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Enantioselective α-amination enabled by a BINAM-derived phase-transfer catalyst†

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Chiral anion phase-transfer of aryldiazonium cations was utilized to achieve highly enantioselective α-amination of carbonyl compounds. A broad scope of indanone- and benzosuberone-derived substrates was amenable to this strategy. Critical to obtaining high levels of enantioselectivity was the use of BINAM-derived phosphoric acids. The utility of this transformation was demonstrated through facile conversion of diazene products to valuable α-amino acid derivatives.

Chiral amines are attractive targets for enantioselective methodology due to their prominent representation amongst bioactive molecules and chiral catalysts.[1] Particularly attractive are α-amino acids, which are utilized directly as building blocks for pharmaceuticals, natural products, agrochemicals, and as precursors for commonly employed chiral ligands.[1] Several methods exist that provide access to enantioenriched, protected amines.[2] The use of dialkyl azodicarboxylates as masked electrophilic nitrogen sources in auxiliary-directed,[3] organocatalytic[4] and transition metal catalyzed[5] amination reactions is prevalent. These methodologies furnish highly enantioenriched hydrazines that can be converted to amines after multiple chemical operations.

We hypothesized that the use of aryldiazonium cations as electrophilic nitrogen sources within a chiral anion phase-transfer (CAPT) manifold could provide a complementary enantioselective amination method.[6] In this scenario, chiral anion phase-transfer of an insoluble aryldiazonium cation would generate a soluble N-electrophilic, chiral diazonium ion pair. This species could react with nucleophilic carbonyl derivatives to provide enantioenriched α-diazenated compounds (Fig. 1a and b). Importantly, this methodology would complement established α-amination methodologies in several ways. Firstly, well-established methods for reductive cleavage of azo compounds such as **2** would provide facile access to unprotected α-amino acid derivatives (**3**).[7] Secondly, straightforward preparation of complex aryldiazonium cations from readily available anilines would facilitate development of application-specific amination reagents with tunable reactivity.[8] This manuscript details the successful execution of this hypothesis through the first examples of catalytic, enantioselective α-amination using aryldiazonium cations. This advance is enabled by the preparation of BINAM-derived chiral phosphoric acids (BDPAs) that proved critical to obtaining high levels of enantioinduction.

As a model system, we were attracted to indanone-derived β-ketoesters due to their potential for elaboration into conformationally constrained tyrosine analogues (CCTAs) such as 5-hydroxy-2-aminoindan-2-carboxylic acid (Hai) (**4**),[9] spirohydantoin-derived CGRP antagonists investigated for treatment of migraine headaches (**5**),[10] and amino-indane natural products such as dihydroparfumidine[11] (**6**) (Fig. 1c). We initially found that exposure of β-ketoester **17** to TCyP (**7**), Na_3PO_4, and PhN_2BF_4 provided diazene **18** with excellent conversion, albeit with low enantioselectivity (Table 1).[12]

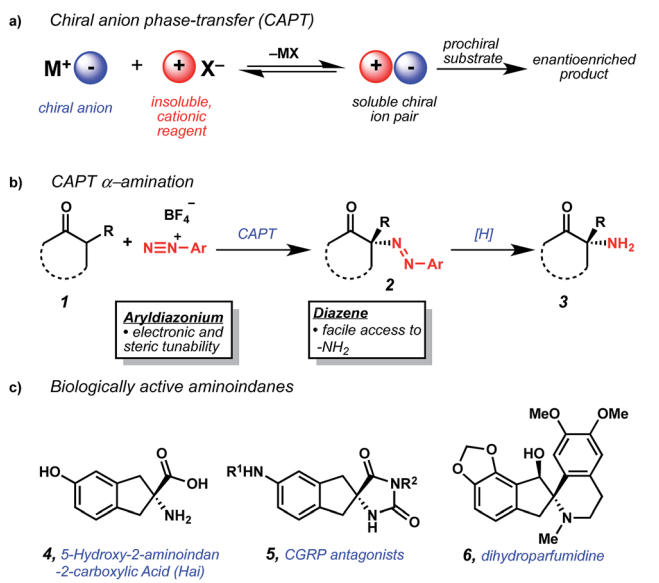

Fig. 1 (a) Chiral anion phase-transfer concept. (b) Application to α-amination. (c) Biologically active amino-indanone derivatives.

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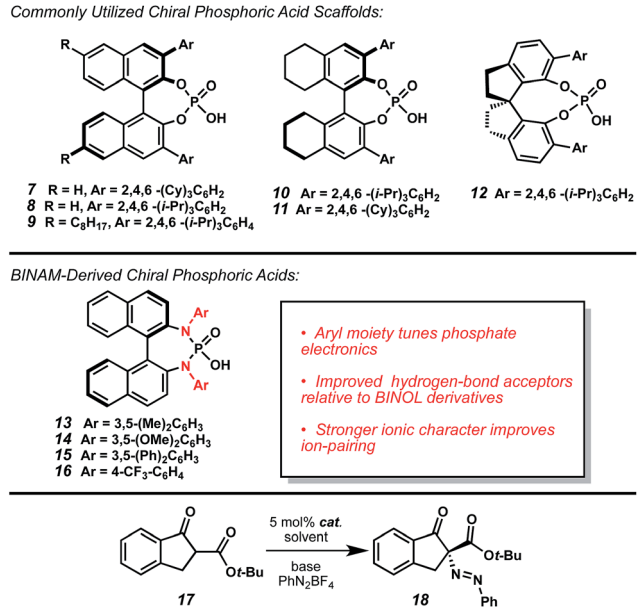
Table 1 Optimization[a,b,c]



Entry	Cat.	Solv.	Base	Conv.[b] (%)	ee[c] (%)
1	**7**	Hexanes	Na_3PO_4	>95	9
2	**8**	Hexanes	Na_3PO_4	>95	7
3	**9**	Hexanes	Na_3PO_4	>95	0
4	**10**	Hexanes	Na_3PO_4	>95	2
5	**11**	Hexanes	Na_3PO_4	>95	7
6	**12**	Hexanes	Na_3PO_4	>95	4
7	**7**	Hexanes	$NaHCO_3$	>95	21
8	**7**	Hexanes	NaH_2PO_4	>95	34
9	**13**	Hexanes	NaH_2PO_4	>95	−7
10	**14**	Hexanes	NaH_2PO_4	>95	4
11	**15**	Hexanes	NaH_2PO_4	>95	5
12	**16**	Hexanes	NaH_2PO_4	>95	87
13	**16**	2-MeTHF	NaH_2PO_4	>95	10
14	**16**	Toluene	NaH_2PO_4	>95	40
15	**16**	Cyclohexane	NaH_2PO_4	>95	90

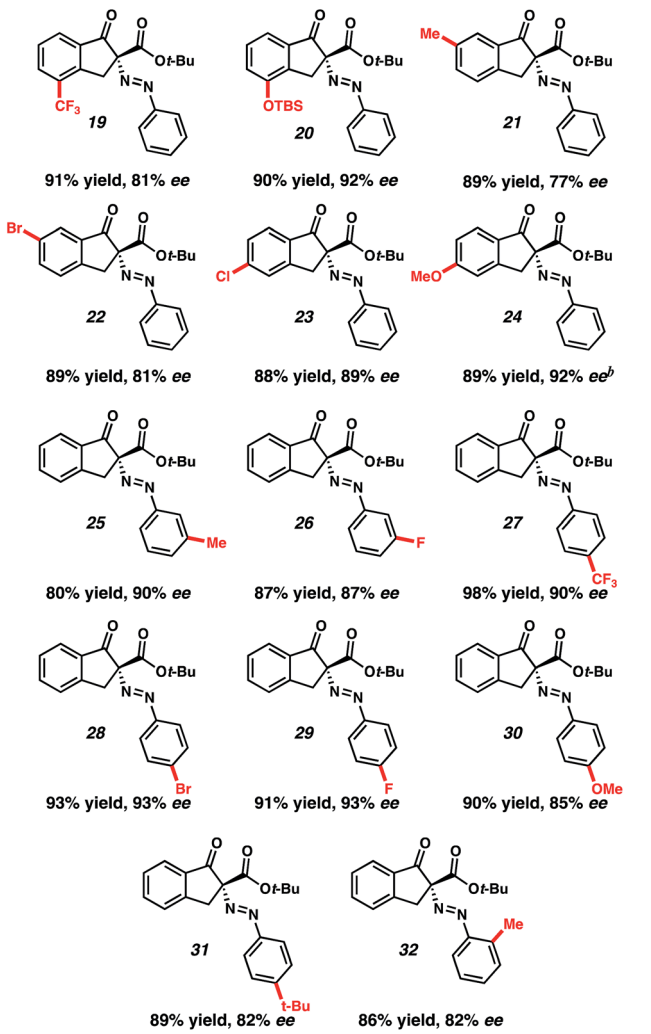
[a] Conditions: **17** (1 equiv.), cat. (**13–16**) (5 mol%), base (6 equiv.), PhN_2BF_4 (1.2 equiv.), solvent (0.025 M), rt, 2–24 h. [b] Conversion based on consumption of starting material as determined by ^1H NMR. [c] Determined by chiral phase HPLC.

With this encouraging result in hand, a screen of CAPT catalysts and inorganic bases was undertaken (Table 1). Examination of the commonly employed chiral phosphate scaffolds did not identify a catalyst capable of providing improved enantioselectivity (entries 1–6); however, linear screening carried out with TCyP (7) proved fruitful, as use of weaker bases, such as NaH_2PO_4, increased enantioselectivity to 34% ee while maintaining excellent conversion (entry 7, 8).

Challenged by low levels of enantioselectivity using common chiral phosphate scaffolds, we undertook efforts to design novel CAPT catalysts. We were drawn to the BINAM-derived phosphoric acids (BDPAs, Table 1, **13–16**) first prepared by Ishihara and coworkers,[13] as they offer two potential improvements over BINOL-derived phosphates (**7–11**): first, we hypothesized that the nitrogen lone pairs would improve hydrogen-bonding interactions with the substrates relative to traditional chiral phosphoric acid catalysts (**7–12**).[14] Second, increased resonance donation from the nitrogens could improve ion-pairing with the diazonium cation. Furthermore, this catalyst system would be highly modular, allowing for variation of both the ionic character and the hydrogen-bonding strength *via* synthetic modulation of the N-aryl groups.[15]

A small library of BDPAs was prepared (**13–16**). Upon examination of these catalysts under our diazenation conditions (Table 1, entries 9–12), we were pleased to find that electron-poor BDPA **16** provided the diazenated product (**18**) in excellent conversion and 87% ee (entry 12). Fine-tuning of solvent (entries 13–15) identified cyclohexane as optimal, yielding indanone **18** in 90% ee (entry 8).

Table 2 Substrate scope[a,b,c,d]

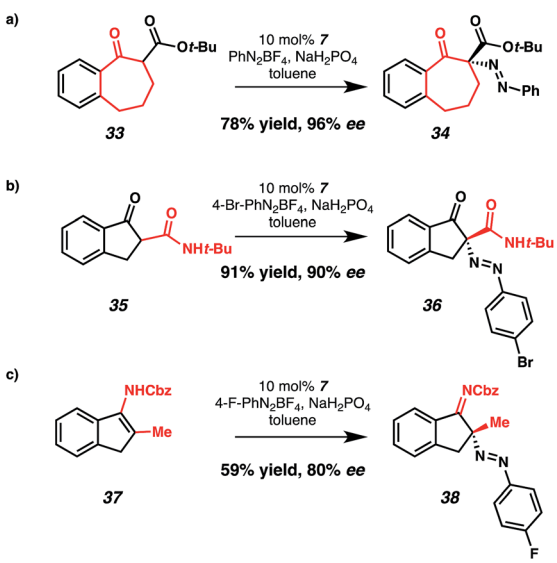


[a] Conditions: nucleophile (1 equiv.), **16** (10 mol%), NaH_2PO_4 (6 equiv.), ArN_2BF_4 (1.2 equiv.), cyclohexane (0.025 M). [b] Conditions: nucleophile (1 equiv.), **17** (10 mol%), NaH_2PO_4 (6 equiv.), ArN_2BF_4 (1.2 equiv.), MTBE (0.025 M). [c] Isolated yield. [d] Enantiomeric excess determined by chiral phase HPLC.

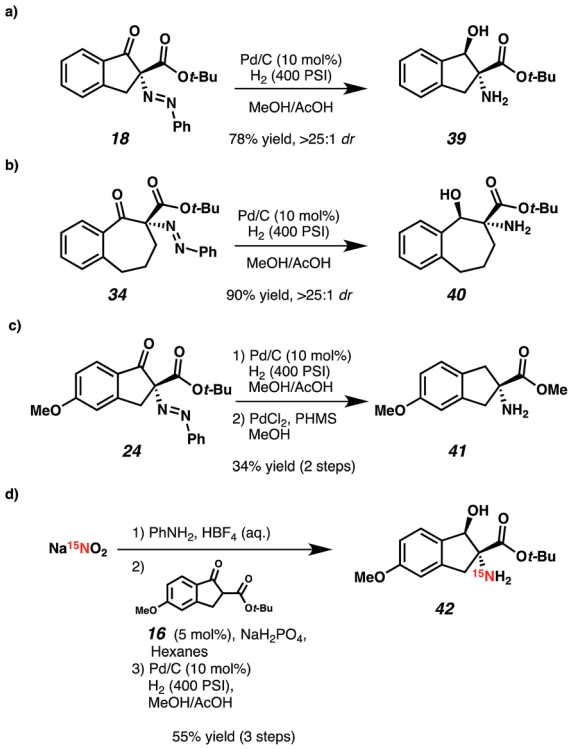
With optimized reaction conditions in hand, we investigated the scope of this reactivity. Indanones with electron-rich (**20**, **21**, **24**, Table 2) and electron-poor (**19**, **22**, **23**) substitution at the −4, −5, and −6 positions provided their corresponding diazenes in good yields and enantioselectivities. Importantly, both protected phenol and halogenated derivatives (**20** and **22–24**) were competent under the reaction conditions, permitting derivatization of the reaction products. Additionally, substitution of the diazonium aryl group with electron-poor, as well as electron-rich, groups at *-ortho*, *-meta*, and *-para* position provided excellent yields and good to excellent enantioselectivities (Table 2, **25–32**).

Additional ketone derivatives were amenable to CAPT diazenation with slight modification of the reaction conditions (Scheme 1). Benzosuberone derivative **33** was a suitable nucleophile, affording diazene **34** in 96% ee and 78% yield. Use of β-ketoamide **35** provided diazene **36** in 90% ee and 91% yield. We were pleased to find that nonstabilized enamide **37** underwent enantioselective C–N bond formation, providing imine **38** in 80% ee and 59% yield.

We were pleased to find that hydrogenation of indanone **18** and benzosuberone **34** under standard conditions smoothly formed their respective β-hydroxy amino acid derivatives with excellent diastereoselectivity and without loss of enantioenrichment (Scheme 2, **39** and **40**). Additionally, compound **24** was reduced to protected CCTA **41**, a synthetic precursor of Hai (**4**) using standard heterogeneous Pd/C conditions followed by homogeneous reduction with polymethylhydrosiloxane (PHMS) and $PdCl_2$ (Scheme 2c).[16] Importantly, enantioenriched compounds akin to amine **41** (Scheme 1c) have been previously prepared *via* classical resolution in 9 steps.[9b] Furthermore, as CCTAs such as Hai (**4**) are utilized for study of protein conformation,[9] we envisioned that ^{15}N-labeling would be of great utility, and a powerful application of our methodology. Towards this end, isotopically enriched amino indanone **42** was prepared in a three-step sequence from inexpensive $Na^{15}NO_2$. It is noteworthy that the use of an azodicarboxylate electrophile for this application would require two equivalents of isotopically enriched nitrogen.



Scheme 1 Diazenation of additional substrates.



Scheme 2 Applications of diazene products.

Conclusions

In closing, we have developed a method for the enantioselective α-diazenation of enolate derivatives. This work was enabled by the development of novel BDPAs. The presented methodology possesses a broad scope, allowing for diazenation of diverse nucleophiles. As an application of our methodology, several diazenes were directly reduced to provide amino acid derivatives. Furthermore, facile ^{15}N-labeling was demonstrated through preparation of protected amino acid **42**.

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