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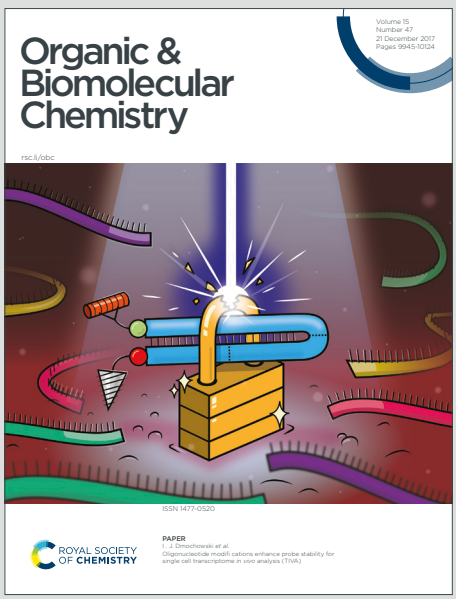

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COMMUNICATION

Highly Diastereoselective Synthesis of 3-Methylenetetrahydropyrans by Palladium-Catalyzed Oxa-[4+2] Cycloaddition of 2-Alkenylbenzothiazoles

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A highly diastereoselective synthesis of 3-methylenetetrahydropyrans *via* palladium-catalyzed oxa-[4+2] cycloaddition of 2-alkenylbenzothiazoles with allyl carbonates bearing a nucleophilic alcohol side chain is presented. This synthetic methodology tolerates a wide variety of 2-alkenylbenzothiazoles and afforded the desired 3-methylenetetrahydropyrans in good yields and excellent dr. In addition, further derivatizations resulted in new scaffolds, making them useful synthetic precursors.

Functionalized 3-methylenetetrahydropyrans constitute synthetically valuable building blocks in organic synthesis and are characteristic structural motifs in numerous biologically active natural products and pharmaceuticals.[1] Thus, considerable effort has been directed towards the development of new methods for the rapid construction of diversely substituted 3-methylenetetrahydropyrans.[2] These methods include intramolecular radical cycloaddition,[2i] Claisen rearrangement,[2f] palladium-catalyzed umpolung cycloaddition,[2h] and Ni-catalyzed reductive coupling.[2g] However, most of these transformations involved substrate limitation or harsh condition that are difficult to handle, thus leaving us much room for exploring.

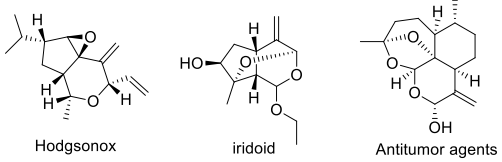

Fig. 1 Typical examples of 3-methylenetetrahydropyran-containing natural products and pharmaceuticals.

In the past decades, the cycloaddition reactions utilizing palladium-stabilized zwitterions provided a powerful strategy to access functional heterocycles.[3] Various allyl precursors were introduced to generate allylpalladium species under palladium(0) catalyst. For instance, trimethylenemethane,[4] vinyl cyclopropanes,[5] vinyl epoxides[6] or vinylethylene carbonates[7] have been widely used as C3 synthons to conduct [3+n] cycloaddition reactions. Moreover, the approaches involved [4+n] cycloadditions with vinyl benzoxazinones[8] or γ-methylidene-δ-valerolactones[9] have been well studied to synthesize diverse functionalized heterocyclic compounds.

In view of the six-member ring of 3-methylenetetrahydropyrans, the intermolecular [3+3] or [4+2] cycloadditions through palladium-stabilized zwitterions enabled a facile and straightforward tool for the formation of this intriguing scaffold. In this context, Klumpp and co-workers reported the pioneering work on palladium-catalyzed regioselective [3+3] cycloadditions of 2-(chloromagnesiomethyl)-2-alkenyl ethers with epoxides to provide synthetic important 1,3-oxazolidines in high yields (Scheme 1a).[10] Guo described a palladium-catalyzed decarboxylative [4+2] cycloaddition of 2-methylidenetrimethylene carbonate with alkenes to construct chiral tetrapyran-fused spirocyclic scaffolds (Scheme 1b).[11] However, rarely have allyl carbonates bearing a nucleophilic alcohol been used for intermolecular cycloaddition, and to our knowledge, only two examples of [4+2] cycloadditions were reported to generate 3-methylenetetrahydropyrans. In 2016, the group of You developed palladium catalyzed [4+2] cycloaddition of indole with allyl carbonates bearing a nucleophilic alcohol *via* dearomatization strategy to synthesize polycyclic indoline with 3-methylenetetrahydropyran moiety (Scheme 1c, left). [12] Later, Yao and co-workers employed electrophilic *para*-quinone methides as reaction partner and obtained spirocyclic framework containing 3-methylenetetrahydropyran ring through palladium-catalyzed [4+2] cycloaddition (Scheme 1c, right).[13] In aim to develop new methods for the efficient synthesis of 3-methylenetetrahydropyran scaffolds, we report herein a formal [4+2] cycloaddition of activated alkene with allyl carbonates bearing a nucleophilic alcohol for the quick access of

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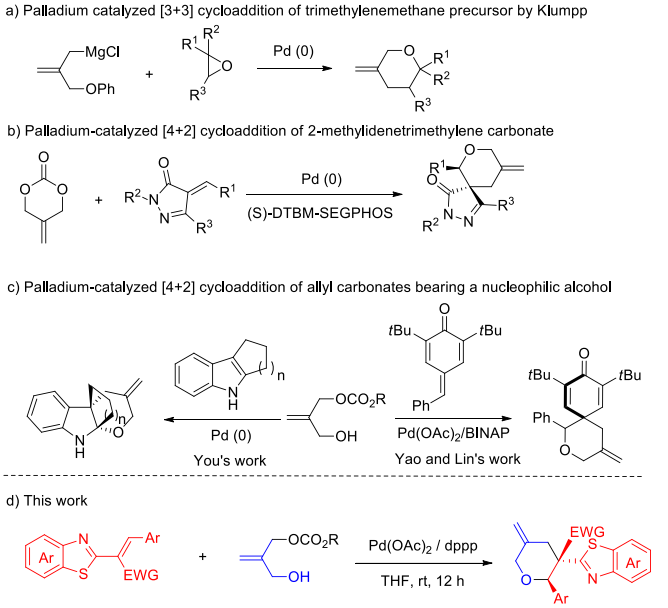


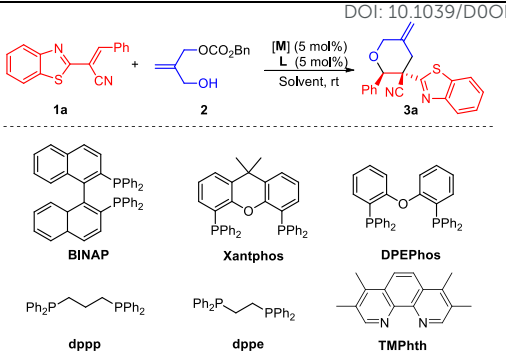
Scheme 1 Palladium-catalyzed cycloaddition reaction for the synthesis of 3-methylenetetrahydropyran skeleton.

functionalized 3-methylenetetrahydropyrans with our prolonged interest on cycloaddition.[14]

Initially, the reaction of 2-alkenylbenzothiazole with allyl carbonates bearing a nucleophilic alcohol side chain was chosen as a model reaction and commenced our study in the presence of $Pd(OAc)_2$ (5 mol%) and BINAP (5 mol%). The results of condition optimization were collected in Table 1. To our delight, the reaction proceeded smoothly in THF at room temperature for 15 h and produced the desired 3-methylenetetrahydropyran **3a** in 95% yield and excellent diasteroselectivity (entry 1). Intriguely, other palladium salts or iridium complex resulted in no reaction (entries 2-6). Changing to Et_2O as solvent gave inferior result in terms of yield (entry 7). While a quick screening of other solvents such as toluene, MeCN, DCM or dioxane (entries 8-11) did not afford the cycloadduct **3a**. We then moved our attention toward the phosphine ligands. Bidentate phosphines such as Xantphos, DPEPhos, dppe and dppp led to similar catalytic results to that of BINAP (entries 12-15). The dppp emerged as the optimal candidate delivering the target cycloadduct **3a** in 95% yield and >20:1 dr within 12 h (entry 14). However, the switch of monodentate triphenylphosphine or bidentate nitrogen ligand exhibited no reactivity (entries 16-17). Finally, the optimal conditions were identified by using $Pd(OAc)_2$ (5 mol%) and dppp (5 mol%) as the catalyst in THF at room temperature for 12 h, with the desired 3-methylenetetrahydropyrans **3a** formed in 95% yield (entry 14).

Under the optimized conditions, we next investigated the substrate scope of this palladium-catalyzed oxa-[4+2] cycloaddition and the results are summarized in Table 2. In most cases, the reaction proceeded smoothly for a variety of 2-alkenylbenzothiazoles bearing either electron-withdrawing or electron-donating groups on the aromatic group (R) and afforded the corresponding cycloadducts **3a-j** with good to

Table 1 Optimization of the reaction conditions.[a]

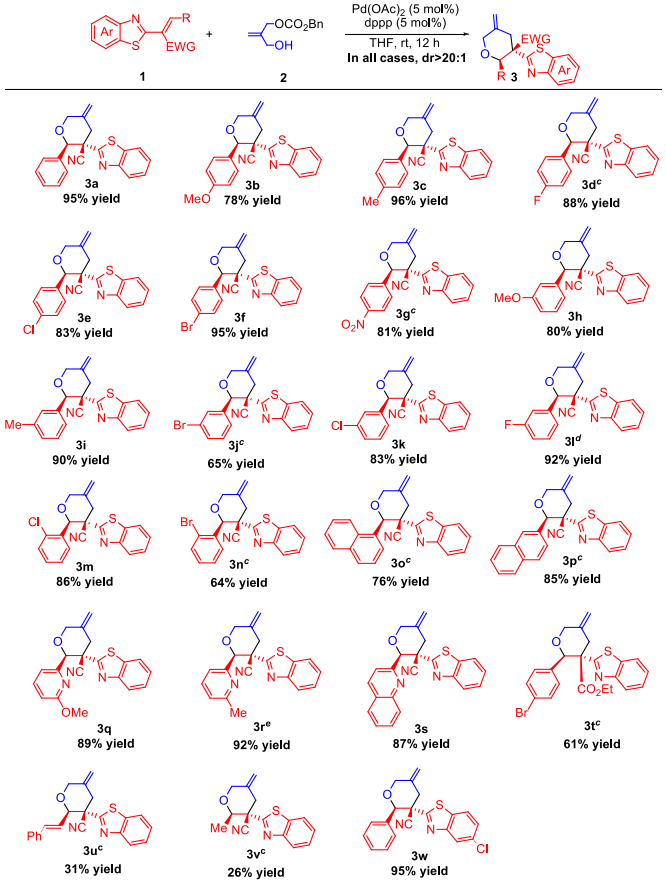


Entry	[M] (mol %)	Ligand (mol %)	Solvent	t (h)	dr (%)[c]	Yield (%)[b]
1	$Pd(OAc)_2$	BINAP	THF	15	>20:1	95
2	$Pd_2(dba)_3$	BINAP	THF	24	-	NR
3	$Pd(dba)_2$	BINAP	THF	24	-	NR
4	$Pd_2(dba)_3\ CHCl_3$	BINAP	THF	24	-	NR
5	$Pd(MeCN)_2Cl_2$	BINAP	THF	24	-	NR
6	$[IrCl(cod)_2]_2$	BINAP	THF	24	-	NR
7	$Pd(OAc)_2$	BINAP	Et_2O	12	>20:1	85
8	$Pd(OAc)_2$	BINAP	Dioxane	24	-	NR
9	$Pd(OAc)_2$	BINAP	Toluene	24	-	NR
10	$Pd(OAc)_2$	BINAP	DCM	24	-	NR
11	$Pd(OAc)_2$	BINAP	MeCN	24	-	NR
12	$Pd(OAc)_2$	Xantphos	THF	12	>20:1	90
13	$Pd(OAc)_2$	DPEPhos	THF	72	>20:1	88
14	$Pd(OAc)_2$	dppp	THF	12	>20:1	95
15	$Pd(OAc)_2$	dppe	THF	12	>20:1	90
16	$Pd(OAc)_2$	PPh_3	THF	24	-	NR
17	$Pd(OAc)_2$	TMPhth	THF	24	-	NR

[a] General conditions: **1a** (0.1 mmol), **2** (0.15 mmol), [Pd] (5 mol %), and **L** (5 mol %) in solvent (1.0 mL) at room temperature. [b] All yields refer to the isolated yields. [c] The dr values were determined by ^1H NMR spectroscopy. NR = No reaction.

excellent yields and excellent diastereoselectivities. Introduction of electron-donating groups (-OMe, -Me) and electron-withdrawing groups (-F, -Cl, -Br, $-NO_2$) at the *para*-position of phenyl ring of 2-alkenylbenzothiazoles led to the corresponding 3-methylenetetrahydropyrans **3b-g** in good to excellent yields. In addition, cycloadducts **3h-l** with *meta*-substituted phenyl substitution were obtained in 65-92% yields. Moreover, the presence of a substituent at the *ortho*-position was well tolerated to afford good yields of **3m** and **3n** . 2-Naphthyl or 1-naphthyl group could also be used as the substituent on R, giving the desired **3o** and **3p** in 76-85% yields at 50 °C for 24 h. Pleasingly, heteroaryl groups, such as 2-pyridyl and 2-quininyl were also worked well under the standard reaction conditions or at 50 °C. The desired cycloadducts **3q-s** were obtained in 87-92% yields. Variation of R on 2-alkenylbenzothiazoles **1** to alkenyl group displayed lower reactivity and resulted in the desired **3u** in 31% yield. Moreover, 2-alkenylbenzothiazoles with aliphatic substitutes on R successfully provided the desired **3v**, albeit with a low yield (26%). Finally, substrate **1w** bearing a chloro substituent on the benzothiazole ring also reacted with allyl carbonates **2** smoothly, giving the expected products **3w** with 95% yield. The relative configuration of the substituted 3-methylenetetrahydropyrans was confirmed by single crystal X-ray analysis of the product **3a** (Fig. 2).[15]

Table 2 Screening of Substrate Scope.[a]



[a] Standard conditions: **1a** (0.1 mmol), **2** (0.15 mmol), $Pd(OAc)_2$ (5 mol%), and dppp (5 mol%) in THF (1.0 mL) at room temperature for 12 h. All dr values were >20 : 1 as determined from the crude ^1H NMR spectra. [b] All yields refer to the isolated yields. [c] 50 °C, 24 h. [d] rt, 24 h. [e] 50 °C.

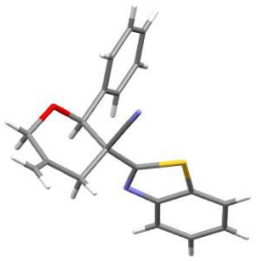
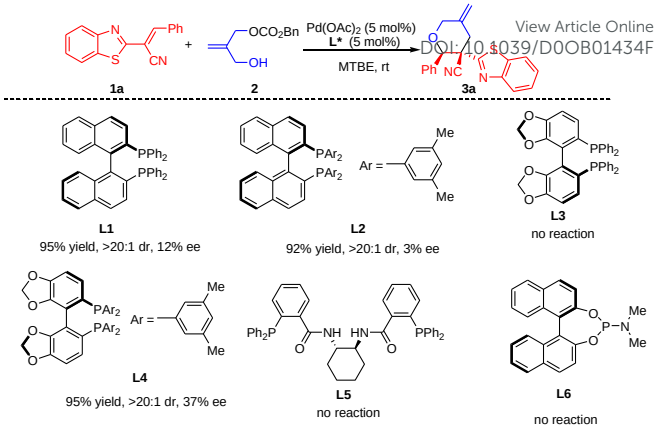


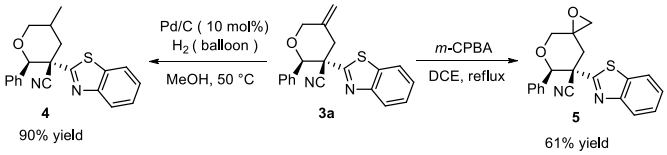
Fig. 2 Single-crystal X-ray diffraction analysis of **3a**.

To further investigate this transformation, we then turn our attention to the asymmetric oxa-[4+2] cycloaddition reaction. First, we performed the above model reaction in the presence of $Pd(OAc)_2$ and (*R*)-BINAP with the ether-type solvent of THF and MTBE, respectively. As a result, MTBE was proved to be better for the improvement of enantioselectivity (12% ee *vs* 5% ee). Subsequently, an extensive screening of chiral bidentate ligands was examined (Scheme 2). Unfortunately, only axially chiral bisphosphine ligand realized the enantioselectivity and gave **3a** in 95% yield and up to 37% ee. when employing (*R*)-DM-SEGphos **L4** as chiral ligand. Trost ligand **L5** and monodentate phosphoramidite ligand **L6** were also tested, however, the reactions failed to afford the desired **3a**.



Scheme 2 Enantioselective studies of this methodology.

To demonstrate the potential utility of 3-methylenetetrahydropyrans, further synthetic transformation of **3a** was performed. As shown in Scheme 3, hydrogenation of **3a** in the presence of H_2 and 10 mol% Pd/C selectively reduced the C=C double bond, forming **4** in 90% yield and >20:1 dr. The oxidation of exocyclic double bond was also achieved by using *m*-CPBA, which provided 61% yield of spirocyclic epoxide **5** in single diasteromer.



Scheme 3 Derivatization of the product **3a**. Reaction conditions: (a) 10 mol% Pd/C, H_2 (balloon), MeOH, 50 °C, 12 h; (b) *m*-CPBA (1.8 equiv.), DCE, reflux, 24 h.

Conclusions

In summary, we have developed an efficient strategy for the highly diastereoselective synthesis of 3-methylenetetrahydropyrans *via* palladium catalyzed oxa-[4+2] cycloaddition of 2-alkenylbenzothiazoles with allyl carbonates bearing a nucleophilic alcohol side chain. The reaction features good functional group tolerance, allowing efficient access to a wide variety of highly substituted 3-methylenetetrahydropyrans under mild conditions. Further transformations of the cycloadducts demonstrated the synthetic utility of this process and provided useful tetrahydropyran derivatives. Investigations concerning the asymmetric study, as well as the use of this methodology are currently underway in our laboratory.

Conflicts of interest

There are no conflicts to declare.

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15 CCDC 2011625 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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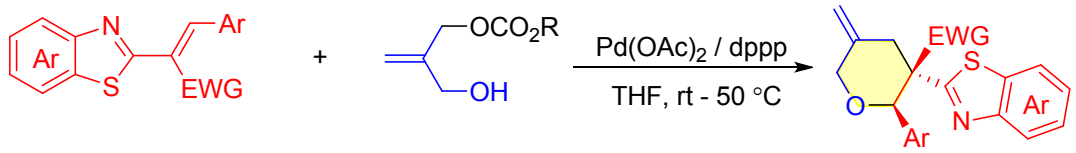
A highly diastereoselective synthesis of 3-methylenetetrahydropyrans *via* palladium-catalyzed oxa-[4+2] cycloaddition of 2-alkenylbenzothiazoles with allyl carbonates bearing a nucleophilic alcohol side chain is described



23 examples
26-96% yield
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