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Pd-catalyzed cross-coupling reactions of the cycloadducts from 3,5-dibromo-2-pyrone and their synthetic applications towards various mono- and polycyclic compounds

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Abstract—Bicylolactones from Diels–Alder (D–A) cycloadditions of 3,5-dibromo-2-pyrone can undergo various palladium catalyzed cross coupling reactions to afford a series of alkenyl, alkynyl and aryl bicyclolactones. The resulting coupled products can be readily converted into various 3-OH cyclohexenes via lactone ring openings, while those bearing dienyl units underwent highly diastereoselective D–A cycloadditions with selected dienophiles to furnish multiply functionalized polycarbocycles.

Bicyclolactones prepared from Diels–Alder (D–A) cycloadditions of 2-pyrones are highly versatile synthetic building blocks that have been used for generations of various structurally diverse natural and unnatural complex molecules including taxol and a series of vitamin D_3 derivatives.[1] As a result of the study on the cycloadditions of 3,5-dibromo-2-pyrone, we have prepared a variety of stereochemically defined and functionally rich bicyclolactones.[2] In the report,[2b] we have shown that the vinyl bromide group in the bicyclolactone **1** could be used as a handle to attach methyl acrylate group via conventional Heck reaction (Scheme 1).

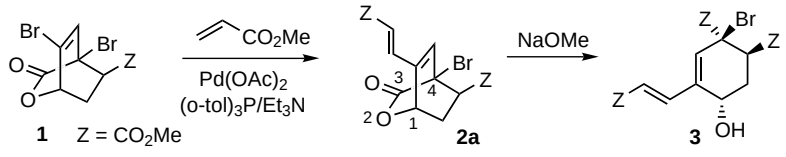
Lactone ring opening reaction of **2a** would provide the functionally rich and stereochemically defined 3-cyclohexenol derivative **3**, potential synthetic precursors to hexahydrobenzofuran and hexahydrobenzopyran types of biologically important natural products including phomactins and candelaides.[3]

Realization of its potential synthetic utilities prompted us to investigate other coupling reactions on the cycloadduct **1**. In this article, we wish to report its Pd-catalyzed coupling reactions with various functional groups as well as the synthetic applications of the resulting coupled products.

Table 1 summarizes the results on the coupling reactions of **1** with alkenyl, alkynyl and aromatic functionalities. As shown in Table 1, all the coupling reactions took place exclusively at C7 (vinyl bromide) rather than C4 (bridgehead bromide), despite the possible Pd couplings at the bridgehead bromide as have been previously reported in other systems.[4]

Lactone ring openings of the coupled products **2a–d** with NaOMe/MeOH, however, resulted in the formation of aromatic compounds **4a–d** in good yields (85–91%), presumably through the concomitant 1,2-elimination of HBr, followed by aromatization (Scheme 2).

Although the reaction itself may have usages in the synthesis of the related aromatic compounds, it suffers



1 Z = CO_2Me **2a** **3**

Scheme 1.

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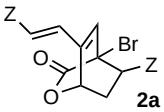
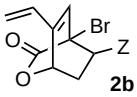
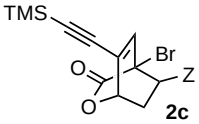
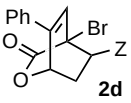
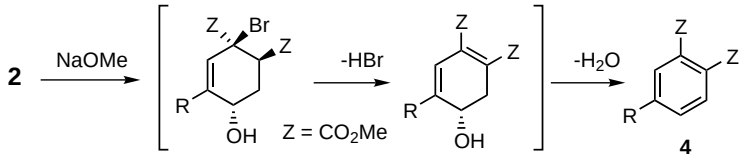
Table 1. Pd-catalyzed cross-coupling reactions of the bicyclolactone **2**

entry	R-Y	condition	product	yield
1	 Z = CO_2Me	$Pd(OAc)_2/(tol)_3P$/ Et_3N/MeCN/reflux	 **2a**	82%
2		$Pd(Ph_3P)_4$/toluene/ reflux	 **2b**	65%
3		$Pd(PPh_3)_2Cl$ /CuI/ Et_3N/dioxane/RT	 **2c**	86%
4	$PhB(OH)_2$	$Pd(Ph_3P)_4/Na_2CO_3$/ toluene/reflux	 **2d**	72%
5	$PhSnBu_3$	$Pd(Ph_3P)_4$/toluene/r eflux		58%



Scheme 2. Eliminations of HBr, followed by aromatization.

from the loss of the valuable stereochemistry created from the cycloadditions. In order to prevent the aromatizations, we needed to remove the bromine group at the bridgehead position in the coupled products prior to the lactone ring cleavage reactions.

While the debrominations using the standard Bu_3SnH/AIBN condition proceeded well on both **2a** and **2d**, the same reactions on **2b** and **2c** were accompanied with the additions of Bu_3SnH across the pendant multiple bonds. Further change of the reaction sequence was thus necessary, rendering the removal of the bridgehead bromine group (C4) to be done at the initial cycloadduct stage (**1**). Fortunately, the bridgehead bromide was readily removed under typical Bu_3SnH/AIBN condition with high selectivity over the vinyl bromide to provide the monobromo-bicyclolactone **5**.[2b]

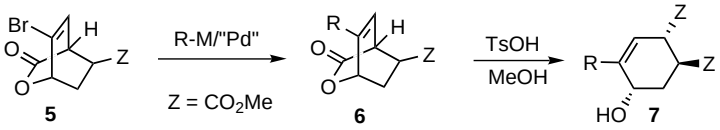
The actual coupling reactions with **5** turned out to be significantly better than **1**, providing the coupled products **6a–d** in 78–99% isolated yields. The actual lactone ring opening reactions were later found to be much better with TsOH/MeOH system, providing the corresponding 3-OH-cyclohexenes **7a–d** in good isolated yields as summarized in Table 2.

The coupled products **2a** and **2b** as well as **6a** and **6b** are equipped with dienyl units, thus may function as potent dienes.[5] A preliminary study showed that **2b** indeed underwent facile D–A cycloadditions with various dienophiles, when heated in CH_2Cl_2 at 100°C in a sealed tube, furnishing the cycloadducts **8a–d** in good isolated yields (Table 3).

Interestingly, all the D–A cycloadditions were highly diastereoselective, producing virtually a single diastereomer, in each case, out of four possible stereoisomers. Stereochemical assignments of the cycloadducts would have been difficult. Fortunately, nor-bromo-bicyclic diene **6a** furnished two diastereomers **9-*endo*** and **9-*exo*** upon cycloadditions with N-Et maleimide (NEM) (Scheme 3).

Each isomer isolated was completely characterized with COSY, TOCSY and ROESY. The difference in the coupling constants between H_b and H_c of the *endo* **9A** and those of the *exo* **9B** is relatively small (8.8 and 9.8 Hz, respectively), but quite distinctive. Energy minimization of **9A** and **9B** using MM force field showed the dihedral angles of H_b and H_c in **9A** and **9B** to be 32.7° and 142.7° (corresponding to 8.24 and 9.13 Hz). With this stereochemical analysis at hand, we treated the cycloadduct **8b** with Bu_3SnH to remove the bridgehead Br group. The ^1H NMR spectrum of the resulting debrominated product turned out to be identical to that of **9A**.

Table 2. Couplings followed by acidic methanolysis of **5**



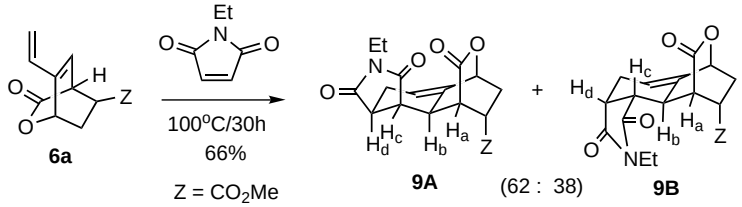
5 **6** **7**

R-M	6[a]	yield	7	yield
$SnMe_3$	**6a**	80%	**7a**	65%
CO_2Me	**6b**	82%	**7b**[b]	70%
TMS	**6c**	99%	**7c**	86%
$PhB(OH)_2$	**6d**	85%	**7d**	80%
$PhSnBu_3$	**6d**	78%		

a) Coupling conditions are the same as those in Table 1.
b) Due to the instability, the alcohol was directly protected with TBS.

Table 3. D–A cycloadditions of **2a**

diene	dienophile	condition	cycloadduct	yield
2b	CO_2Me / CO_2Me	100°C/8h	**8a**	70
	NEt	100°C/30h	**8b**	66
		100°C/48h	**8c**	58
		100°C/24h	**8d**	61



6a **9A** **9B**

Scheme 3. D–A cycloaddition of **5a** with NEM.

Unambiguous stereochemical assignment of **8c** and **8d** was not an easy task, especially without the aid of the corresponding *exo*-adducts. They were assigned tentatively to the *endo*-isomers as shown in Table 3, based on the relatively small coupling constants of the H_b and H_c (6.8 Hz for **8c** and 7.5 Hz for **8d**).

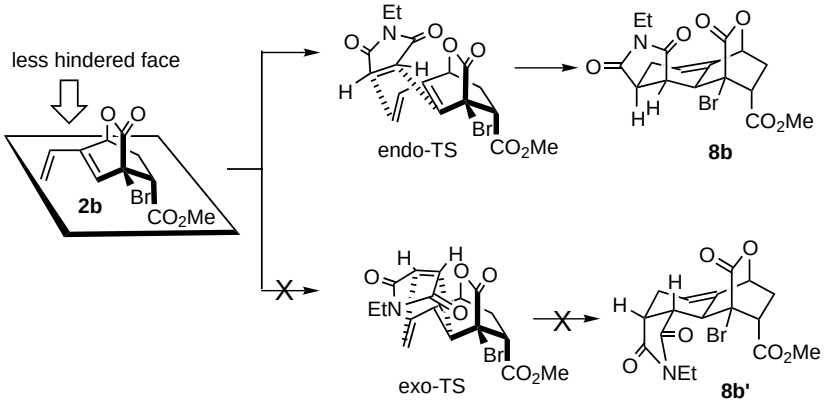
We believe that the dienophiles approach to the diene **2b** preferably from the sterically less hindered, top face (the bottom face is severely blocked by the COOMe group). Subsequent formation of the energetically more favorable *endo*-TS would lead to the corresponding *endo*-cycloadduct as depicted below, concluding the highly effective doubly stereoselective D–A cycloaddition (Scheme 4).[5b] The *exo*-TS would be further destabilized in this case, by the steric repulsion between the bridgehead Br and the carbonyl group of the incoming NEM, which may explain the much poorer *endo*/*exo* selectivity in the cycloaddition of the nor-Br **6a** (vide supra).

Cycloadditions of the nor-Br-cycloadduct **6a** with other dienophiles also proceeded as well, but produced aromatized products, when reacted with aforementioned dienophiles under the identical reaction conditions (Table 4).

Apparently, the presence of the bridgehead Br-group plays an important role in the prevention of the aromatization. When the cycloadduct **8a** or **8c** does aromatize, there would be a severe allylic strain between the bridgehead Br and the proximal ester or carbonyl groups in the imaginary aromatic products (Scheme 5). The corresponding allylic strains are much smaller in the aromatized products of the nor-Br cycloadducts **10a** and **10b**, which therefore proceeded all the way to the aromatization.

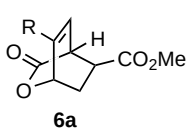
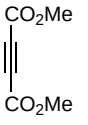
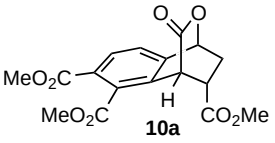
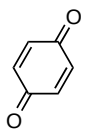
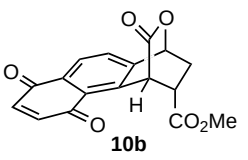
We have also studied the dienyl characters of the lactone ring opened products. The cyclohexenes **7a** and **7b** (Table 1) underwent smooth D–A cycloadditions with N-Et maleimide and benzoquinone, but with no stereoselectivity, furnishing complex mixtures of isomeric cycloadducts (data not shown).

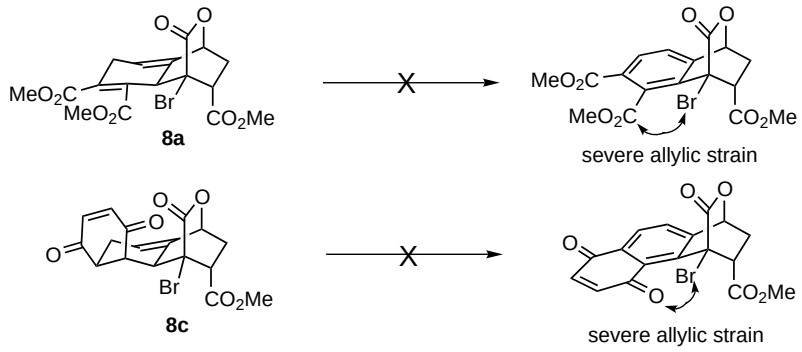
In summary, we have demonstrated that the cycloadducts from 3,5-dibromo-2-pyrone underwent facile Pd-catalyzed cross-coupling reactions with alkenyl, alkynyl and aryl functionalities. The resulting coupled bicyclolactones can be readily converted into various stereospecifically substituted mono- and polycarbocycles.[6]



Scheme 4. Proposed mode of the cycloaddition of **2b** with NEM for the exclusive formation of the *endo*-adduct **8b**.

Table 4. D–A cycloadditions of **6a** with other dienophiles

diene	dienophile	condition	cycloadduct	yield
 **6a**		100°C/8h	 **10a**	70
		100°C/48h	 **10b**	58



Scheme 5. Severe allylic strains prevent the aromatizations of **8a** and **8c**.

Acknowledgements

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6. All new compounds were fully characterized with ^{1}H NMR, ^{13}C NMR, IR and HRMS.