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Chiral amines are attractive targets for enantioselective methodology due to their prominent representation amongst bioactive molecules and chiral catalysts.<sup>1</sup> Particularly attractive are  $\alpha$ -amino acids, which are utilized directly as building blocks for pharmaceuticals, natural products, agrochemicals, and as precursors for commonly employed chiral ligands.<sup>1</sup> Several methods exist that provide access to enantioenriched, protected amines.<sup>2</sup> The use of dialkyl azodicarboxylates as masked electrophilic nitrogen sources in auxiliary-directed,<sup>3</sup> organocatalytic<sup>4</sup> and transition metal catalyzed<sup>5</sup> 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 aryl diazonium cations as electrophilic nitrogen sources within a chiral anion phase-transfer (CAPT) manifold could provide a complementary enantioselective amination method.<sup>6</sup> In this scenario, chiral anion phase-transfer of an insoluble aryl diazonium cation would generate a soluble N-electrophilic, chiral diazonium ion pair. This species could react with nucleophilic carbonyl derivatives to provide enantioenriched  $\alpha$ -diazinated compounds (Fig. 1a and b). Importantly, this methodology would complement established  $\alpha$ -amination methodologies in several ways. Firstly, well-established methods for reductive cleavage of azo compounds such as **2** would provide facile access to unprotected  $\alpha$ -amino acid derivatives (**3**).<sup>7</sup> Secondly, straightforward preparation of complex aryl diazonium cations from readily available anilines would facilitate development of application-specific amination reagents with tunable reactivity.<sup>8</sup> This manuscript details the successful execution of this

hypothesis through the first examples of catalytic, enantioselective  $\alpha$ -amination using aryl diazonium 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  $\beta$ -ketoesters due to their potential for elaboration into conformationally constrained tyrosine analogues (CCTAs) such as 5-hydroxy-2-aminoindan-2-carboxylic acid (**4**),<sup>9</sup> spirohydantoin-derived CGRP antagonists investigated for treatment of migraine headaches (**5**),<sup>10</sup> and amino-indane natural products such as dihydroparfumidine<sup>11</sup> (**6**) (Fig. 1c). We initially found that exposure of  $\beta$ -ketoester **17** to TCyP (**7**),  $\text{Na}_3\text{PO}_4$ , and  $\text{PhN}_2\text{BF}_4$  provided diazene **18** with excellent conversion, albeit with low enantioselectivity (Table 1).<sup>12</sup>

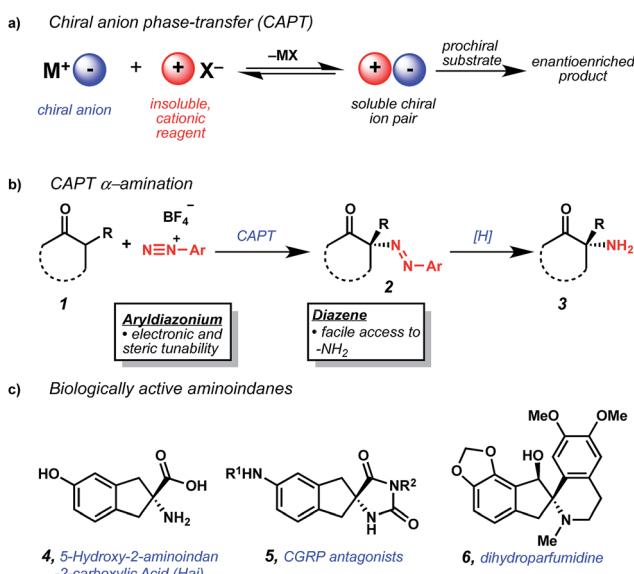


Fig. 1 (a) Chiral anion phase-transfer concept. (b) Application to  $\alpha$ -amination. (c) Biologically active amino-indanone derivatives.

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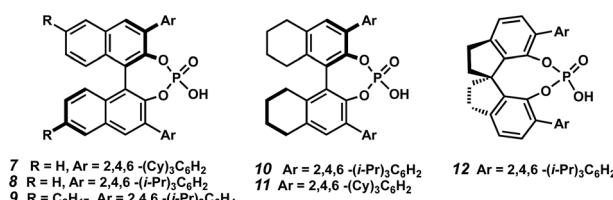
† Electronic supplementary information (ESI) available: Procedures and characterization data. CCDC 1025135. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4sc02494j

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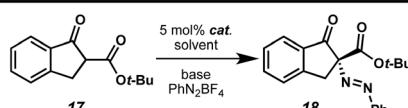
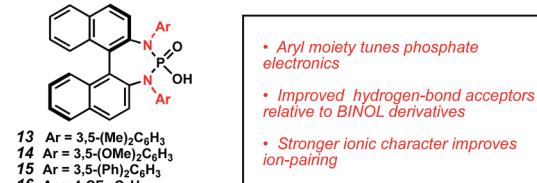


Table 1 Optimization<sup>a,b,c</sup>

Commonly Utilized Chiral Phosphoric Acid Scaffolds:



BINAM-Derived Chiral Phosphoric Acids:



Entry	Cat.	Solv.	Base	Conv. <sup>b</sup> (%)	ee <sup>c</sup> (%)
1	7	Hexanes	Na <sub>3</sub> PO <sub>4</sub>	>95	9
2	8	Hexanes	Na <sub>3</sub> PO <sub>4</sub>	>95	7
3	9	Hexanes	Na <sub>3</sub> PO <sub>4</sub>	>95	0
4	10	Hexanes	Na <sub>3</sub> PO <sub>4</sub>	>95	2
5	11	Hexanes	Na <sub>3</sub> PO <sub>4</sub>	>95	7
6	12	Hexanes	Na <sub>3</sub> PO <sub>4</sub>	>95	4
7	7	Hexanes	NaHCO <sub>3</sub>	>95	21
8	7	Hexanes	NaH <sub>2</sub> PO <sub>4</sub>	>95	34
9	13	Hexanes	NaH <sub>2</sub> PO <sub>4</sub>	>95	-7
10	14	Hexanes	NaH <sub>2</sub> PO <sub>4</sub>	>95	4
11	15	Hexanes	NaH <sub>2</sub> PO <sub>4</sub>	>95	5
12	16	Hexanes	NaH <sub>2</sub> PO <sub>4</sub>	>95	87
13	16	2-MeTHF	NaH <sub>2</sub> PO <sub>4</sub>	>95	10
14	16	Toluene	NaH <sub>2</sub> PO <sub>4</sub>	>95	40
15	16	Cyclohexane	NaH <sub>2</sub> PO <sub>4</sub>	>95	90

<sup>a</sup> Conditions: 17 (1 equiv.), cat. (13–16) (5 mol%), base (6 equiv.), PhN<sub>2</sub>BF<sub>4</sub> (1.2 equiv.), solvent (0.025 M), rt, 2–24 h. <sup>b</sup> Conversion based on consumption of starting material as determined by <sup>1</sup>H NMR.

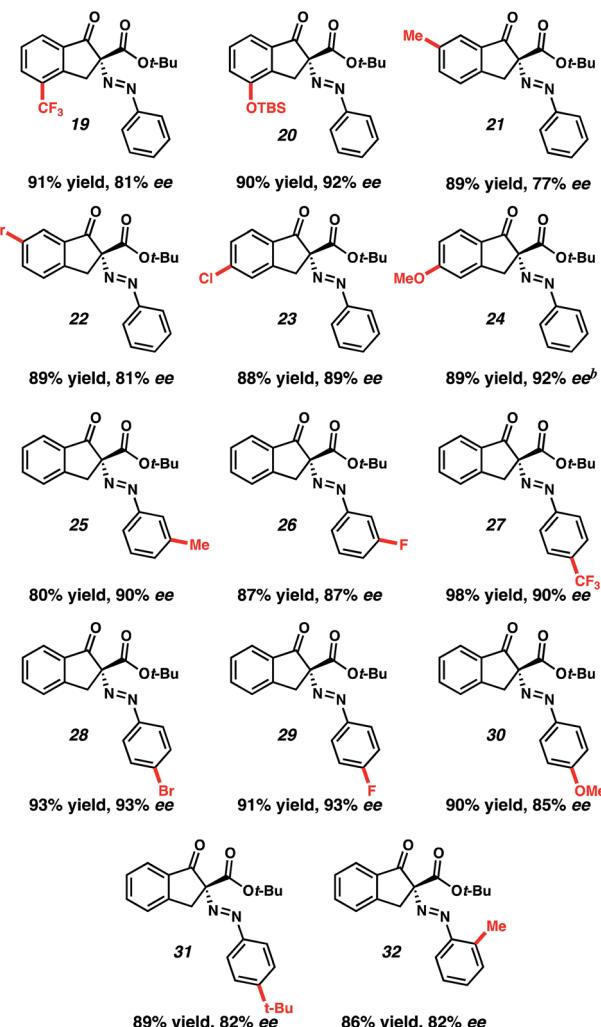
<sup>c</sup> Determined by chiral phase HPLC.

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<sub>2</sub>PO<sub>4</sub>, 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,<sup>13</sup> 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).<sup>14</sup> 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.<sup>15</sup>

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<sup>a,b,c,d</sup>

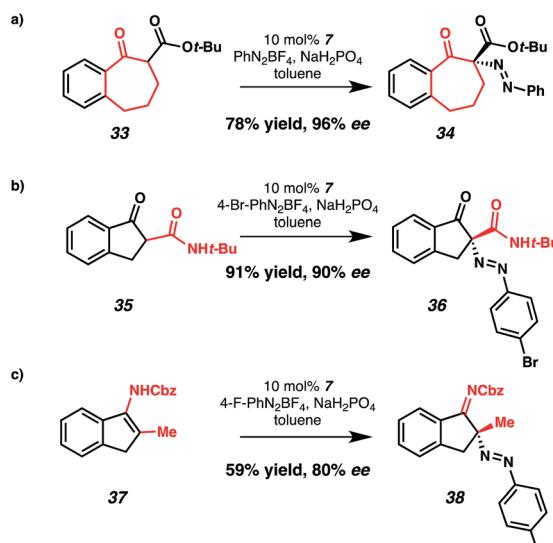
<sup>a</sup> Conditions: nucleophile (1 equiv.), 16 (10 mol%), NaH<sub>2</sub>PO<sub>4</sub> (6 equiv.), ArN<sub>2</sub>BF<sub>4</sub> (1.2 equiv.), cyclohexane (0.025 M). <sup>b</sup> Conditions: nucleophile (1 equiv.), 17 (10 mol%), NaH<sub>2</sub>PO<sub>4</sub> (6 equiv.), ArN<sub>2</sub>BF<sub>4</sub> (1.2 equiv.), MTBE (0.025 M). <sup>c</sup> Isolated yield. <sup>d</sup> Enantioselective excess determined by chiral phase HPLC.



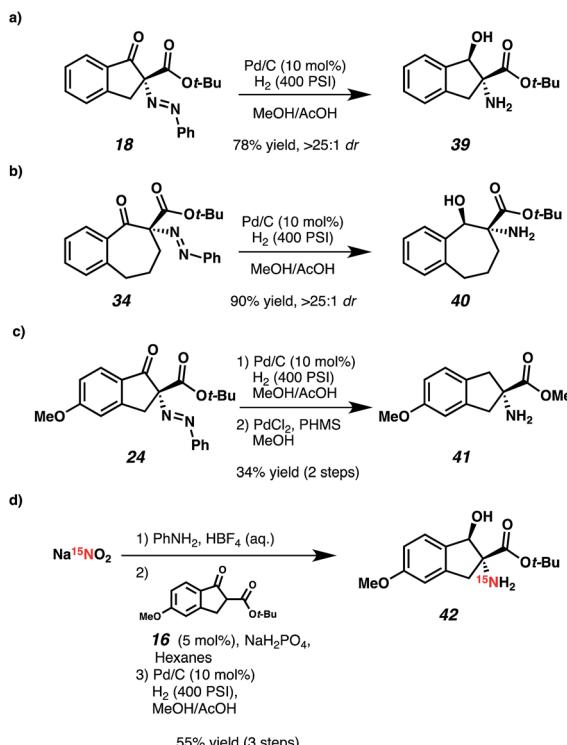
With optimized reaction conditions in hand, we investigated the scope of this reactivity. Indanones with electron-rich (20, 21, 24, Table 2) and electron-poor (19, 22, 23) substitution at the *-4*, *-5*, and *-6* positions provided their corresponding diazenes in good yields and enantioselectivities. 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  $\beta$ -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  $\beta$ -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  $\text{PdCl}_2$  (Scheme 2c).<sup>16</sup> Importantly, enantioenriched compounds akin to amine 41 (Scheme 1c) have been previously prepared *via* classical resolution in 9 steps.<sup>9b</sup> Furthermore, as CCTAs such as Hai (4) are utilized for study of protein conformation,<sup>9</sup> we envisioned that  $^{15}\text{N}$ -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  $\text{Na}^{15}\text{NO}_2$ . It is



Scheme 1 Diazenation of additional substrates.



Scheme 2 Applications of diazene products.

noteworthy that the use of an azodicarboxylate electrophile for this application would require two equivalents of isotopically enriched nitrogen.

## Conclusions

In closing, we have developed a method for the enantioselective  $\alpha$ -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  $^{15}\text{N}$ -labeling was demonstrated through preparation of protected amino acid 42.

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## Notes and references

- (a) T. C. Nugent, *Chiral amine synthesis: methods, developments and applications*, John Wiley & Sons, 2011; (b) M. T. Reetz, *Angew. Chem., Int. Ed.*, 1991, **30**, 1531–1546.

2 (a) E. Erdik, *Tetrahedron*, 2004, **60**, 8747–8782; (b) C. Najera and J. Sansano, *Chem. Rev.*, 2007, **107**, 4584–4671; (c) J. M. Janey, *Angew. Chem., Int. Ed.*, 2005, **44**, 4292–4300.

3 (a) L. A. Trimble and J. C. Vederas, *J. Am. Chem. Soc.*, 1986, **108**, 6397–6399; (b) C. Gennari, L. Colombo and G. Bertolini, *J. Am. Chem. Soc.*, 1986, **108**, 6394–6395; (c) D. A. Evans, T. C. Britton, R. L. Dorow and J. F. Dellaria, *Tetrahedron*, 1988, **44**, 5525–5540; (d) D. A. Evans, T. C. Britton, R. L. Dorow and J. F. Dellaria, *J. Am. Chem. Soc.*, 1986, **108**, 6395–6397.

4 (a) A. Bøgevig, K. Juhl, N. Kumaragurubaran, W. Zhuang and K. A. Jørgensen, *Angew. Chem., Int. Ed.*, 2002, **41**, 1790–1793; (b) B. List, *J. Am. Chem. Soc.*, 2002, **124**, 5656–5657; (c) H. Konishi, T. Y. Lam, J. P. Malerich and V. H. Rawal, *Org. Lett.*, 2010, **12**, 2028–2031; (d) M. Terada, M. Nakano and H. Ube, *J. Am. Chem. Soc.*, 2006, **128**, 16044–16045; (e) R. He, X. Wang, T. Hashimoto and K. Maruoka, *Angew. Chem., Int. Ed.*, 2008, **47**, 9466–9468; (f) C. L. Zhu, F. G. Zhang, W. Meng, J. Nie, D. Cahard and J. A. Ma, *Angew. Chem., Int. Ed.*, 2011, **50**, 5869–5872; (g) D. G. Blackmond, A. Moran, M. Hughes and A. Armstrong, *J. Am. Chem. Soc.*, 2010, **132**, 7598–7599; (h) C. Liu, Q. Zhu, K. W. Huang and Y. Lu, *Org. Lett.*, 2011, **13**, 2638–2641; (i) T. Y. Liu, H. L. Cui, Y. Zhang, K. Jiang, W. Du, Z. Q. He and Y. C. Chen, *Org. Lett.*, 2007, **9**, 3671–3674.

5 (a) D. A. Evans and S. G. Nelson, *J. Am. Chem. Soc.*, 1997, **119**, 6452–6453; (b) G. Cecere, C. M. König, J. L. Alleva and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2013, **135**, 11521–11524; (c) K. Juhl and K. A. Jørgensen, *J. Am. Chem. Soc.*, 2002, **124**, 2420–2421; (d) T. Mashiko, N. Kumagai and M. Shibasaki, *J. Am. Chem. Soc.*, 2009, **131**, 14990–14999.

6 (a) H. M. Nelson, S. H. Reisberg, H. P. Shunatona, J. S. Patel and F. D. Toste, *Angew. Chem., Int. Ed.*, 2014, **53**, 5600–5603; (b) R. J. Phipps, G. L. Hamilton and F. D. Toste, *Nat. Chem.*, 2012, **4**, 603–614.

7 H. M. Pinheiro, E. Touraud and O. Thomas, *Dyes Pigm.*, 2004, **61**, 121–139.

8 (a) A. Roglans, A. Pla-Quintana and M. Moreno-Manas, *Chem. Rev.*, 2006, **106**, 4622–4643; (b) H. Bonin, E. Fouquet and F.-X. Felpin, *Adv. Synth. Catal.*, 2011, **353**, 3063–3084.

9 (a) R. M. Pinder, B. H. Butcher, D. A. Buxton and D. J. Howells, *J. Med. Chem.*, 1971, **14**, 892–893; (b) F. N. Murigi, G. S. Nichol and E. A. Mash, *J. Org. Chem.*, 2010, **75**, 1293–1296; (c) H. I. Mosberg, A. L. Lomize, C. Wang, H. Kroona, D. L. Heyl, K. Sobczyk-Kojiro, W. Ma, C. Mousigian and F. Porreca, *J. Med. Chem.*, 1994, **37**, 4371–4383; (d) T. Deeks, P. A. Crooks and R. D. Waigh, *J. Med. Chem.*, 1983, **26**, 762–765; (e) M. T. Cox, Opiate Receptor Antagonists, *US Pat.*, 4464358 A, 7 August 1984.

10 (a) M. R. Wood, K. M. Schirripa, J. J. Kim, R. A. Bednar, J. F. Fay, J. G. Bruno, E. L. Moore, S. D. Mosser, S. Roller, C. A. Salvatore, J. P. Vacca and H. G. Selnick, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 6827–6830; (b) C. A. Stump, I. M. Bell, R. A. Bednar, J. F. Fay, S. N. Gallicchio, J. C. Hershey, R. Jolley, C. Kreatsoulas, E. L. Moore, S. D. Mosser, A. G. Quigley, S. A. Roller, C. A. Salvatore, S. S. Sharik, C. R. Theberge, C. B. Zartman, S. A. Kane, S. L. Graham, H. G. Selnick, J. P. Vacca and T. M. Williams, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 2572–2576; (c) I. M. Bell and H. G. Selnick, Monocyclic Amide CGRP Receptor Antagonists, *US Pat.*, 172,205, 14 July 2011.

11 Z. H. Mardirossian, H. G. Kiryakov, J. P. Ruder and D. B. MacLean, *Phytochemistry*, 1983, **22**, 759–761.

12 The connectivity and absolute stereochemistry of **18** was confirmed by X-ray crystallography. See the ESI† for diffraction data.

13 (a) M. Hatano, T. Ikeno, T. Matsumura, S. Torii and K. Ishihara, *Adv. Synth. Catal.*, 2008, **350**, 1776–1780; (b) M. Terada, K. Sorimachi and F. Uraguchi, *Synlett*, 2006, **1**, 133–136.

14 Hydrogen-bonding of chiral anion phase-transfer catalysts to substrates has been evoked in several transition state models, see: (a) X. Yang, R. J. Phipps and F. D. Toste, *J. Am. Chem. Soc.*, 2014, **136**, 5225–5228; (b) R. J. Phipps and F. D. Toste, *J. Am. Chem. Soc.*, 2013, **135**, 1268–1271; (c) J. Wu, Y.-M. Wang, A. Driljevic, V. Rauniar, R. J. Phipps and F. D. Toste, *Proc. Natl. Acad. Sci. U. S. A.*, 2013, **110**, 13729–13733.

15 See the ESI† for the syntheses of BDPAs.

16 H. Wang, L. Li, X.-F. Bai, J.-Y. Shang, K.-F. Yang and L.-W. Xu, *Adv. Synth. Catal.*, 2013, **355**, 341–347.

