

Catalytic Enantioselective Cyclization and C3-Fluorination of Polyenes

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S Supporting Information

ABSTRACT: (Xylyl-phanephos)Pt²⁺ in combination with XeF₂ mediates the consecutive diastereoselective cation-olefin cyclization/fluorination of polyene substrates. Isolated yields were typically in the 60–69% range while enantioselectivities reached as high as 87%. The data are consistent with a stereoretentive fluorination of a P₂Pt-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 nonenolate-based carbon nucleophiles.^{3–5} Fluorinated steroids (Scheme 1), in particular, are important bioactive compounds with a deficiency of methods for their synthesis.^{6–8}

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 heterocycles with control of absolute and relative stereochemistry.

Electrophilic Pt(II) complexes are effective initiators of C–C bond forming cation-olefin cascades.^{9–11} 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][BF₄] reacts with XeF₂ to yield C–F products (eq 1)

Scheme 1. Common Fluorinated Steroids

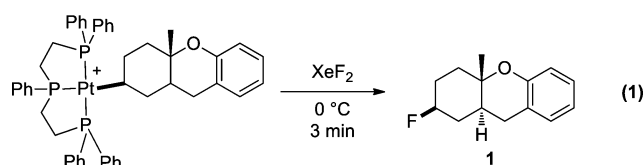
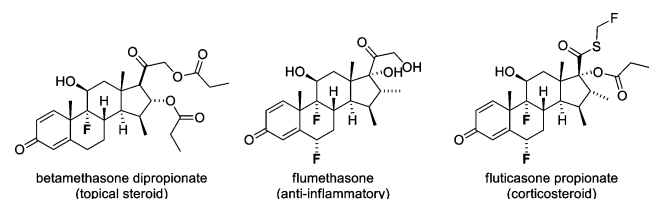


Table 1. Selected Optimizing Conditions

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 ₂ NH	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

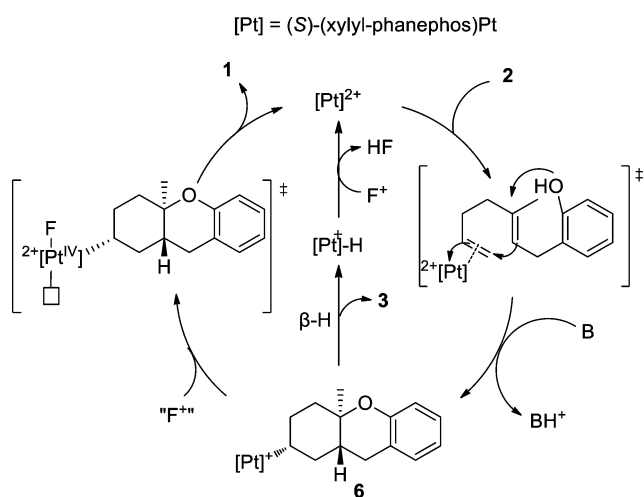
^aUncorrected GC percentages. ^bDetermined by chiral GC.

suggested that the desired interception might be capable of competing with β-H elimination.¹²

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 AgBF₄ and NCC₆F₅ to generate the “active” [(S)-(xylyl-phanephos)Pt(NCC₆F₅)₂][(BF₄)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.

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Scheme 2. Proposed Catalytic Cycle for Electrophilic Fluorination



In screening a variety of electrophilic fluorine sources, it was discovered that only XeF₂ effectively competed with β -H elimination. Other less reactive F⁺ sources showed a predominance 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 XeF₂ and acid is known to enhance the F⁺ potential of XeF₂,¹⁴ we surmised that the HF byproduct of cyclization was activating the XeF₂. 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, nitromethane was the optimum solvent. A catalyst formulation comprised of 10 mol % (S)-(xylyl-phanephos)PtI₂, 25 mol % AgBF₄, 30 mol % NCC₆F₅, and stoichiometric quantities of XeF₂ and TMSOMe at 0 °C provided 1 in 67% yield and with a 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, a high conversion of substrate occurred within 3 h; however, the reactions were allowed to proceed for 24 h at 0 °C to ensure complete consumption of the XeF₂. For the substrate classes in Table 2, no Brønsted acid derived products such as 5 were observed, and a single diastereomer consistent with stereoretentive fluorination of the intermediate P₂Pt-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 after cyclization/Pt–C fluorination. In this case, extra XeF₂ 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

Table 2. Catalytic Electrophilic Fluorination^a

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

^aConditions: 10 mol % (S)-(xylyl-phanephos)PtI₂, 25 mol % AgBF₄, 30 mol % NCC₆F₅, 1.1 equiv of TMS-OMe, 1.1 equiv of XeF₂, 0.4 mL of CD₃NO₂, 0 °C, 24 h. Starting material is mass balance of reaction.

^bIsolated yield, % ee determined by chiral GC. ^cGC yield. ^dReaction run using 1.6 equiv of XeF₂. ^ePercentage is fluorinated elimination species only. ^fReaction with 20 mol % polystyrene-bound piperidine base run with no TMS-OMe; see SI for details. ^gDue to the volatility of this compound, a GC yield is reported. ^hContains 23% unidentified species; mass balance is unreacted starting material. Cannot separate the unidentified species from the product; therefore GC yield is reported.

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 (³¹P 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.^{Sd,f,i,k,17}

In summary, we illustrate that P₂Pt-dicationic catalysts can mediate the enantioselective cation-olefin cyclization/fluorination reactions of polyenes to yield C3-fluorinated carbocycles. The key feature of the putative catalytic cycle is the selective reaction of XeF₂ with P₂Pt-alkyl cations over P₂Pt-dications, which enables the sequential cyclization/fluorination.

■ ASSOCIATED CONTENT

■ Supporting Information

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>.

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Notes

The authors declare no competing financial interest.

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