COMMUNICATION

Synthesis of Axially Chiral CF_3-Substituted 2-Arylpyrroles by Sequential Phosphine-Catalyzed Asymmetric [3+2] Annulation and Oxidative Central-to-Axial Chirality Transfer

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Abstract: A sequential phosphine-catalyzed asymmetric [3+2] annulation and oxidative central-to-axial chirality transfer strategy has been developed using aldimines and allenoates as substrates. This approach is operationally simple, allowing for rapid access to a range of axially chiral CF_3-containing 2-arylpyrroles with high enantiomeric excess. Furthermore, an atroposelective synthesis of esaxerenone is presented, illustrating the practical potential of the reported method.

Despite the initial discovery of atropisomerism by Christie and Kenner in 1922,[1] the importance of axial chirality only received due recognition in 1980s, when BINAP (2,2' bis(diphenylphosphino)-1,1'-binaphthyl) was introduced as an axially chiral ligand in rhodium-catalyzed asymmetric hydrogenation reaction.[2] Thereafter, the prevalence of axial chirality in bioactive molecules and drug discovery,[3] and its extensive applications in asymmetric catalysis[4] have triggered massive investigations on catalytic asymmetric synthesis of axially chiral molecular scaffolds.

While significant efforts have been directed to the construction of more common axially chiral biaryls,[5] atroposelective synthesis of a chiral axis between a five-membered heterocycle and an aryl group has been much less investigated.[6] Such synthetic endeavors are inherently challenging, as the wider angles induced by five-membered heterocycles would lead to lower energy barriers between different atropisomers, in comparison to their six-membered biaryl counterparts. Arylpyrroles are widely present in natural products and bioactive molecules.[7] In particular, 2-arylpyrroles represent a very useful structural motif in drug discovery. For instance, esaxerenone (MINNEBRO®),[8] a recently approved drug for the treatment of hypertension, contains an axially chiral 2-arylpyrrole backbone and a trifluoromethyl (CF_3) moiety.[9] The CF_3 group is a very useful bioisostere to a methyl group in medicinal chemistry, known to enhance pharmacological activities and properties of drug candidates.[10] As illustrated in Figure 1, many investigational and approved drugs contain a 2-arylpyrrole and/or a CF_3 moiety. We therefore sought to develop a catalytic atroposelective synthetic approach for facile synthesis of CF_3-containing axially chiral 2-arylpyrroles.

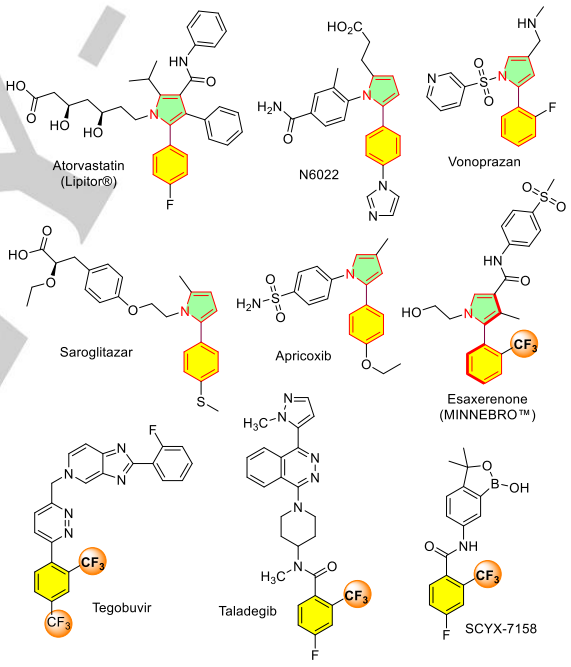


Figure 1. Biologically important 2-arylpyrroles and CF_3-containing drugs.

When the asymmetric synthesis of atropisomeric 2-arylpyrroles is concerned, Tan reported an organocatalytic asymmetric *N*-alkylation reaction to create enantioenriched atropisomeric alkenes, before subsequent cyclization to furnish axially chiral 2-arylpyrrole frameworks (Fig. 2a).[11] Recently, Mei also disclosed a chiral phosphoric acid-catalyzed asymmetric Attanasi reaction to obtain 1-(1-amino-pyrrol-2-yl)naphthalen-2-ols (NPNOLs) bearing an axially chiral C2-arylpyrrole framework. (Fig. 2b)[12] To devise an efficient catalytic asymmetric strategy for the synthesis of atropisomeric 2-arylpyrroles, we envisioned that a central-to-axial chirality transfer[13] process may be utilized. For derivatizing the key centrally chiral precursor (**A**) with a nitrogen atom properly positioned for the subsequent 2-pyrrole ring formation,

phosphine-catalyzed [3+2] annulation reaction[14] between an allenoate and a CF_3-containing imine offers a reliable and straightforward solution (Fig. 2c). Herein, we document an atroposelective synthesis of CF_3-containing 2-arylpyrroles, and our strategy features a phosphine-catalyzed asymmetric [3+2] cycloaddition to form a stereogenic carbon chiral center, which is followed by an oxidative central-to-axial chirality transfer process to deliver 2-arylpyrrole containing an axially chiral axis.

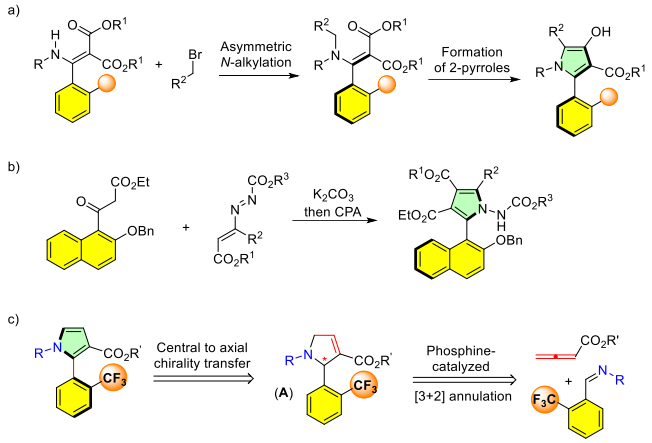
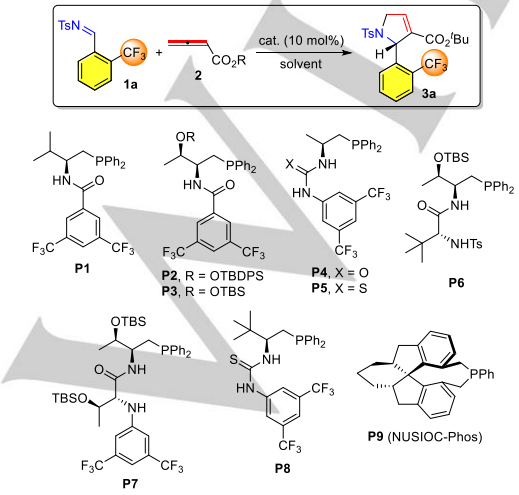


Figure 2. a) Tan's strategy. b) Mei's strategy. c) Our working hypothesis.

We first focused on the phosphine-catalyzed [3+2] annulation between 2-CF_3 substituted *N*-tosylaldimine **1a** and allenoates to construct the chiral 2-pyrroline ring, and the results are summarized in Table 1. We screened a number of amino acid-derived bifunctional phosphines,[15] as well as our recently developed NUSIOC-Phos,[16] and found that L-thr-derived **P3** gave most promising results (entries 1–9). Subsequent solvent screening confirmed toluene was the solvent of choice (entries 10–14). When allenoates bearing different ester moieties were employed, enantioselectivity of the annulation was markedly improved; in the presence of **P3**, the [3+2] annulation between imine **1a** and *tert*-butyl allenoate formed 3-pyrroline **3a** in 94% yield with 95% ee (entry 17).

Table 1. Optimizing [3+2] annulation conditions.[a]

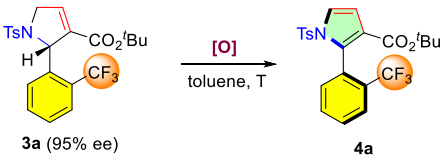


Entry	R	Solvent	Cat.	Yield (%)[b]	ee (%)[c]
1	Bn	toluene	**P1**	90	69
2	Bn	toluene	**P2**	93	71
3	Bn	toluene	**P3**	95	71
4	Bn	toluene	**P4**	87	59
5	Bn	toluene	**P5**	88	<5
6	Bn	toluene	**P6**	91	29
7	Bn	toluene	**P7**	91	40
8	Bn	toluene	**P8**	82	<5
9	Bn	toluene	**P9**	95	70
10	Bn	EtOAc	**P3**	85	54
11	Bn	THF	**P3**	90	66
12	Bn	CH_2Cl_2	**P3**	88	62
13	Bn	1,4-dioxane	**P3**	79	64
14	Bn	Et_2O	**P3**	54	57
15	$CHPh_2$	toluene	**P3**	92	58
16		toluene	**P3**	94	35
17	^{t}Bu	toluene	**P3**	94	95

[a] Reaction conditions: **1a** (0.12 mmol), **2** (0.1 mmol), and the catalyst (0.01 mmol) in the solvent specified (1.0 mL) at room temperature for 4 h. [b] Isolated yield. [c] Determined by HPLC analysis on a chiral stationary phase. THF = tetrahydrofuran, Ts = 4-toluenesulfonyl, TBS = *tert*-butyldimethylsilyl, TBDPS = *tert*-butyldiphenylsilyl.

Having obtained the crucial centrally chiral intermediate **3a** with a properly positioned nitrogen atom, we next proceeded to explore the oxidative central-to-axial chirality transfer reaction, for the simultaneous creation of 2-pyrrole ring and construction of axial chirality around the pyrrole and aryl rings. Various oxidants were examined, and the results are summarized in Table 2. DDQ, commonly employed for the oxidative dehydrogenation reactions, was found to inefficient (entries 1 & 2). Among other oxidants screened, only CrO_3, PCC, and PDC were moderately effective (entries 3–13). Finally, we discovered that the employment of $Pb(OAc)_4$ furnished the desired atropisomer **4a** in excellent yield and chirality conversion (entry 15).

Table 2. Central-to-axial chirality transfer.[a]



Entry	Oxidant	Solvent	T (°C)	*t* (h)	Yield (%)[b]	ee (%)[c]
1	DDQ	Toluene	RT	12	0	-
2	DDQ	Toluene	110	12	90	29
3	MnO_2	Toluene	60	12	0	-
4	CrO_3	Toluene	RT	12	0	-
5	CrO_3	Toluene	60	48	50	68
6	PCC	Toluene	60	48	47	55
7	PCC	DCE	RT	48	37	69
8	PDC	Toluene	RT	12	0	-
9	PDC	Toluene	60	48	52	71
10	CAN	Toluene	60	48	Trace	-
11	$CuCl_2{\cdot}2H_2O$	CH_2Cl_2	60	48	0	-
12	$FeCl_3{\cdot}6H_2O$	CH_2Cl_2	60	48	0	-
13	$PhI(OAc)_2$	Toluene	60	48	Trace	-
14	$Pb(OAc)_4$	Toluene	60	24	50	90
15[d]	$Pb(OAc)_4$	Toluene	60	48	82	90

[a] Reaction conditions: **3a** (0.1 mmol) and the oxidant (0.12 mmol) in toluene (1.0 mL). [b] Isolated yield. [c] Determined by HPLC analysis on a chiral stationary phase. [d] Reaction was filtered after 24 h and another 0.12 mmol of oxidant was added. DCE = Dichloroethane, DDQ = 2,3-Dichloro-5,6-Dicyanobenzoquinone, PCC = Pyridinium chlorochromate, PDC = Pyridinium dichromate, CAN = Ceric ammonium nitrate.

We subsequently proceeded to establish the reaction scope, and the results are depicted in Figure 3. To make the overall transformation operationally simple, we established an efficient protocol; a sequential [3+2] cycloaddition and oxidative central-to-axial chirality transfer offered the overall same efficiency as the stepwise reactions. Different halogenated *N*-tosylaldimine substrates were well-tolerated, and good yields and ee values were attainable (**4b–d**, **4h–4i**). *N*-Tosylaldimines containing an electron-donating methoxy group (**4e**), an electron-withdrawing trifluoromethyl group (**4f**), or a cyclopropyl (**4g**) at the 4-position were all found to be suitable substrates. Moreover, the reaction was applicable to *N*-tosylaldimines containing a 4-aryl or hetero-aryl substituent (**4j**–**4m**). The Ts protection on nitrogen can be replaced by a number of other sulfonamide protective groups, and in all the cases studied, consistently excellent enantiomeric excesses were obtained (**4n**–**4u**).

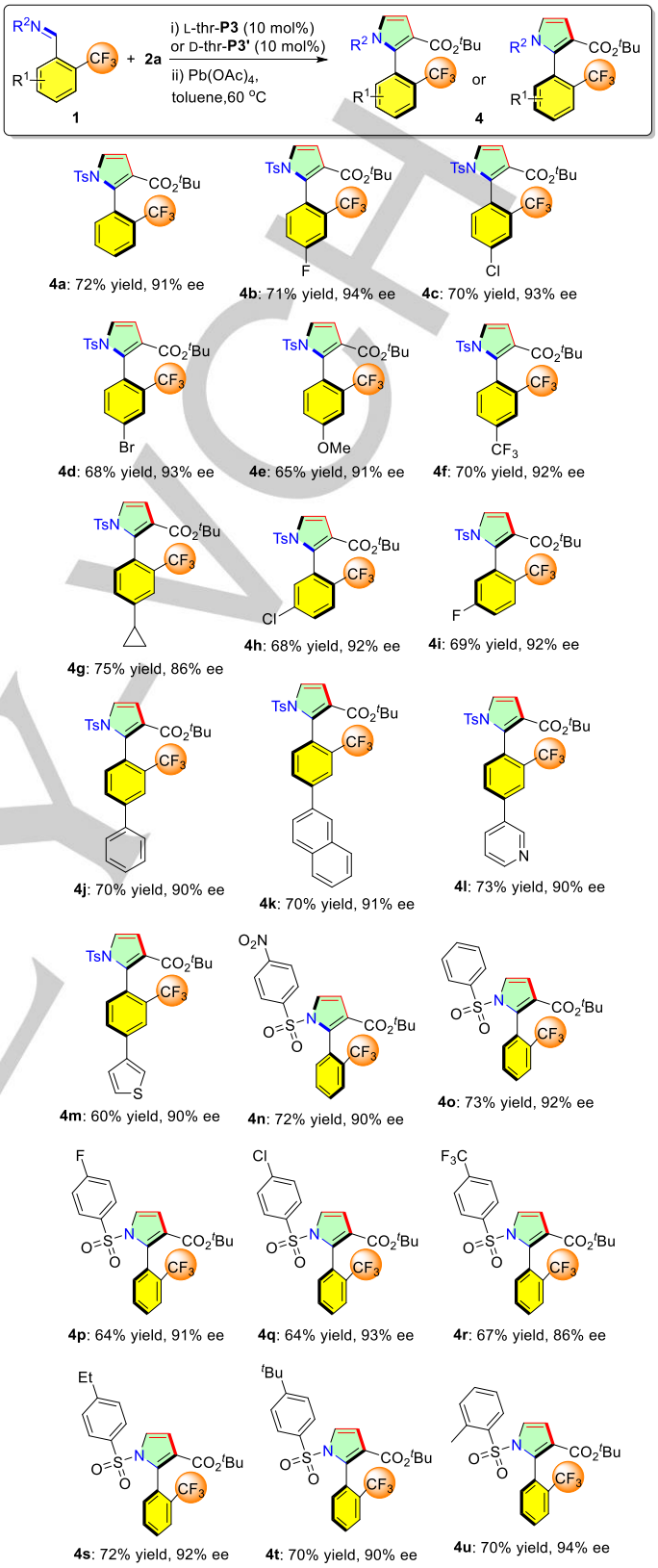
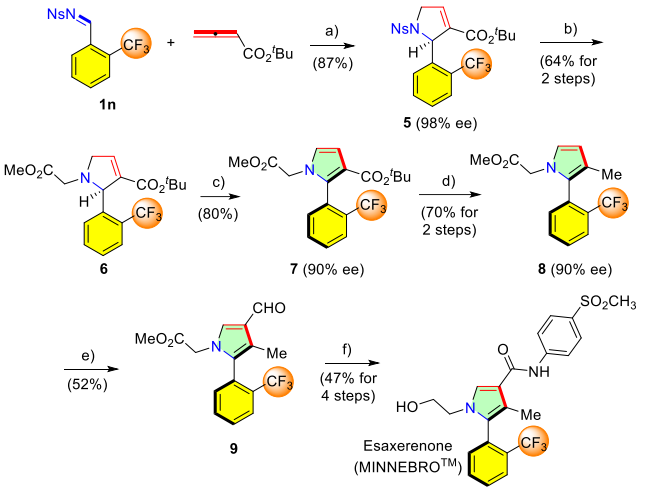


Figure 3. Substrate scope. Reaction conditions: i) **1** (0.12 mmol), **2a** (0.1 mmol), and **P3** or **P3'** (0.01 mmol) in toluene (1.0 mL) for 4 h. ii) $Pb(OAc)_4$ (0.12 mmol) was added at 60°C for 24 h. Reaction was filtered after 24 h and another 0.12 mmol of $Pb(OAc)_4$ was added and stirred at 60 °C for additional 24 h. Isolated yields. The ee values were determined by HPLC analysis on a chiral stationary phase. The absolute configurations of the products were assigned by analogy, on the basis of X-ray crystallographic analysis of **3d'** (CCDC No. 2177489)[17] and **4d'** (CCDC No. 2177532)[18] (see the SI for details).



a) **P3'** (10 mol%), toluene, rt; b) PhSH, Cs_2CO_3, then MeO_2CCH_2Br, DMF, rt; c) $Pb(OAc)_4$, toluene, 60 °C; d) TFA, CH_2Cl_2, rt, followed by BH_3, THF, 0 °C; e) $C(Cl)_2O^nBu$, $TiCl_4$, CH_2Cl_2, 0 °C; f) i) $KMnO_4$, acetone/H_2O 2:1; ii) $SOCl_2$, toluene; iii) $NH_2PhSO_2CH_3$; iv) $LiBH_4$, THF.

Figure 4. Asymmetric synthesis of esaxerenone.

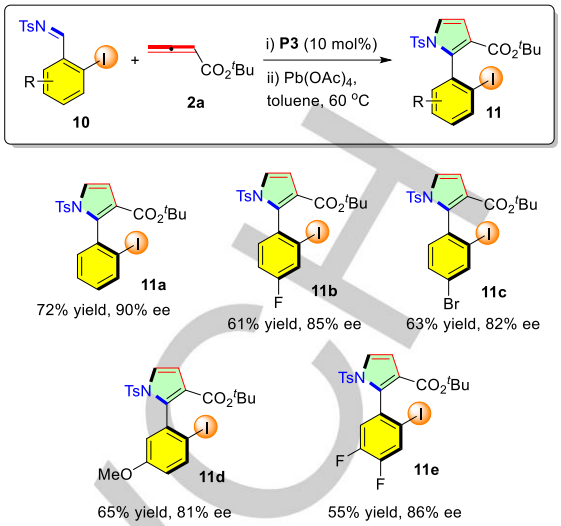


Figure 5. Axially chiral iodo-containing 2-arylpyrroles.

To illustrate the practicality of our methodology, we performed the first asymmetric synthesis of esaxerenone, an approved drug for the treatment of hypertension. Using *N*-nosylaldimine **1n** as the starting material, phosphine-catalyzed [3+2] annulation smoothly delivered chiral pyrrolidine **5** in 87% yield with 98% ee. However, the cleavage of *p*-nosyl group after the oxidative central-to-axial chirality transfer led to complete racemization. To circumvent this problem, we converted the nosyl group to a methyl acetate, which was subjected to our established lead (IV) tetraacetate-induced oxidative central-to-axial transfer to furnish axially chiral **7**. Acid hydrolysis of the *tert*-butyl ester moiety followed by a borane reduction then afforded advanced intermediate **8**. For the subsequent formylation reaction, we employed dichloromethyl *n*-butyl ether, reported by Kimura and co-workers,[19] and obtained aldehyde **9** as the desired regioisomer. At last, oxidation using $KMnO_4$ in an acetone/water mixture, followed by an amide formation and a $LiBH_4$ reduction completed the atroposelective synthesis of esaxerenone (Figure 4).

The strategy we introduced herein has broad applicability, which we envisaged may be utilized for atroposelective synthesis of various 2-arylpyrroles. In a preliminary investigation, we carried out phosphine-catalyzed [3+2] annulation of iodo-imines **10** with allenoate **2a** to create centrally chiral pyrrolines, followed by a $Pb(OAc)_4$-mediated central-to-axial transfer to deliver a number of axially chiral iodo-containing 2-arylpyrroles (Figure 5). As the conditions implemented were unchanged, the lower ee values recorded are likely to be caused from the unoptimized [3+2] annulation conditions which were better suited for the CF_3 substituent. We believe our method will serve as a viable tool for atroposelective synthesis of a range of 2-arylpyrroles with further ongoing investigations towards different viable substituents at the 2-positions.

In conclusion, we have developed a straightforward sequential phosphine-catalyzed [3+2] annulation and oxidative central-to-axial chirality transfer strategy to synthesize axially chiral 2-arylpyrroles. A good range of functionalized CF_3-containing 2-arylpyrroles were obtained in decent yields and with excellent enantioselectivities. The practical use of our methodology has been demonstrated in the first asymmetric synthesis of esaxeranone. We believe the method disclosed herein will find broad applications in atroposelective synthesis of pyrrole derivatives and beyond.

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Keywords: axial chirality • atroposelectivity • phosphine catalysis • [3+2] annulation • chirality transfer

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[17] Deposition Number 2177489 contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe.

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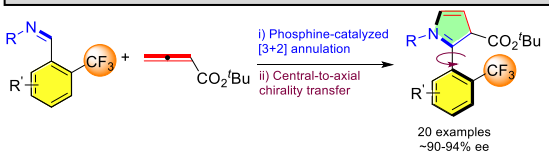

A sequential phosphine-catalyzed asymmetric [3+2] annulation and oxidative central-to-axial chirality transfer strategy has been developed, allowing for rapid access to a range of axially chiral CF_3-containing 2-arylpyrroles with high enantiomeric excess. The practicality of the method is also illustrated in the atroposelective synthesis of esaxerenone.