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ARTICLE

Synthesis of bicyclic ethers by a palladium-catalyzed oxidative cyclization–redox relay–π-allyl-Pd cyclization cascade reaction†

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Bicyclic ether scaffolds are found in a variety of natural products and are of interest in probe and drug discovery. A palladium-catalyzed cascade reaction has been developed to provide efficient access to these scaffolds from readily available linear diene–diol substrates. A Pd redox-relay process is used strategically to transmit reactivity between an initial oxypalladative cyclization and a subsequent π-allyl-Pd cyclization at remote sites. The reaction affords a variety of bicyclic ether scaffolds with complete diastereoselectivity for *cis*-ring fusion.

Introduction

Bicyclic ether scaffolds are found in diverse natural products, such as chafuroside B (**1**), a photoprotective agent,[1] goniofupyrone (**2**), a NADH oxidase inhibitor,[2] and panacene (**3**), a shark antifeedant[3] (**Figure 1a**). Our lab has a long-standing interest in developing efficient, flexible methods to access natural product-based scaffolds for probe and drug discovery.[4] While these bicyclic ether natural products and related scaffolds have typically been synthesized using sequential annulation reactions,[1a,2a,2b,3,5] we envisioned that such bicycles might be accessed efficiently from simple substrates using a cascade reaction.[6] Indeed, biomimetic polyepoxide polycyclization cascades have been used previously to synthesize polycyclic ethers.[7] We sought to pursue a conceptually distinct approach, in which a redox-relay reaction[8] could be used to connect successive cyclization reactions at two remote sites to afford bicyclic ethers products (**Figure 1b**).

Redox-relay reactions (also known as chain-running, chain-walking, and metal-walking) have attracted much current interest due to their ability to transmit reactivity tracelessly through saturated portions of a molecule.[8-9] We recently reported a tandem intramolecular oxypalladation–redox-relay reaction to generate functionalized tetrahydrofurans.[4f] Building upon this work, we envisioned that, under Pd(II) catalysis, a linear diene–diol substrate (**4**) could undergo an initial annulation via oxidative cyclization (**5**)[10], followed by a redox-relay process in which Pd migration terminates at an olefin to generate a π-allyl-Pd species (**6**), which could then

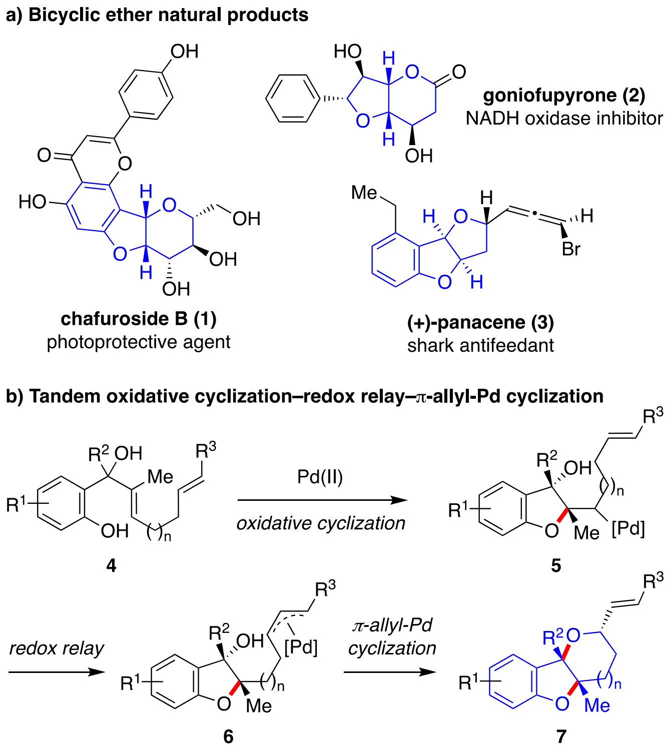

Fig. 1 (a) Bicyclic ether scaffolds (blue) are found in a variety of natural products. (b) Proposed Pd-catalyzed tandem oxidative cyclization–redox relay–π-allyl-Pd cyclization cascade transmits reactivity tracelessly between two remote cyclization reactions to generate bicyclic ether scaffolds.

undergo a second annulation (**7**).[11] While redox-relay processes have been integrated both before and after annulation reactions,[4f,11b] this would be the first example in which a redox-relay process would be used to link two successive annulation reactions, provided that a single catalyst system could be identified to catalyze all three processes.

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Herein, we report the successful implementation of this new synthetic construct. The reaction provides a wide range of bicyclic ethers with various substituents and ring sizes, with complete diastereoselectivity for *cis*-ring fusion. Mechanistic studies suggest that this selectivity results from an equilibrium process that overcomes poor diastereoselectivity in the initial oxidative cyclization. Modest diastereoselectivity in the second, π-allyl-Pd cyclization is readily addressed by functionalization and epimerization of the side chain, concurrently providing a handle for further derivatization.

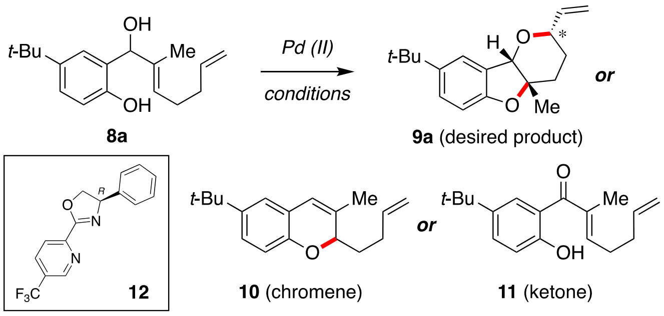
Results and discussion

Development of Pd-catalyzed bicyclization cascade reaction.

To investigate this concept, we synthesized diene–diol substrate **8a** in 4 modular steps from methyl vinyl oxirane (**Figure S1**).[12] Initial attempts to effect the cascade reaction of diene–diol **8a** using our previously described conditions for THF synthesis ($PdCl_2$, benzoquinone)[4f] produced chromene **10** rather than the desired bicyclic ether **9a** (**Table 1**, entry 1). We posited that this undesired side reaction was caused by adventitious acid from the catalyst, which promotes elimination of the benzylic alcohol followed by phenol *endo*-cyclization. Indeed, treatment of diene–diol **8a** with HCl or TFA also produced chromene **10** (**Table S1**).[12] Use of other solvents did not suppress this side reaction (entries 2–4), and addition of Cs_2CO_3 resulted in substrate decomposition (entry 5). Use of $Pd(OAc)_2$ led instead to oxidation product **11** (entry 6) while $Pd(TFA)_2$ again gave chromene **10** (entry 7).

Recognizing the requirement for a basic catalyst system to suppress chromene formation, we evaluated Sigman's Pd–PyrOx(**12**) catalyst, which has been used with $Ca(OH)_2$.[9k] While direct application of the reported reaction conditions to our sterically-encumbered substrate gave no reaction (entry 8), increasing the temperature to 80 °C led to preferential formation of the desired bicyclic product (±)-**9a** (entry 9 and **Table S2** and **Table S3**).[12] Residual chromene (**10**) formation may arise from Pd-mediated 6-*endo* cyclization of the substrate **8a** followed by β-elimination of the benzylic alcohol,[13] and could be suppressed further in cyclopentyl methyl ether (CPME) or dioxane (entries 10, 11 and **Table S4**).[12] Replacement of PyrOx ligand **12** with 2,2-bipyridine resulted in exclusive formation of the oxidation side product **11** (entry 12 and **Table S5**), which also increased using PyrOx analogues with electron-donating pyridyl substituents (**Table S6**).[12] Conversely, PyrOx analogues with more electron-withdrawing substituents resulted in incomplete, stalled reactions. Finally, fine-tuning of catalyst loading afforded optimized conditions (9 mol% $Pd(OTs)_2(MeCN)_2$, 12 mol% **12**) that provided bicyclic ether **9a** in 60% isolated yield (**Figure 2a**), with complete *cis*-diastereoselectivity across the ring fusion and 4:1 dr (α/β) at the vinyl side chain (assigned by nOe and X-ray analyses).[12] Importantly, the side chain was readily equilibrated to the α-diastereomer (20:1 dr) by conversion of the vinyl group to the corresponding methyl ester **17** in two steps and 85% yield, which concurrently provided a functional group handle for downstream derivatization (**Figure 2b**).

Table 1 Discovery and optimization of Pd-catalyzed bicyclization cascade reaction.



entry	reagents	solvent	temp (°C)	product ratio[a] (**8a** : **9a** : **10** : **11**)
1	$PdCl_2$, BQ[b]	THF	65	0 : 0 : 100 : 0
2	$PdCl_2$, BQ[b]	PhH	65	51 : 0 : 49 : 0
3	$PdCl_2$, BQ[b]	DMF	75	0 : 0 : 100 : 0
4	$PdCl_2$, BQ[b]	dioxane	75	0 : 0 : 100 : 0
5	$PdCl_2$, BQ, Cs_2CO_3[c]	dioxane	75	Decomp
6	$Pd(OAc)_2$, BQ[b]	THF	65	86 : 0 : 0 : 14
7	$Pd(TFA)_2$, BQ[b]	THF	65	68 : 0 : 32 : 0
8	$Pd(OTs)_2(CH_3CN)_2$, BQ, **12**, $Ca(OH)_2$[d]	$PhCF_3$	22	100 : 0 : 0 : 0
9	$Pd(OTs)_2(CH_3CN)_2$, BQ, **12**, $Ca(OH)_2$[d]	$PhCF_3$	80	6 : 62 : 27 : 5
10	$Pd(OTs)_2(CH_3CN)_2$, BQ, **12**, $Ca(OH)_2$[d]	CPME	80	0 : 85[e] : 10 : 5
11	$Pd(OTs)_2(CH_3CN)_2$, BQ, **12**, $Ca(OH)_2$[d]	dioxane	80	0 : 82 : 3 : 14
12	$Pd(OTs)_2(CH_3CN)_2$, BQ, 2,2-bipyridine, $Ca(OH)_2$[d]	$PhCF_3$	80	0 : 0 : 0 : 100

[a]Ratios of major products determined by ^{1}H-NMR analysis of crude reaction product; all products racemic. [b]10 mol% Pd catalyst, 2 equiv benzoquinone, 16 h. [c]10 mol% $PdCl_2$, 2 equiv benzoquinone, 2 equiv Cs_2CO_3, 16 h. [d]8 mol% $Pd(OTs)_2(MeCN)_2$, 3 equiv benzoquinone, 10 mol% PyrOx ligand **12** or 2,2-bipyridine, 1 equiv $Ca(OH)_2$, 3 Å MS, 16 h. [e]4:1 dr, major diastereomer as shown (*). *Abbreviations*: BQ = 1,4-benzoquinone; CPME = cyclopentylmethyl ether; decomp = decomposition; DMF = *N*,*N*-dimethylformamide; TFA = trifluoroacetic acid; THF = tetrahydrofuran; Ts = *p*-toluenesulfonyl.

Scope of Pd-catalyzed bicyclization cascade reaction.

We next investigated the scope of the bicyclization cascade. Substrates **8b-f** (**Figure S1**)with substituents *para* to the phenol were designed to evaluate electronic effects. All were successfully converted to bicyclic products **9b–f** (**Figure 2a**), with electron-withdrawing substituents resulting in slightly lower yields (**9c,d**) while an electron-donating substituent resulted in increased yield (**9f**). Complete diastereoselectivity for *cis*-ring fusion was observed in all cases, with diastereoselectivity at the vinyl side chain modestly favoring the α-diastereomer. Bicyclic ether **9b** was also synthesized effectively on 1-mmol and 1-g scales.

To assess the impacts of substituents at other positions, we synthesized additional substrates by variations on the general route.[12] Consistent with the electronic trends above, dimethoxy-substituted scaffold **13** was formed in good yield from the corresponding electron-rich phloroglucinol substrate

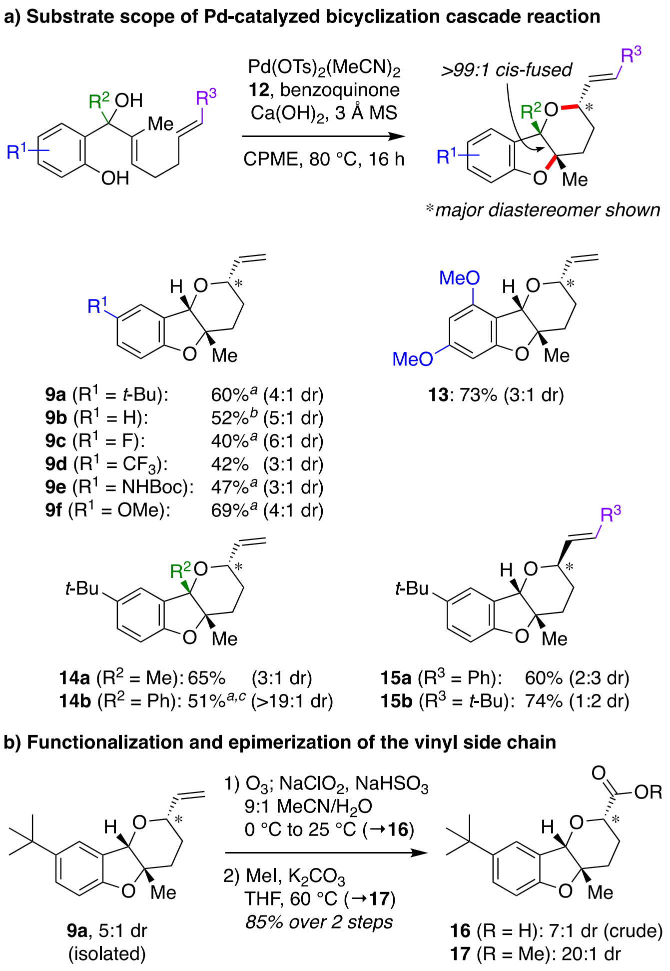


Fig. 2 (a) Substrate scope of the Pd-catalyzed bicyclization cascade reaction. Yields reported are an average of two independent experiments on ≈40-mg scale. dr values are reported for crude reaction products based on ^{1}H-NMR analysis. All products are racemic. *Reaction conditions*: 9 mol% $Pd(OTs)_2(MeCN)_2$, 12 mol% **12**, 3 equiv benzoquinone, 1 equiv $Ca(OH)_2$, 300 mg/mmol 3 Å MS, CPME, 80 °C, 16 h. [a]Diastereomers separable by column chromatography, combined yield shown. [b]Also prepared on 1-mmol scale (42%) and 1-g scale (38%). [c]Reaction time 40 h. (b) Functionalization of the vinyl side chain allows epimerization to major diastereomer.

(not shown).[12] Tertiary alcohol nucleophiles (R^2) were accommodated in the second, π-allyl-Pd cyclization (**14a**, **14b**), including a highly activated bis-benzylic/allylic alcohol (**14b**). Inclusion of the large angular phenyl substituent in **14b** required longer reaction time but also afforded complete α-diastereoselectivity at the vinyl side chain. Substitution of the terminal olefin (R^3) was also tolerated, surprisingly with inverted β-diastereopreference at the side chain (**15a**, **15b**).

We next explored alternate alkyl chain lengths (**Figure 3**).[12] The 1,4-dienes **18a–d** underwent the desired cascade reaction to form [5,5]-bicyclic products **19a–d** in good to excellent yields. Interestingly, inverted β-diastereopreference was observed at the vinyl side chain (nOe analysis).[12] In contrast, attempted cyclization of 1,6-diene **20** yielded mainly unreacted starting material and a complex mixture of products, rather than the desired [5,7]-bicyclic ether **21**.

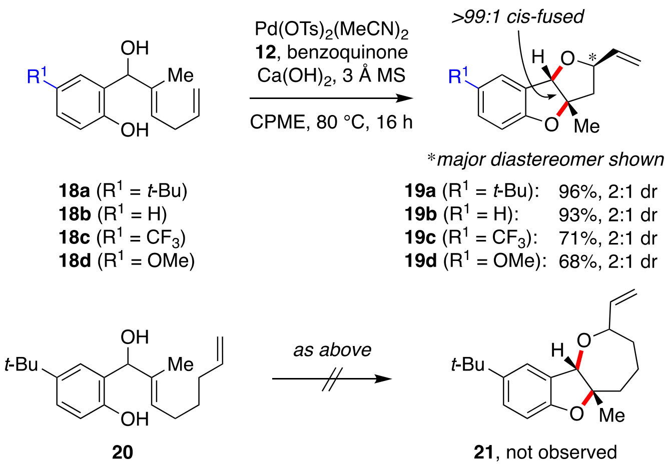


Fig. 3 Extension of bicyclization cascade to [5,5]- and [5,7]-ring systems. *Reaction conditions*: 9 mol% $Pd(OTs)_2(MeCN)_2$, 12 mol% **12**, 3 equiv benzoquinone, 1 equiv $Ca(OH)_2$, 3 Å MS, CPME, 80 °C, 16 h. Yields reported are an average of two independent experiments on ≈40-mg scale. All products are racemic.

Because the initial oxidative cyclization forms a 5-membered ring in all cases, this indicates that the π-allyl-Pd cyclization plays an important role in the efficiency of the overall cascade.

Mechanistic studies of Pd-catalyzed bicyclization cascade reaction.

We carried out preliminary studies to probe the mechanism of the cascade reaction. Exclusive formation of *cis*-fused products requires complete diastereoselectivity in the initial oxidative cyclization, which is highly unusual for 5-membered ring-forming oxypalladations.[4f,10c,14] In contrast, we found that substrates unable to undergo the second, π-allyl-Pd cyclization formed monocyclic products with little or no diastereoselectivity (**Figure S2a**). Based on these results, we propose that *cis*-fusion in the cascade reaction results from an equilibrium process, in which the initial oxidative cyclization[13b,15] and redox-relay steps are reversible,[9a,16] while the π-allyl-Pd cyclization is irreversible but does not proceed to *trans*-fused products due to ring strain in the transition state, ultimately leading to formation of solely *cis*-fused products under the Curtin–Hammett principle (**Figure S2b**). The π-allyl-Pd cyclization is presumed to proceed with inversion of configuration relative to Pd for alkoxides.[17] Thus, the mixture of vinyl side chain diastereomers arises from a mixture of π-allyl-Pd diastereomers formed from single-bond rotamers present during the redox-relay process.[9h] Reactions with enantioenriched substrates and catalysts did not identify any matched/mismatched cases, consistent with substrate control over this stereocenter.[12]

Conclusions

Strategic use of a redox-relay process to transmit reactivity between two successive cyclization reactions has provided versatile, efficient access to bicyclic ether scaffolds from readily available, linear diene–diol substrates. The redox-relay process leverages a Pd migration terminating at an olefin to generate a reactive π-allyl-Pd species, a useful synthetic construct that has received limited attention to date.[18] The reaction provides complete diastereoselectivity for *cis*-ring fusion despite poor diastereoselectivity in the initial oxidative cyclization. Mechanistic studies are consistent with reversibility of this first cyclization and an equilibrium process in which ring fusion diastereoselectivity is ultimately dictated by the downstream, irreversible π-allyl-Pd cyclization. While the resulting vinyl side chain is formed with modest diastereoselectivity, this site is readily epimerized in high diastereoselectivity for preparative applications. It may also be possible in the future to control the diastereoselectivity of this π-allyl-Pd cyclization with new catalyst designs. Future efforts will focus on further investigations of reaction mechanism, expansion of reaction scope, and applications to natural product and library synthesis.

Conflicts of interest

There are no conflicts of interest to declare.

Acknowledgements

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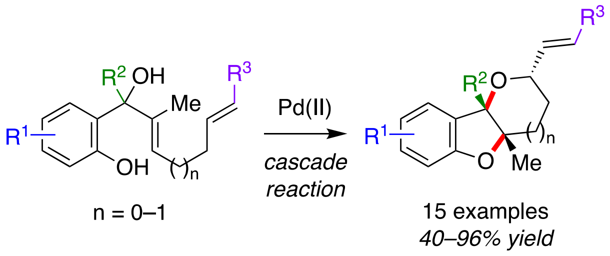
Table of Contents Graphic



A redox-relay process links two successive Pd-catalyzed cyclization reactions at remote sites to afford bicyclic ether products from readily available linear diene–diol substrates.