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Catalytic Enantioselective Cyclization and C3-Fluorination of Polyenes

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Abstract

(xylyl-phanephos)Pt^{2+} in combination with XeF_2 mediates the consecutive diastereoselective cation-olefin cyclization/fluorination of polyene substrates. Isolated yields were typically in the 60s while enantioselectivies reached as high as 87%. The data are consistent with a stereoretentive fluorination of a P_2Pt-alkyl cation intermediate.

The fluorination of pharmaceutical drug candidates is an important strategy for masking metabolic hot spots.[1] Despite recent progress with electrophilic fluorinating reagents,[2] the synthesis of such compounds is still challenging and many deficiencies remain, especially in the asymmetric fluorination of non-enolate-based carbon nucleophiles.[3,4,5] Fluorinated steroids (Scheme 1), in particular, are important bioactive compounds with a deficiency of methods for their synthesis.[6,7,8]

De novo syntheses of carbocycles with the flexibility for F-incorporation are rare, though such methods would considerably expand the accessibility of such privileged structures.[1] Transition metal catalyzed cyclizations, if suitably coupled to M-C fluorination reactions,[4] could provide a route to complex fluorinated carbo- and hetero-cycles with control of absolute and relative stereochemistry.

Electrophilic Pt(II) complexes are effective initiators of C-C bond forming cation-olefin cascades.[9,10,11] The fate of the organometallic intermediate of these cascades can be controlled through ligand choice, and when the supporting ligand is a diphosphine, this intermediate is susceptible to β-H elimination and leads to net dehydrogenated products. If this complex could instead be intercepted by a Pt-C fluorination reaction, a catalytic cyclization/fluorination protocol would result with concomitant access to C3-fluorinated compounds.[6d] The rapidity and stereospecificity with which [(triphos)Pt-R][BF_4] reacts with XeF_2 to yield C-F products (Eq. 1) suggested that the desired interception might be capable of competing with β-H elimination.[12]

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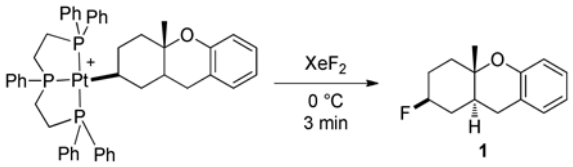
Characterization data for all new compounds and synthetic procedures are included in the Supporting information. This material is available free of charge via the Internet at http://pubs.acs.org.



(1)

In the diphosphine catalyst series that we have examined, (*S*)-xylyl-phanephos ((*S*)-(–)-4,12-bis[di(3,5-xylyl)phosphine]-[2,2]-paracyclophane) has consistently provided the highest enantioselectivity for various cyclization chemistries. As a starting point for our catalytic cyclization/fluorination goal, we adapted conditions previously optimized for cyclization/β-H elimination reactions.[10b] The modified conditions included use of $AgBF_4$ and NCC_6F_5 to generate the "active" [(*S*)-(xylyl-phanephos)Pt(NCC_6F_5)$_2$][(BF_4)$_2$] catalyst. Subsequent addition of a base (to facilitate cyclization), substrate and an electrophilic fluorine source generated the desired product (**1**) as a single (stereoretentive) isomer, along with variable quantities of β-H eliminated product (**3**) and the Brønsted product (**5**) (Table 1); several additional phosphines are included for comparison.

In screening a variety of electrophilic fluorine sources, it was discovered that only XeF_2 effectively competed with β-H elimination. Other less reactive F^+ sources showed predominant to exclusive β-H elimination to **3**.[13] In addition to the desired **1**, over fluorination to **4** was also observed. Since controls showed that **1** does not react with XeF_2 and acid is known to enhance the F^+ potential of XeF_2,[14] we surmised that the HF byproduct of cyclization was activating the XeF_2. This problem was easily solved by the addition of TMSOMe as an HF sponge, which additionally obviates the need for a base.[15]

Optimization studies included testing multiple bisphosphines, solvents, and other TMS-X derivatives.[15] Once again (*S*)-xylyl-phanephos was uniquely enantioselective (~75%) for controlling the % ee of the cation-olefin cascades. Of the tested HF scavengers, TMSOMe was the most effective inhibitor of double fluorination and like previous ionic cascades, nitro-methane was the optimum solvent. A catalyst formulation comprised of 10 mol% (*S*)-(xylyl-phanephos)PtI_2, 25 mol% $AgBF_4$, 30 mol% NCC_6F_5 and stoichiometric quantities of XeF_2 and TMSOMe at 0 °C provided **1** in 67% yield and with 75% enantiomeric excess.[16]

These optimized conditions were subsequently applied to a variety of alcohol and phenol terminated dienes and trienes (Table 2). In most cases, high conversion of substrate occurred within three hours, however, the reactions were allowed to proceed for 24 h at 0 °C to ensure complete consumption of the XeF_2. For the substrate classes in Table 2, no Brønsted acid derived products like **5** were observed, and a single diastereomer consistent with stereoretentive fluorination of the intermediate P_2Pt-alkyl cation, was observed.

As shown in Table 2, variants on the phenol termini were well tolerated, except for α-naphthol (entry 3), wherein competitive fluorination of the aryl ether product occurs even with TMSOMe. In situ monitoring indicated that aryl fluorination occurred post cyclization / Pt-C fluorination. In this case, extra XeF_2 was used to compensate for the difluorination stoichiometry. Unexpectedly, *para*-substituents improved the ee's (entries 4–7).

Dienyl- and trienyl alcohols and phenols were also viable substrates though they behaved peculiarly. In the case of entries 8 and 9, the yields were poor under standard conditions, but could be recovered by exchanging TMSOMe for a polystyrene-bound piperidine base (see

Table 1). In contrast, the triene alcohol in entry 10 performed better under the standard conditions. These base effects are not yet understood.

In situ monitoring of a cyclization/fluorination of **2** indicated that the alkyl cation (as the nitrile adduct, **6**) serves as the catalyst resting state (^{31}P NMR). These data support our current view of the mechanism (Scheme 2), that has **6** competitively undergoing β-H elimination or F^+ attack to generate a $[Pt]^{IV}R(F)$ dication, which undergoes a stereoretentive reductive elimination to **1**. Neither the $[Pt]^{IV}$ nor the [Pt]-H species are observable by NMR, however, literature precedence suggests that both routes are viable.[17,5d,5f,5i,5k]

In summary, we illustrate that P_2Pt-dicationic catalysts can mediate the enantioselective cation-olefin cyclization/fluorination reactions of polyprenoids to yield C3-fluorinated carbocycles. The key feature of the putative catalytic cycle is the selective reaction of XeF_2 with P_2Pt-alkyl cations over P_2Pt-dications, which enables the sequential cyclization/fluorination.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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13. A comprehensive list of F^+ reagents and TMS-X sources tested during optimization is available in the supporting information.

14. (a) Tius MA. Tetrahedron. 1995; 51:6605.(b) Tramšek M, Žemva B. J Fluorine Chem. 2006; 127:1275.

15. NMR data and a comprehensive list of tested silyl ethers are available in the supporting information.

16. Note that in the absence of [Pt] no conversion of starting material was observed.

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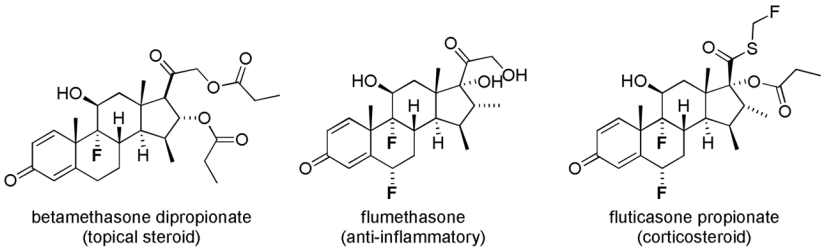
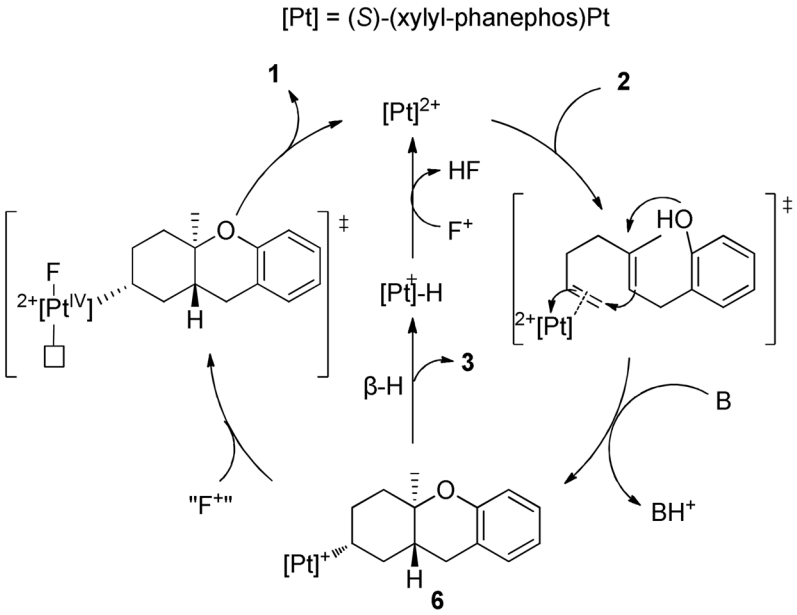


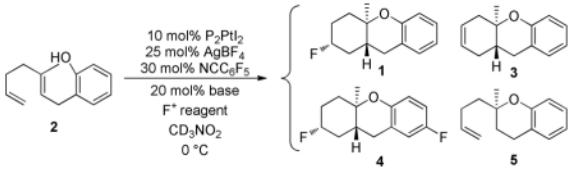
Scheme 1.
Common fluorinated steroids.

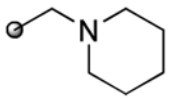
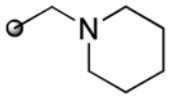
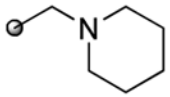


Scheme 2.
Proposed catalytic cycle for electrophilic fluorination.

Table 1

Selected optimizing conditions.



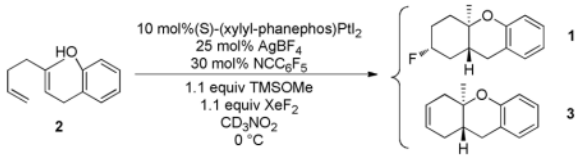
Entry	P_2	Base	% 1[a] (%ee)[b]	%3[a]	%4[a]	%5[a]
1	(*R*)-DTBM-SEGPHOS	None	20	14	0	57
2	(*R*)-DTBM-SEGPHOS	Ph_2NH	34	28	trace	14
3	(*R*)-DTBM-SEGPHOS		63(13)	8	11	0
4	(*R*)-xylyl-MeO-BIPHEP		85(5)	10	3	0
5	(*S*)-xylyl-phanephos		72(75)	7	3	trace

[a] Uncorrected GC percentages

[b] Determined by chiral GC.

Table 2

Catalytic electrophilic fluorination.[a]



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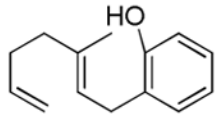
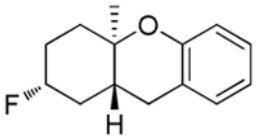
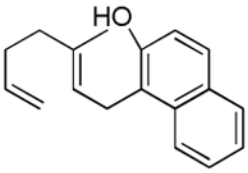
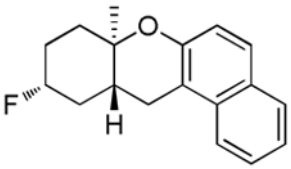
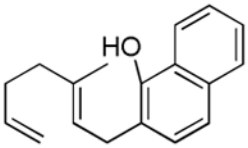
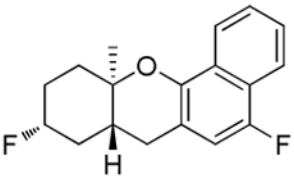
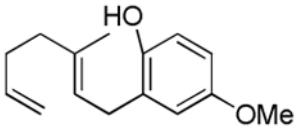
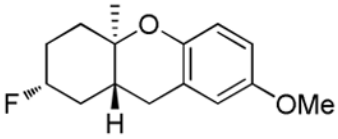
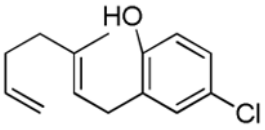
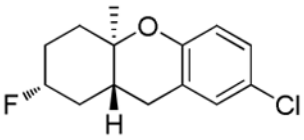
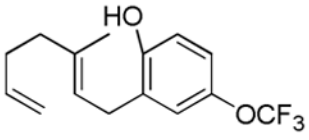
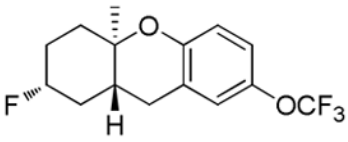
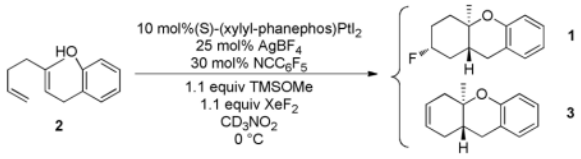
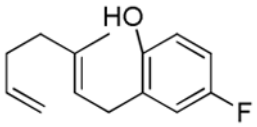
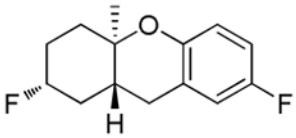
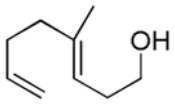
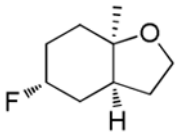
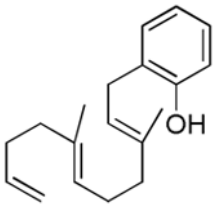
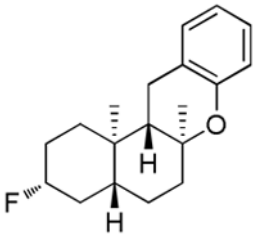
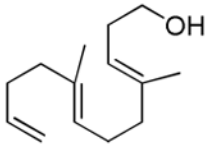
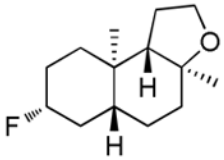
1			67% (75)	14%
2			67% (73)	15%
3[d]			49% (86)	15%[e]
4			56% (81)	16%
5			60% (87)	13%
6			68% (83)	24%



Entry	Polyene	Product	Yield 1 (%ee)[b]	Yield 3[c]
7			80% (81)	trace
8[f]			63%[g]	22%
9[f]			69% (10)	10%[e]
10[h]			56% (78)	0%

[a]Condtions: 10 mol% (*S*)-(xylyl-phanephos)PtI$_2$, 25 mol% AgBF$_4$, 30 mol% NCC$_6$F$_5$, 1.1 equiv TMS-OMe, 1.1 equiv XeF$_2$, 0.4 mL CD$_3$NO$_2$, 0 °C, 24 h. Starting material is mass balance of reaction.

[b]Isolated yield, % ee determined by chiral GC.

[c]GC yield.

[d]Reaction run using 1.6 equiv XeF$_2$.

[e]Percentage is fluorinated elimination species only

[f]Reaction with 20 mol% polystyrene-bound piperidine base run, no TMS-OMe, see SI for details.

[g]Due to the volatility of this compound, a GC yield is reported.

[h]Contains 23% unidenfied species, mass balance is unreacted starting material. Cannot separate the unidentified species from the product, therefore GC yield reported.