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Chiral Anion Phase Transfer of Aryldiazonium Cations: An Enantioselective Synthesis of C3-Diazenated Pyrroloindolines**

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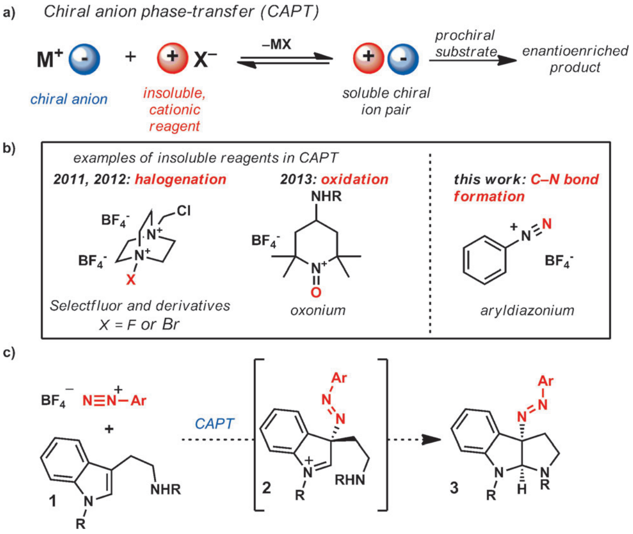
Abstract: *Herein is reported the first asymmetric utilization of aryldiazonium cations as a source of electrophilic nitrogen. This is achieved through a chiral anion phase-transfer pyrroloindolinization reaction that forms C3-diazenated pyrroloindolines from simple tryptamines and aryldiazonium tetrafluoroborates. The title compounds are obtained in up to 99 % yield and 96 % ee. The air- and water-tolerant reaction allows electronic and steric diversity of the aryldiazonium electrophile and the tryptamine core.*

Chiral anion phase-transfer (CAPT) catalysis has recently arisen as an effective strategy in enantioselective catalysis (Scheme 1 a).[1] In particular, electrophilic halo-functionalization reactions of alkenes using Selectfluor (Scheme 1 b) and its derivatives have proven broadly effective, delivering a wide scope of valuable halogenated products in high yields and excellent enantioselectivities.[1f–m] Inspired by the substrate generality exhibited by CAPT halo-functionalization and other oxidative reactions,[1n,o] it has been a long-standing goal in our research group to identify additional cationic electrophiles amenable to this strategy (Scheme 1 b).



Scheme 1. a) General chiral anion phase-transfer process, b) cationic reagents employed, and c) application of chiral anion phase-transfer catalysis to pyrroloindolinization.

We were specifically interested in cations comprised of electrophilic nitrogen atoms, as asymmetric electrophilic C–N bond formation remains a synthetic challenge.[2] Aryldiazonium salts were recognized as candidates, as their N-electrophilicity has been exploited to diazenate several classes of carbon nucleophiles in a nonstereoselective fashion, including aromatic compounds,[3] enolates,[4] and heteroaromatic compounds.[5] Reports of Gomberg–Bachmann–Hey biaryl syntheses[3b] and azo-coupling reactions[3a,c] that utilize aryldiazoniums under phase-transfer conditions further encouraged our efforts in this area. Furthermore, although azo compounds have been utilized extensively in materials science,[6] commodities,[7] and chemical biology[8] for their photochemical properties, studies of enantioenriched diazenes within these contexts are rare.

When considering transformations suitable for providing proof-of-principle for CAPT of diazonium cations, we were drawn to several enantioselective pyrroloindolinization reactions[9,10] and recent total syntheses in which C3-diazenated pyrroloindolines were key intermediates (prepared in a six-step diastereoselective sequence).[11] Furthermore, Zhang and Antilla have recently reported a highly efficient and enantioslective method for the preparation of C3-hydrazinated pyrroloindolines[9] utilizing azodicarboxylate electrophiles; however, no such transformation using diazonium cations to directly provide C3-diazenated products in either a racemic or an asymmetric fashion has been reported.

We envisioned that CAPT of an insoluble aryldiazonium salt would provide a soluble chiral ion pair poised for attack at the terminal diazonium nitrogen atom by tryptamine **1** (Scheme 1 c). The resulting enantioenriched indolinium intermediate (**2**) could then cyclize to yield the desired pyrroloindoline structural motif **3**. Herein we report the successful execution of this synthetic hypothesis to enable the preparation of highly enantioenriched pyrroloindolines from simple tryptamine derivatives, thereby providing the first example of catalytic, enantioselective C–N bond formation by utilizing aryldiazonium cations as an electrophilic source of nitrogen.

As a consequence of the demonstrated success of the benzamide group in CAPT catalysis,[1h–k] our efforts began with the readily prepared tryptamine derivative **4** (Table 1). We were pleased to find that exposure of tryptamine **4** to 3 equivalents of Na_3PO_4, 1 equivalent of phenyldiazonium

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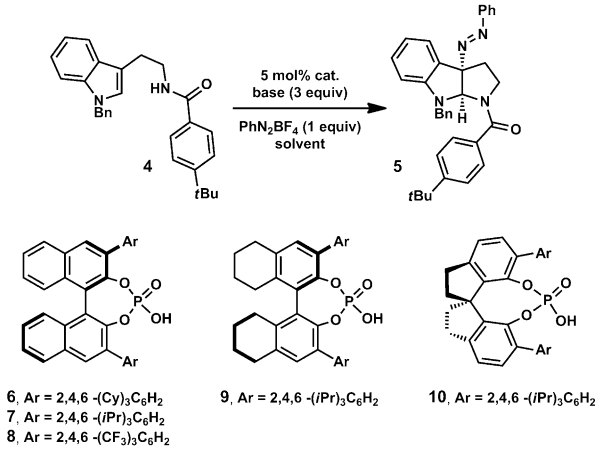
Table 1: Optimization experiments.



Entry	Cat.	Solv.	Base	Conv. [%][a]	*ee* [%][b]
1	**6**	hexanes	Na$_3$PO$_4$	>95	35
2	**7**	hexanes	Na$_3$PO$_4$	>95	62
3	**8**	hexanes	Na$_3$PO$_4$	>95	4
4	**9**	hexanes	Na$_3$PO$_4$	>95	44
5	**10**	hexanes	Na$_3$PO$_4$	>95	81
6	**10**	pentane	Na$_3$PO$_4$	>95	82
7	**10**	pet. ether	Na$_3$PO$_4$	>95	84
8	**10**	acetone[c]	Na$_3$PO$_4$	>95(21[d])	51
9	**10**	Et$_2$O	Na$_3$PO$_4$	52[d]	88
10	**10**	MTBE	Na$_3$PO$_4$	99[d]	91
11	**10**	MTBE[e]	Na$_3$PO$_4$	>95	90
12	**10**	MTBE	NEt$_3$	<5	–
13	**10**	MTBE	K$_2$CO$_3$	>95	90
14	**10**	MTBE	K$_3$PO$_4$	>95	91
15	–	MTBE	Na$_3$PO$_4$	<5	–
16	**10**	MTBE	–	<5	–

[a] Estimated from ^{1}H NMR spectroscopy. [b] Determined by HPLC on a chiral stationary phase. [c] The aryldiazonium salts are soluble in acetone. [d] Yield of isolated product. [e] 10 equiv H$_2$O.

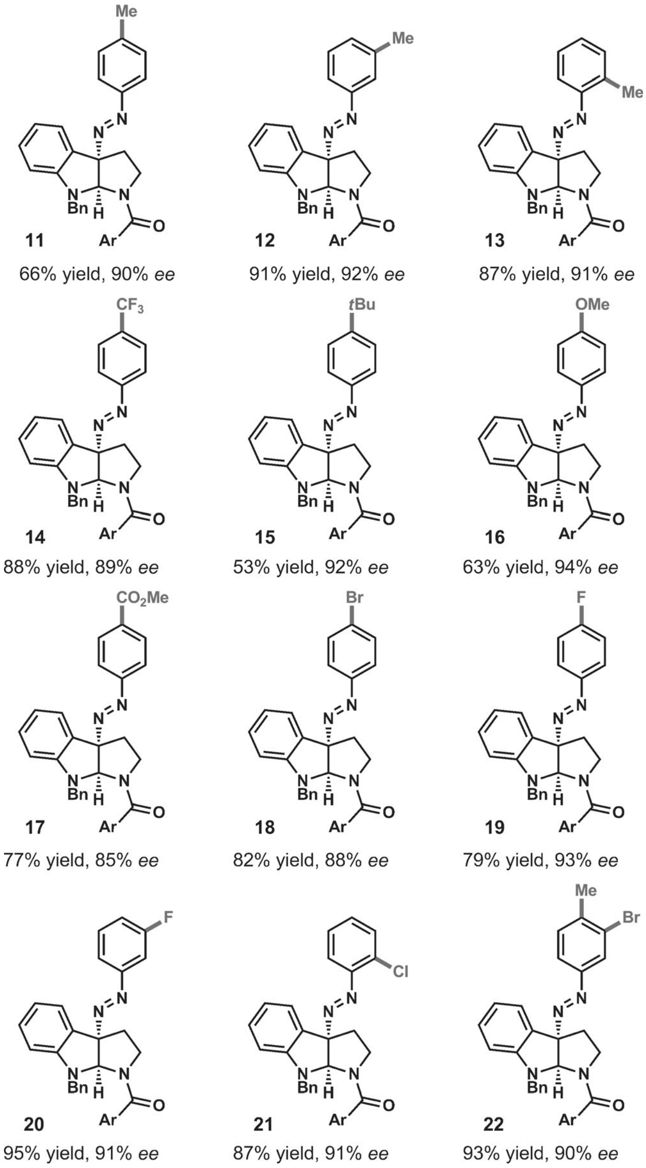
tetrafluoroborate, and 5 mol% of (*S*)-TCyP (**6**) in hexane provided the desired pyrroloindoline **5** with good conversion and moderate enantioselectivity (35% *ee*; Table 1, entry 1).

With this initial result, a phase-transfer catalyst screen was undertaken that focused on three distinct chiral phosphoric acid scaffolds (**6**–**8**, **9**, and **10**). BINOL-derived (*S*)-TRIP (**7**) delivered the desired compound in 62% *ee*. (entry 2). Partially saturated (*S*)-H8-TRIP (**9**) proved to be suboptimal, furnishing the product in 44% *ee* (entry 4). Finally, the SPINOL-derived (*R*)-STRIP[11] (**10**) was found to be the most selective catalyst, yielding the product in 81% *ee* (entry 5).

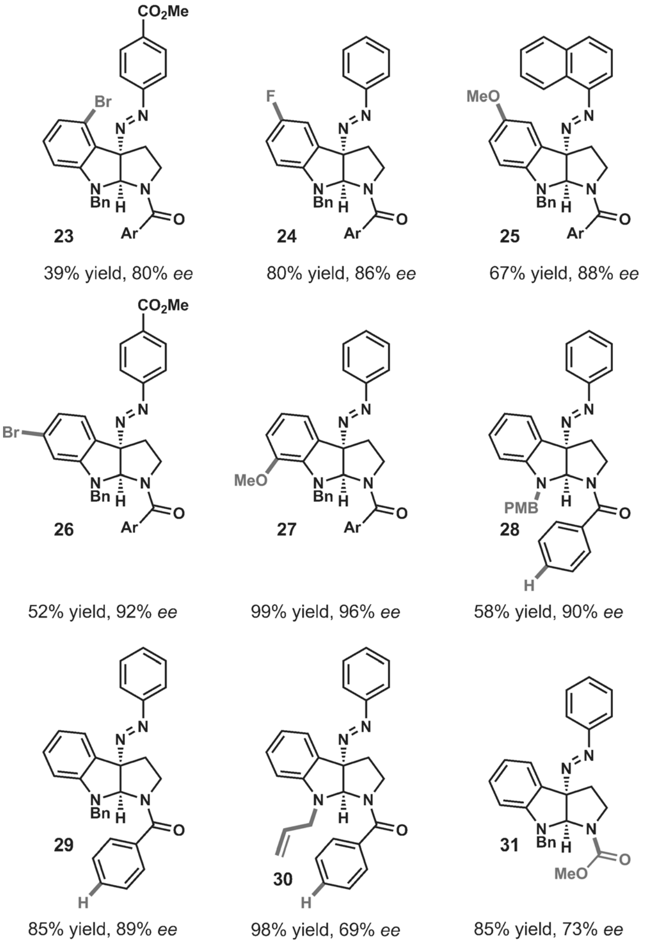
Having identified (*R*)-STRIP (**10**) as our optimal catalyst, an extensive screen of solvent and base was undertaken. Notably, hydrocarbon solvents such as pentane and petroleum ether provided the product with equivalent enantioselectivities (81%, 82%, and 84% *ee*, entries 5–7). The use of ethereal solvents provided a significant improvement in enantioselectivity (88% *ee*, entry 9), with methyl *tert*-butyl ether (MTBE) furnishing the product in 99% yield and 91% *ee* (entry 10).[13,14]

Soluble, organic bases such as triethylamine attenuated product formation, while inorganic bases performed well (entries 12–14). Notably, the addition of excess water did not affect the selectivity or yield of the reaction (entry 11). Omission of the base or catalyst under heterogeneous conditions prevented conversion, and both the selectivity and efficiency were eroded under homogeneous conditions, thus supporting our hypothesis of a phase-transfer process (entries 8, 15, and 16).[15]

With our optimized conditions in hand, we explored the aryldiazonium scope (Scheme 2). The reaction conditions were tolerant of both electron-rich and electron-poor substitution of the *p*-, *m*-, and *o*-positions of the aryldiazonium (**11**–**22**). Notably, difunctionalized aryldiazonium salts were competent under the reaction conditions (Scheme 2, **22** and Scheme 3, **25**).



Scheme 2. Aryldiazonium scope. Conditions: **4** (1 equiv), (*R*)-STRIP (**10**; 5 mol%), Na$_3$PO$_4$ (3 equiv), ArN$_2$BF$_4$ (1 equiv), MTBE, RT, 2–8 h. Yields are of isolated products. The *ee* values were determined by HPLC on a chiral stationary phase. The relative and absolute configuration was assigned by analogy to **5**. Ar = 4-(*t*Bu)C$_6$H$_4$.



23 39% yield, 80% *ee*

24 80% yield, 86% *ee*

25 67% yield, 88% *ee*

26 52% yield, 92% *ee*

27 99% yield, 96% *ee*

28 58% yield, 90% *ee*

29 85% yield, 89% *ee*

30 98% yield, 69% *ee*

31 85% yield, 73% *ee*

Scheme 3. Tryptamine scope.[a–e] Conditions: **4** (1 equiv), (*R*)-STRIP (**10**; 5 mol%), Na_3PO_4 (3 equiv), ArN_2BF_4 (1 equiv), MTBE, RT, 2–8 h. Yields are of isolated products. The *ee* values were determined by HPLC on a chiral stationary phase. The relative and absolute configuration was assigned by analogy to **5**. Ar = 4-(*t*Bu)C_6H_4.

To probe tryptamine scope, several derivatives of **5** were prepared and examined under our optimized conditions (Scheme 3). Substitution of the indole 5-, 6- or 7-positions allowed for highly selective product formation (**24**–**27**). Electron-poor diazonium cations were employed for substrates containing bromine substitution to provide improved reactivity, and good stereoselectivities were achieved, albeit with diminished yields (4-CO_2Me in **23** and **26**).[16] Electron-withdrawing substituents on the indole nitrogen atom prevented reactivity. Moreover, replacement of the benzyl group with a *p*-methoxybenzyl (PMB) group (**28**) had no deleterious effect on the enantioselectivity, nor did removal of the *tert*-butyl group from the benzamide (**28**, **29**). Protection of the exocyclic tryptamine-N atom as a carbamate (**31**) or the endocyclic indole-N atom with an allyl group (**30**) resulted in diminished, but synthetically useful enantioselectivities.

In closing, we have demonstrated the utility of aryldiazonium cations as electrophilic nitrogen sources in enantioselective transformations. A chiral anion phase-transfer reaction process provides C3-diazenated pyrroloindolines in good to excellent enantioselectivities and yields, with diverse functionality. Furthermore, through highly enantioselective electrophilic C–N bond formation, this approach represents a significant expansion of phase-transfer methods. Efforts to further utilize these novel compounds are currently underway.[17]

Experimental Section

A suspension of the tryptamine (0.05 mmol), Na_3PO_4 (24 mg, 0.15 mmol, 3 equiv), and (*R*)-STRIP (1.8 mg, 0.0025 mmol, 5 mol%) in MTBE (0.5 mL) was stirred vigorously at 20°C for 15 min. The aryldiazonium salt (0.05 mmol, 1 equiv) was added rapidly in one portion to this suspension. The reactions were stirred until TLC analysis indicated completion (1–12 h). The bright yellow reaction mixtures were filtered through cotton wool and the volatiles were removed by rotary evaporation. The crude product was dissolved in hexanes and loaded onto a 1 cm column and eluted with 5:95 EtOAc/hex to yield yellow foams. The products were generally stable for several months neat, in protic solvents, or in pyridine.

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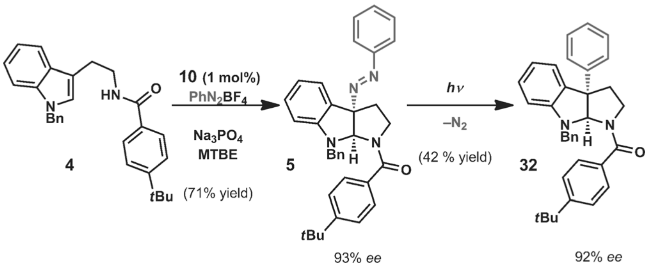
[13] The absolute configuration and connectivity were determined unambiguously by X-ray diffraction, see the Supporting Information for details.

[14] Reduction of the catalyst loading to 1 mol% resulted in decreased efficiency (71% yield), without loss of stereoselectivity (93% *ee*). See scheme in Ref. [17].

[15] It is noteworthy that although no significant reaction occurs in the absence of a CAPT catalyst under heterogeneous conditions (Table 1, entry 15), the observed enantioselectivity in the homogeneous reaction (entry 8) introduces the possibility of additional counterion effects.

[16] We found that sterically bulky diazoniums helped to improve the enantioselectivity of 4-methoxytryptamines, as in **25** (Scheme 3).

[17] Photolysis of a deoxygenated sample of diazene **5** smoothly provided C3-arylated pyrroloindoline **32** in 78% conversion (42% yield of isolated product) and 92% *ee*.



Asymmetric Catalysis

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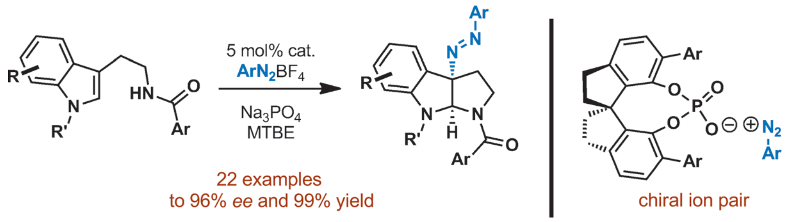
Chiral Anion Phase Transfer of Aryldiazonium Cations: An Enantioselective Synthesis of C3-Diazenated Pyrroloindolines



Live and let diazene: Chiral anion phase transfer of aryldiazonium cations has been utilized to prepare C3-diazenated pyrroloindolines. The air- and water-tolerant reaction allows electronic and steric diversity in the aryldiazonium electrophile and the tryptamine core, with the products being obtained in up to 99% yield and 96% *ee* (MTBE = methyl *tert*-butyl ether).