusticidin B



in the synthesis of several bioactive natural products.[9,10] The synthesis of anti-HIV natural products justicidin B and retrojusticidin B was planned from product **6e**.[11] The sterically unhindered ester in compound **6e** was regioselectively hydrolyzed by using potassium trimethylsilonate in THF at room temperature to form compound **7** in 87% yield (Scheme 4). The chemoselective reduction of an acid functionality in **7** with a borane dimethyl sulfide complex followed by an acidic workup gave the justicidin B (**8**) in 76% yield.[9] Alternatively, chemoselective ester reduction of the sodium salt of compound **7** with the lithium borohydride followed by an acidification gave a column chromatographically separable mixture of expected major product retrojusticidin B (**9**) in 67% yield and minor product justicidin B (**8**) in 28% yield.[9] Starting from diene **4b**, the total synthesis of justicidin B (**8**) and retrojusticidin B (**9**) was completed in three steps with 44% and 39% overall yields respectively. The analytical and spectral data obtained for both natural products were in complete agreement with reported data.[9−11]

In summary, a novel palladium-promoted [2 + 2 + 2] cocyclization of arynes and apparently conjugated unsymmetrical dienes to arylnaphthalene frameworks with the stepwise formation of two new carbon−carbon bonds has been described. The versatility of this method is demonstrated through the concise synthesis of justicidin B and retrojusticidin B and formal synthesis of several analogous bioactive natural products. The described convergent approach is general in nature and would provide a facile pathway for the synthesis of various symmetrical/unsymmetrical arylnaphthalene lignans. The present strategy for the generation of biaryl systems without the aryl−aryl coupling is noteworthy.[12]

Acknowledgment. R.M.P. thanks CSIR, New Delhi, for the award of a research fellowship. N.P.A. thanks the Department of Science and Technology, New Delhi for financial support.

Supporting Information Available. Experimental procedures; tabulated analytical and spectral data; and ^1H NMR, ^{13}C NMR, and DEPT spectra of compounds **3**, **5**, **6a**−**f**, and **7**−**9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.