Oxygen Heterocycles

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Palladium-Catalyzed Asymmetric Synthesis of 2-Alkynyl Oxacycles**

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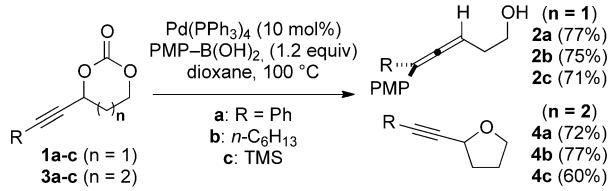
The stereodefined synthesis of saturated heterocycles is an area of prime importance in organic chemistry, these motifs being widespread in both natural products and pharmaceuticals. Tetrahydrofurans (THFs) and tetrahydropyrans (THPs) in particular are not only valuable building blocks in synthesis,[1] but are among the most common structural motifs of bioactive heterocycles.[2] Oxacycles functionalized with unsaturated substituents represent a subclass of distinct synthetic utility, and the development of stereocontrolled routes for their synthesis is an important aim.[3] Whilst *E*-alkenyl THFs and THPs can be readily prepared using intramolecular etherifications,[1c,4] the stereoselective synthesis of alkynyl[5] or *Z*-alkenyl oxacycles[4e] presents a significantly greater challenge.

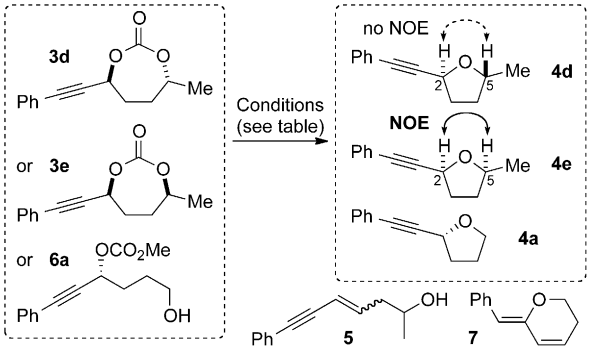
In the course of investigations into the palladium-catalyzed synthesis of allenyl alcohols from propargylic cyclic carbonates (Scheme 1),[6] we discovered that whilst the six-membered cyclic carbonates **1a–c** successfully afforded the β-allenyl alcohols **2a–c** under Suzuki cross-coupling conditions,[7] the seven-membered cyclic carbonates **3a–c** exclusively gave the unexpected 2-alkynyl tetrahydrofurans **4a–c**. We recognized that this side reaction might offer a new and general method to prepare alkyne-substituted oxacycles, and report here the optimization of this process and its application to the highly stereoselective synthesis of polysubstituted 2-alkynyl THFs and THPs.



Scheme 1. Palladium-catalyzed Suzuki cross-coupling reactions of propargylic cyclic carbonates. PMP = 4-methoxyphenyl.

To investigate the stereoselectivity of the cyclization, we prepared the diastereomeric disubstituted cyclic carbonates **3d** and **3e** (Table 1),[8] the relative stereochemistry of the former being confirmed through single-crystal X-ray diffraction.[9] We initially tested the cyclization of **3d** solely in the presence of $[Pd(PPh_3)_4]$ (1 mol%), which to our surprise led

Table 1: Optimization of the cyclization of cyclic and acyclic carbonates.[a]



Entry	Substr.	Catalyst	Additive (equiv)	Prod. ratio[b]	*ee* [%][c]	Yield [%][d]
1	**3d**	$[Pd(PPh_3)_4]$	none	0:0:100	–	84
2	**3d**	$[Pd(PPh_3)_4]$	$PMPB(OH)_2$ (1.2)	90:10:0	–	79
3	**3e**	$[Pd(PPh_3)_4]$	$PMPB(OH)_2$ (1.2)	10:90:0	–	83
4	**3d**	$[Pd(PPh_3)_4]$	$B(OMe)_3$ (1.2)	49:3:48	–	–[e]
5	**3d**	$[Pd(PPh_3)_4]$	$B(OH)_3$ (1.2)	80:20:0	–	85
6	**3d**	$[Pd(PPh_3)_4]$	PPTS (1.2)	95:5:0	–	85
7	**3d**	$[Pd(PPh_3)_4]$	PPTS (0.1)	99:1:0	–	99[f]
8	**3e**	$[Pd(PPh_3)_4]$	PPTS (0.1)	5:95:0	–	99[f]
9	**6a**	$[Pd(PPh_3)_4]$	PPTS (0.1 or 1.2)	–	–	n.r.
10	**6a**	$[Pd(PPh_3)_4]$	$B(OH)_3$ (1.1)	100:0	20	99
11	**6a**	$[Pd(dba)_2]$/dppp	none	44:56	96	–[e]
12	**6a**	$[Pd(dba)_2]$/dppb	none	77:23	97	–[e]
13	**6a**	$[Pd(dba)_2]$/dppf	none	83:17	97	95[g]
14	**6a**	$Pd(OAc)_2$/dppf	none	82:18	97	95
15	**6a**	$Pd(OAc)_2$/dppf	$B(OH)_3$ (0.5)	100:0	96	99

[a] Reactions conducted in dioxane at 100°C; reaction times 2–30 min; entries 1–8 performed using $[Pd(PPh_3)_4]$ (1 mol%), entries 9–15 performed using 5 mol% [Pd] and 10 mol% ligand; **3d** and **3e** prepared with >99:1 d.r.; **6a** prepared with 98% *ee*. [b] From **3d** and **3e**: ratio of **4d**/**4e**/**5**; From **6a**: ratio of **4a**/**7**; ratios determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [c] Determined by HPLC on a chiral stationary phase. [d] Combined yield of isolated products. [e] Not determined. [f] Reaction conducted at 50°C. [g] Product inseparable from dba. PPTS = pyridinium *p*-toluenesulfonate, dppp = 1,3-bis(diphenylphosphino)propane, dba = dibenzylideneacetone, dppb = 1,4-bis(diphenylphosphino)butane, dppf = 1,1′-bis(diphenylphosphino)ferrocene.

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[+] X-ray crystal structure analysis of **3d**.

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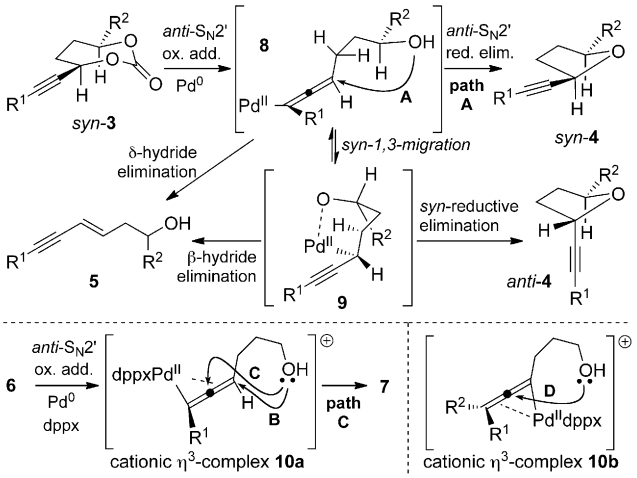
to the exclusive formation of enyne **5** (Table 1, entry 1, 84%, $E/Z = 58{:}42$). On repeating the reaction in the presence of arylboronic acid, the desired reactivity was restored, with **3d** and **3e** leading to a complementary 9:1 mixture of THF products **4d** and **4e** respectively (Table 1, entries 2 and 3). In each case, the major diastereomer was formed with retention of configuration of the propargylic stereocenter, as evidenced by NOE enhancements between H2 and H5 in **4e** (arising from carbonate **3e**) which were absent in **4d**.[8] To investigate whether the boronic acid was acting as a Brønsted or Lewis acid, we conducted a screen of other additives. Whilst trimethyl borate delivered **4d** with high stereoselectivity (Table 1, entry 4), its ability to prevent enyne formation was reduced, suggesting a purely Lewis acidic role to be unlikely. Boric acid itself was also able to mediate THF formation, albeit with reduced selectivity (Table 1, entry 5). In contrast, PPTS proved most effective in terms of yield and selectivity (Table 1, entry 6); reducing the loading of PPTS and lowering the reaction temperature (to 50°C) led to highly diastereoselective cyclizations for both **3d** and **3e** (Table 1, entries 7 and 8).

With these encouraging results in hand, we turned our attention to the nature of the propargylic leaving group. It was clear that if a cyclic carbonate is used, the hydroxy groups of its diol precursor need not be differentiated; however, its synthesis is likely restricted to seven-membered rings, which in turn limits the ring size of the product oxacycle. We therefore decided to investigate an acyclic carbonate leaving group, with the internal nucleophile now an alcohol rather than the alkoxide we presumed to be generated in situ from the cyclic carbonate. We selected acyclic carbonate **6a** (Table 1) as a test substrate for this chemistry, where Noyori transfer hydrogenation[10] was used to install the propargylic stereocenter (98% *ee*).[8] To our surprise, no reaction was observed under the optimized conditions developed for the cyclic carbonates (i.e. PPTS as additive; Table 1, entry 9); however, reaction in the presence of boric acid gave the tetrahydrofuran **4a** in quantitative yield but a disappointing 20% *ee* (Table 1, entry 10).

We hypothesized that the surprising difference in reactivity and stereoselectivity between the cyclic and acyclic carbonates might arise from the more reactive nature of the alkoxide generated from the cyclic carbonates (compared to the alcohol in **6a**). It has been shown that bidentate phosphine ligands can reduce the extent of stereochemical erosion in propargylic cross-coupling reactions,[6a,11] and we were pleased to find that the combination of $[Pd(dba)_2]$ or $Pd(OAc)_2$ with a range of these ligands led to consistently high stereoselectivity ($\geq 96\%$ *ee*; Table 1, entries 11–14). Despite this success, these reactions suffered from the formation of varying amounts of enol ether **7**, a byproduct which likely forms through competitive attack of the alcohol on the central carbon atom of the allenylpalladium(II) intermediate. For reasons which remain unclear, the production of enol ether **7** could be minimized by using dppf as ligand (Table 1, entries 13 and 14) and eliminated entirely in the presence of boric acid (Table 1, entry 15).

Possible mechanisms for the two cyclizations are illustrated in Scheme 2. For the cyclic carbonate *syn*-**3**, initial *anti*-S_N2' oxidative addition[6c,12] leads, following loss of CO_2 and protonation, to the allenylpalladium intermediate **8**, which can form the major furan product *syn*-**4** through an *anti*-S_N2'-type reductive elimination (path A). It is well-known that allenyl–palladium complexes can undergo *syn*-facial 1,3-migrations to give complexes of type **9**,[13] in this case potentially stabilized by the proximal nucleophile. *Syn* reductive elimination from this species would generate the minor isomer *anti*-**4**. From either intermediate **8** or **9**, a competing hydride elimination, possibly mediated by the alkoxide, could give enyne **5**. For the acyclic carbonates, the high stereoselectivity observed when bidentate phosphine ligands are used may be explained by the intermediacy of the cationic η^3-allenylpalladium(II) complex **10a**,[14] which not only reduces the propensity for 1,3-migration,[6a,11] but also renders the attack of the alcohol stereospecific (path B). However, this intermediate also accounts for the formation of enol ether **7**, which arises from competitive attack of the alcohol on the central allene carbon of **10a** (path C);[14] indeed, enol ether **7** has been prepared in this manner.[15] In fact, the formation of propargylic substitution products from attack of heteroatoms on the terminal allene carbon of complexes such as **10** is rarely observed.[16] This outcome is likely due to the relative positioning of the palladium and nucleophile in the allenylpalladium intermediate, and the resulting trajectory of nucleophilic attack: In the majority of reported cases,[14,15] the palladium is positioned on the allene carbon proximal to the nucleophile, and the trajectory of attack is perpendicular to this alkene (path D, complex **10b**), whereas in our system, the palladium is located on the distal allene carbon, and central carbon attack takes place via an orthogonal trajectory (path C). We speculate that the role of the acidic additives in preventing the formation of **5** or **7** may be to "soften" the alkoxide nucleophile (for example through formation of a borate complex, as proposed by Trost et al. in related allylic etherifications).[17]



Scheme 2. Proposed cyclization mechanisms.

With optimized sets of reaction conditions established, a selection of cyclic and acyclic carbonates were prepared to explore the scope of the reaction for asymmetric oxacycle synthesis (Table 2).[8,18] Pleasingly, the monosubstituted cyclic

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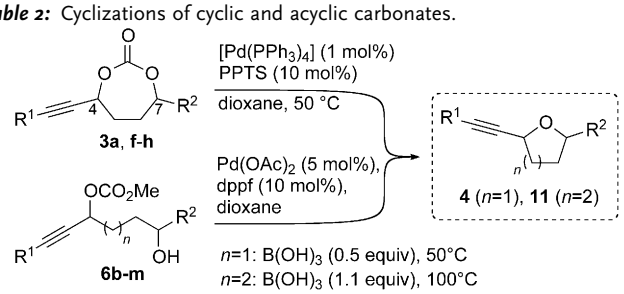
Table 2: Cyclizations of cyclic and acyclic carbonates.



Entry	Substrate[a]	Product[b]	*ee* [%][c]/ *d.r.*[d]	Yield [%][e]
1	**3a**	**4a**	95	99
2	**3f**	**4f**	96	99
3	**3g**	**4g**	98	86[f]
4	**3h**	**4h**	83:17	90[f]
5	**6b**	**4h**	93:7	76[g]
6	**6c**	**4i**	96:4	91[g]
7	**6d**	**11a**	94	99
8	**6e**	**11b**	87	92
9	**6f**	**11c**	90:10	85
10	**6g**	**11d**	95:5	45[h]
11	**6h**	**4j**	95:5	88
12	**6i**	**4k**	95:5	82
13	**6j**	**11e**	97:3	82[i]
14	**6k**	**11f**	96:4	77[i]

Table 2: (Continued)

Entry	Substrate[a]	Product[b]	*ee* [%][c]/ *d.r.*[d]	Yield [%][e]
15	**6l**	**4l**	96:4	75
16	**6m**	**4m**	97:3	81

[a] Substrates prepared with ≥95% *ee*, and >95:5 d.r. where applicable; see the Supporting Information for details. [b] Major product [c] Determined by HPLC on a chiral stationary phase. [d] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [e] Yield of the isolated major diastereomer. [f] Conducted at 100°C. [g] 1.1 equiv $B(OH)_3$. [h] 50% of **6g** consistently recovered. [i] 0.5 equiv $B(OH)_3$.

carbonates **3a**,**f**,**g** delivered the corresponding furans in excellent yield and enantioselectivity (Table 2, entries 1–3), showing that aryl-, alkyl-, and heteroaryl-substituted alkynes are all competent substrates. However, we were surprised to find that the allyl-substituted carbonate **3h**, which closely resembles the methyl-substituted carbonate **3d** used earlier, required elevated temperatures to achieve high conversion and cyclized with inferior stereoselectivity. In contrast, the use of the allyl-substituted acyclic carbonates **6b** and **6c** gave the *anti*- and *syn*-disubstituted THFs **4h** and **4i** with very high diastereoselectivity.

Attention was next turned to THP formation, which would likely be difficult to achieve using a cyclic carbonate because of the problem of preparing the requisite eight-membered ring. We were thus delighted to find that carbonates **6d** and **6e** gave the THPs **11a** and **11b** with excellent yield and *ee* (Table 2, entries 7 and 8), despite the need for a higher temperature (100°C) and additional boric acid. This selectivity was maintained for the disubstituted substrates **6f** and **6g**, which afforded the corresponding 2,6-disubstituted THPs **11c** and **11d** with high selectivity for both isomers (Table 2, entries 9 and 10).

With successful stereoselective cyclizations achieved for relatively simple acyclic systems, we decided to study some more complex substrates to conduct a deeper investigation into aspects of selectivity in the reaction, in particular the preference for the formation of differently sized rings. These experiments were carried out on enantiomerically and diastereomerically pure carbonates containing *syn* 1,2-diols,[8,19] using both diastereomers of each carbonate (relative to the *syn* diol) in order to investigate any differences in the cyclization to *cis* or *trans* oxacycles. Firstly, substrates **6h** and **6i** were evaluated (Table 2, entries 11 and 12), which were designed to test the preference for five- or six-membered ring formation. Perhaps unsurprisingly on kinetic grounds, the THFs **4j** and **4k**, featuring a stereodefined hydroxy group on the furan side chain, proved to be the exclusive products. The homologous substrates **6j** and **6k** (Table 2, entries 13 and 14) lead exclusively to THP formation over the corresponding oxepanes, with very high selectivity for both the 2,6-*anti*- and 2,6-*syn*-THPs. Finally, we pushed the competition between five- and six-membered ring formation to the limit using substrates **6l** and **6m** (Table 2, entries 15 and 16), where cyclization of the tertiary alcohol would give a 2,5,5-trisubstituted furan, whereas the cyclization of the secondary alcohol would give a disubstituted pyran. Remarkably, both of these substrates gave solely the THF products **4l** and **4m**.

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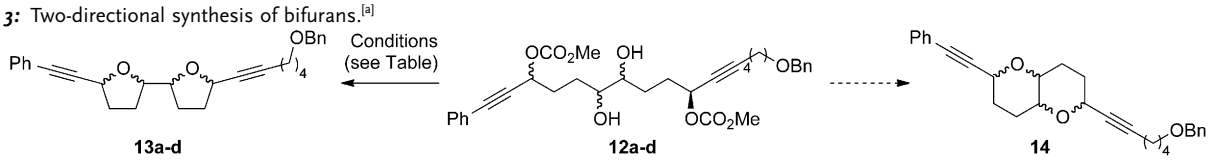
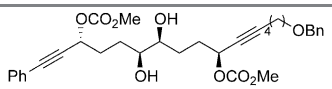
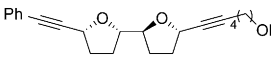
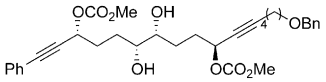
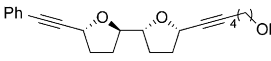
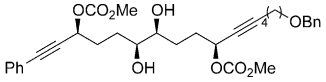
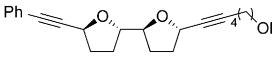
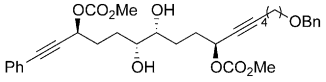
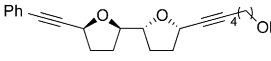
Table 3: Two-directional synthesis of bifurans.[a]



13a-d 12a-d 14

Entry	Substrate[b]	Bifuran product	Yield [%][c]
1	 **12a**	 **13a**	82
2	 **12b**	 **13b**	73
3	 **12c**	 **13c**	71
4	 **12d**	 **13d**	81

[a] Reaction conditions: $Pd(OAc)_2$ (5 mol%), dppf (10 mol%), $B(OH)_3$ (0.5 equiv), dioxane (0.1 M), 75 °C, 16 h. [b] All substrates prepared with 94:6 d.r. and >99% *ee*. [c] Yield of isolated bifuran with >95:5 d.r..

In all six of these more challenging cases, the reactions proceeded with excellent diastereoselectivities (≥95:5) and yields.

These experiments firmly established the regiochemical preferences of the cyclization of diol-containing substrates, and as a final demonstration of the methodology, we contemplated the synthesis of bis-oxacycles, motifs which are commonplace in many natural product families.[2c,e] The high kinetic selectivity exhibited in the cyclization ought to permit the stereodefined synthesis of such frameworks, and towards this end we prepared a selection of substrates to investigate a two-directional formation of bicyclic oxacycles.[8] Our prediction for these substrates (**12a–d**, Table 3) was that the bifuran product **13** would be kinetically favored over the fused-ring pyranopyran **14**. To our delight, the cyclization of all four bis-carbonate diols **12a–d** led exclusively to the formation of the bifuran frameworks **13a–d**, with none of the pyranopyran being detected by ^{1}H NMR and ^{13}C NMR spectroscopic analysis,[20] and in all cases cyclization occurred with the expected retention of stereochemistry at the propargylic center as assigned by ^{1}H NMR NOE enhancements for the 2,5-*syn*-disubstituted furans.[8] The exquisite selectivity observed in this process for the transfer of stereochemistry to the cyclized product thus gives access to multiple permutations of the bifuran ring system using a single synthetic strategy.

In summary, we have developed two distinct catalytic systems for the highly stereoselective synthesis of 2-alkynyl tetrahydrofurans and tetrahydropyrans from cyclic and acyclic carbonates. We have developed a clear understanding of the preference for the formation of different ring sizes, irrespective of steric considerations, and have in addition applied the reaction to the stereocontrolled synthesis of bicyclic oxacycles. Further investigations into the scope of this cyclization, and its application towards selected targets, are ongoing.

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Keywords: alkynes · asymmetric synthesis · cyclization · oxygen heterocycles · palladium

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