

Cite this: *Chem. Sci.*, 2018, 9, 2336Received 5th December 2017
Accepted 23rd January 2018

DOI: 10.1039/c7sc05176j

rsc.li/chemical-science

Diastereo- and enantioselective additions of α -nitro esters to imines for *anti*- α,β -diamino acid synthesis with α -alkyl-substitution†

Daniel J. Sprague, Anand Singh and Jeffrey N. Johnston *

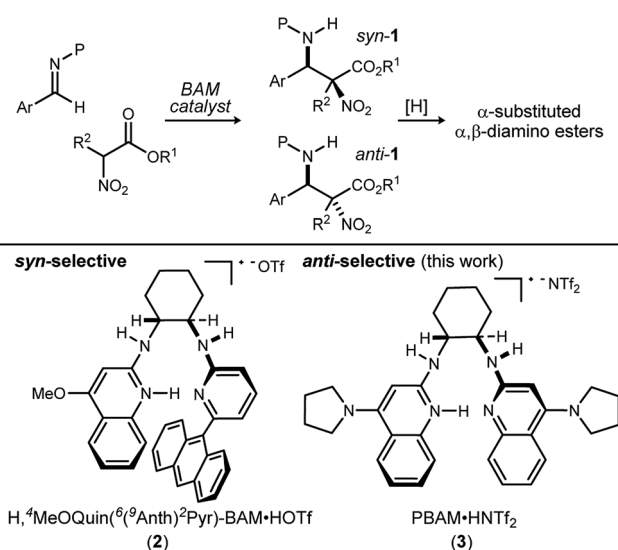
The discovery that a C_2 -symmetric bis(AMidine) [BAM] catalyst promotes an *anti*-selective addition of α -substituted α -nitro esters to imines is described, providing α -substituted α,β -diamino ester products with high diastereo- and enantioselectivity. When compared to the function of a BAM catalyst reported previously, the pair offer a rare example of diastereodivergence using a bifunctional Brønsted acid–base organocatalyst.

Methods to prepare enantioenriched α -amino acids are in demand, and there are few direct solutions to those bearing α -alkyl substituents.¹ Fewer still are methods that deliver α,β -diamino acids bearing α -alkyl substituents.² These unnatural amino acids are desirable precursors to peptide sequences due to their effect on the conformation and activity of the peptide sequences into which they are incorporated.^{3–5} The enantioselective *aza*-Henry (nitro-Mannich) reaction⁶ serves as a convergent approach to α,β -diamino acid derivatives, but its adaptation to α -alkyl- α -nitroester substrates (Scheme 1) is more rare, owing to the congestion provided by the additional substituent. Within this realm are the highly diastereoselective examples of the *anti*-selective reaction by Jorgensen,⁷ Shibasaki,⁸ Wu,⁹ and Huang-Dong.¹⁰ In contrast, *syn*-selective reactions are the exception,¹¹ with reports by us¹² and Ooi.¹³ Diastereodivergence in enantioselective catalysis is a characteristic driving modern catalyst development,^{14–16} and it motivated us to develop an *anti*-selective variant using the same bifunctional Brønsted acid/base catalyst design (Scheme 1).¹² We report the finding that a C_2 -symmetric ligand design, in combination with sterically hindered esters of α -nitro acids, can lead to highly *anti*-diastereoselective and enantioselective additions to *N*-Boc imine electrophiles. This creates a rare example in which a pair of organocatalyzed reactions with generally conserved design features, exhibit diastereodivergence and high selectivity.^{14,17,18}

We previously reported the organocatalytic synthesis of α -substituted *syn*- α,β -diamino acid derivatives *syn*-1.¹² Key to that success was the finding that unsymmetrical quinoline catalyst 2¹⁹ was necessary to achieve adequate reactivity, wherein the

methoxy substituent imparted a more Brønsted basic 2-aminoquinoline for efficient activation of the sterically demanding nitro ester pronucleophile.²⁰ Additionally, hindered aryl esters found synergism with the crowded pocket of 2 to provide high *syn*-selectivity, good yield, and high enantioselection.^{21–23}

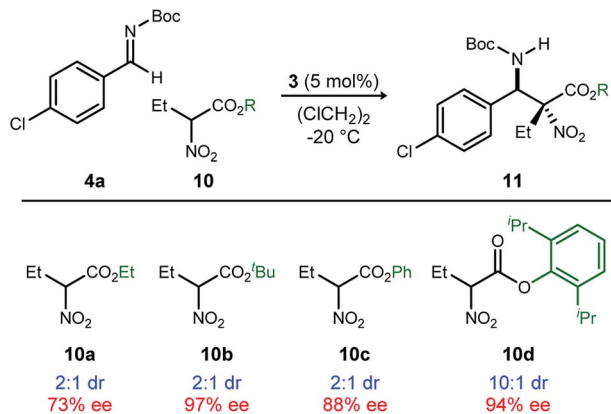
A return to symmetrical catalyst 3²⁴ (Scheme 1) was made in order to examine the impact of a less congested binding pocket to selectivity. In doing so, retention of catalyst activation using a pyrrolidine at the quinoline 4-position was anticipated. In the event, the level of diastereoselection with a small alkyl ester was low, but again increased with ester size (as in Scheme 2) and with the distinction that the *anti*-diastereomer was favored. As before, the ester size works synergistically with the catalyst to



Scheme 1 Development of a diastereodivergent *aza*-Henry reaction of α -alkyl α,β -nitroesters: *syn*-selective (prior work) and *anti*-selective (this work) catalysts using a common bifunctional design.

Department of Chemistry, Vanderbilt Institute of Chemical Biology, Vanderbilt University, Nashville, Tennessee 37235, USA. E-mail: jeffrey.n.johnston@vanderbilt.edu

† Electronic supplementary information (ESI) available. See DOI: 10.1039/c7sc05176j

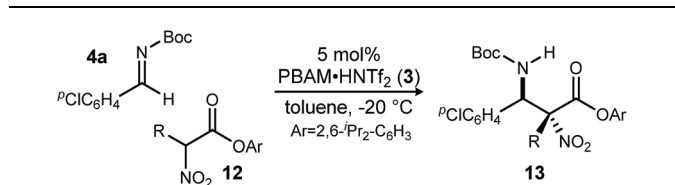


Scheme 2 Determinants of diastereoselection: synergism between catalyst **3** and ester size.

achieve increasing levels of selectivity, particularly diastereoselectivity (**10d** → **11d**, 10 : 1 dr, 94% ee). Finally, changing the solvent to toluene and the counteranion to triflimide afforded a combination producing optimal stereoselectivity (Table 1, entry 1) overall.²⁵

Having maximized the favored ester/catalyst combination to effect high *anti*-selectivity while maintaining high enantioselectivity, we turned to an evaluation of substrate scope. The effect of the size of the alkyl substituent presented by the hindered nitro ester was probed first by increasing chain length (Table 1, entries 1–4) using *p*-Cl-phenyl aldimine **4a** as a standard electrophile. α -Nitro propionate (**12a**), butanoate (**10d/12b**), pentanoate (**12c**), and hexanoate (**12d**) each afforded product in good yield with excellent diastereoselection (11 : 1 → 20 : 1 dr)

Table 1 *anti*-Selective chiral proton-catalyzed additions of α -alkyl α -nitro esters to azomethines: nucleophile scope^a



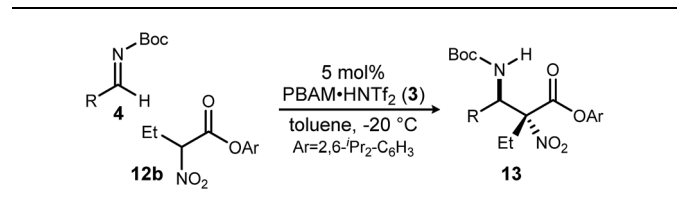
Entry ^a	R	13	dr ^b	ee ^c	Yield ^d
1	Me	a	>20 : 1	99	70
2 ^e	Et	b	>20 : 1	99	66
3	ⁿ Pr	c	>20 : 1	96	72
4	ⁿ Bu	d	11 : 1	97	64
5	Allyl	e	9 : 1	97	71
6	Bn	f	4 : 1	83	65
7	^c Pr	g	15 : 1	98	68
8	ⁱ Pr	h	>20 : 1	93	66
9	^c Hex	i	>20 : 1	87	46

^a All reactions were 0.7 M in imine, used 1.1 equiv. of the α -nitro ester, and had a standard 48 h reaction time. ^b Diastereomer ratios measured using ¹H NMR. ^c Enantiomeric ratios measured using HPLC and a chiral stationary phase. ^d Yields are for isolated, analytically pure adduct. ^e For comparison, use of the triflic acid salt of the catalyst provides this *anti*-product in 17 : 1 dr and 97% ee. *rac*-PBAM (free base) affords the adduct in 2 : 1 dr.

and uniformly high enantioselectivity (96–99% ee). As this substituent is changed further, only those with sp²-hybridization resulted in lower diastereoselection (down to 4 : 1) (Table 1, entries 5–6).[‡] Branching alkyl substituents, however, returned selectivity to >15 : 1 dr (Table 1, entries 7–9). α -Cyclopropyl nitroacetate **12g** afforded product in 68% isolated yield with 15 : 1 dr and 98% ee (Table 1, entry 7), and α -isopropyl nitroacetate **12h** afforded product in 66% isolated yield with >20 : 1 dr and 93% ee (Table 1, entry 8). α -Cyclohexyl nitroacetate **12i** gave the desired diamine derivative in >20 : 1 dr, and 87% ee, albeit in a lower isolated yield (46%, Table 1, entry 9). The lower conversion, and consequently lower isolated yield, reflect the steric bulk surrounding the nucleophilic carbon. Nevertheless, synthetically useful amounts of stereoenriched product **13i** can be obtained under the reaction conditions. An allyl group was incorporated at the α -position in good isolated yield, dr, and high ee (Table 1, entry 5). This installs a handle for further synthetic manipulations.

With these results in hand, α -nitro butanoate **10d/12b** was employed as a standard pronucleophile to evaluate an electronically and sterically diverse group of aldimines in the reaction (Table 2). Electronically neutral aldimines (Table 2, entries 1, 4, 9, 10, and 13) resulted in good isolated yield (54–76%), high diastereoselection (12 : 1 → >20 : 1 dr) and high enantioselectivity (96–99% ee). Notably, sterically demanding 1-naphthyl (Table 2, entry 9) and *para*-phenyl benzaldimine (Table 2, entry 13) were tolerated well, with high stereoselection. Electron deficient aldimines were also competent electrophiles. Trifluoromethylphenyl-substituted imine **4t** (Table 2, entry 12) afforded adduct **13t** in 74% isolated yield with 15 : 1 dr and 97%

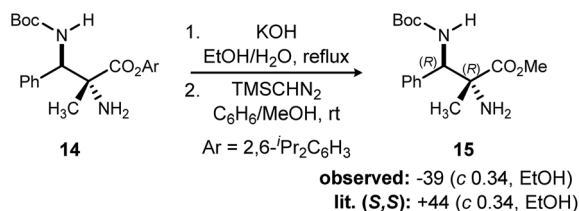
Table 2 *anti*-Selective chiral proton-catalyzed additions of α -alkyl α -nitro esters to azomethines: electrophile scope^a



Entry ^a	R	13	dr ^b	ee ^c	Yield ^d
1	C ₆ H ₅	j	>20 : 1	96	76
2	⁴ Cl-C ₆ H ₄	b	>20 : 1	99	66
3	⁴ Br-C ₆ H ₄	k	>20 : 1	99	71
4	³ Me-C ₆ H ₄	l	12 : 1	97	71
5	³ MeO-C ₆ H ₄	m	5 : 1	96	71
6	⁴ MeO-C ₆ H ₄	n	5 : 1	78	68
7	² Furyl	o	4 : 1	91	63
8	² Thiophene	p	>20 : 1	97	63
9	¹ Naphthyl	q	15 : 1	99	54
10	² Naphthyl	r	>20 : 1	96	70
11	³ Pyridyl	s	9 : 1	96	48
12	⁴ CF ₃ -C ₆ H ₄	t	15 : 1	97	74
13	⁴ Ph-C ₆ H ₄	u	>20 : 1	99	73

^a All reactions were 0.7 M in imine, used 1.1 equiv. of the α -nitro ester, and had a standard 48 h reaction time. ^b Diastereomer ratios measured using ¹H NMR. ^c Enantiomeric ratios measured using HPLC and a chiral stationary phase. ^d Yields are those of isolated, analytically pure adduct.





Scheme 3 Determination of absolute and relative configuration by chemical correlation.

ee. Both chloro- and bromo-substituted imines (Table 2, entries 2 and 3) afforded the corresponding adducts in good yield with excellent diastereoselection (>20 : 1 dr) and enantioselection (99% ee). Thiophenyl and pyridyl aldimines were equally amenable to addition (Table 2, entries 8 and 11). Electron-rich rings (Table 2, entries 5–7) afforded the *aza*-Henry adducts in good yields with notably lower diastereoselectivity, though enantioselectivity was generally maintained. The erosion of diastereoselection may be attributed to a less electrophilic azomethine, leading to a longer electrophile-nucleophile distance in the bond-forming step, or a diminished secondary interaction between the nitro and azomethine. Unfortunately, *N*-Boc ketimines exhibited their typical unreactive nature in this system, likely due to the severe steric congestion in the adducts, despite stirring at room temperature for 7 days. And while some product could be obtained using aliphatic *N*-Boc aldimines in exploratory experiments, selectivities were low.

In addition to absolute and relative stereochemical assignment by X-ray for **11d**,¹² the absolute stereochemistry of adduct **14**²⁶ was assigned *via* chemical correlation to known compound **15**. (*S,S*)-**15** was reported to have a rotation of +44. Synthetic **15** using catalyst **3** exhibited a measured rotation of -39. Therefore, the adducts produced by (*R,R*)-PBAM·HNTf₂ have the configuration of (*R,R*) as depicted in Scheme 3.¹⁰

Conclusions

In conclusion, we have developed the second enantioselective addition of α -alkyl α -nitro esters to imines using chiral proton catalysis, but with *anti*-diastereoselection. Taken together, these reactions are among the first highly selective hydrogen bond-catalyzed reactions exhibiting diastereodivergence. More remarkable is the use of a common catalyst design to reverse diastereoselection without compromise to enantioselection. We hypothesize that the key difference between **2** and **3** is the level of steric congestion in the binding pocket of the catalyst. Future studies will interrogate this hypothesis.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

DJS is grateful for support from the D. Stanley and Ann T. Tarbell Endowment Fund and the Vanderbilt Institute of

Chemical Biology. We are grateful to the National Institute of General Medical Sciences (NIH GM 084333) for financial support, and Dr Maren Pink (Indiana University Molecular Structure Center) for X-ray analysis of the original adducts.

Notes and references

‡ These diastereomers are separable using silica gel chromatography.

- 1 A. E. Metz and M. C. Kozlowski, *J. Org. Chem.*, 2015, **80**, 1–7.
- 2 (a) K. Bera and I. N. N. Namboothiri, *Asian J. Org. Chem.*, 2014, **3**, 1234–1260; (b) C. K. De, N. Mittal and D. Seidel, *J. Am. Chem. Soc.*, 2011, **133**, 16802–16805.
- 3 M. Goodman and S. Ro, in *Burger's Medicinal Chemistry and Drug Discovery*, ed. M. E. Wolff, Wiley, 1995, pp. 803–861.
- 4 (a) W. S. Saari, M. B. Freedman, R. D. Hartman, S. W. King, A. W. Raab, W. C. Randall, E. L. Engelhardt, R. Hirschmann and A. Rosegay, *J. Med. Chem.*, 1978, **21**, 746–753; (b) W. S. Saari, W. Halczenko, D. W. Cochran, M. R. Dobrinska, W. C. Vincek, D. C. Titus, S. L. Gaul and C. S. Sweet, *J. Med. Chem.*, 1984, **27**, 713–717; (c) J. J. Walsh, D. E. Metzler, D. Powell and R. A. Jacobson, *J. Am. Chem. Soc.*, 1980, **102**, 7136–7138.
- 5 T. Degenkolb, A. Berg, W. Gams, B. Schlegel and U. Grafe, *J. Pept. Sci.*, 2003, **9**, 666–678.
- 6 (a) A. Noble and J. C. Anderson, *Chem. Rev.*, 2013, **113**, 2887–2939; (b) R. G. Arrayas and J. C. Carretero, *Chem. Soc. Rev.*, 2009, **38**, 1940–1948.
- 7 K. R. Knudsen and K. A. Jorgensen, *Org. Biomol. Chem.*, 2005, **3**, 1362–1364.
- 8 Z. Chen, H. Morimoto, S. Matsunaga and M. Shibasaki, *J. Am. Chem. Soc.*, 2008, **130**, 2170–2171.
- 9 *anti*-Selective: X. X. Yan, Q. Peng, Q. Li, K. Zhang, J. Yao, X. L. Hou and Y. D. Wu, *J. Am. Chem. Soc.*, 2008, **130**, 14362–14363.
- 10 B. Han, W. Huang, Z. R. Xu and X. P. Dong, *Chin. Chem. Lett.*, 2011, **22**, 923–926.
- 11 *syn*-Diastereoselectivity reported by Wang was later corrected to *anti* (see p. 2902, ref. 6): X. X. Jiang, Y. F. Zhang, L. P. Wu, G. Zhang, X. Liu, H. L. Zhang, D. Fu and R. Wang, *Adv. Synth. Catal.*, 2009, **351**, 2096–2100.
- 12 A. Singh and J. N. Johnston, *J. Am. Chem. Soc.*, 2008, **130**, 5866–5867.
- 13 D. Uraguchi, K. Koshimoto and T. Ooi, *J. Am. Chem. Soc.*, 2008, **130**, 10878–10879.
- 14 S. Krautwald and E. M. Carreira, *J. Am. Chem. Soc.*, 2017, **139**, 5627–5639.
- 15 L. Lin and X. Feng, *Chem.-Eur. J.*, 2017, **23**, 6464–6482.
- 16 M. Bihani and J. C. G. Zhao, *Adv. Synth. Catal.*, 2017, **359**, 534–575.
- 17 Diastereodivergence driven by the electronic character of a ligand: X. X. Yan, Q. Peng, Q. Li, K. Zhang, J. Yao, X. L. Hou and Y. D. Wu, *J. Am. Chem. Soc.*, 2008, **130**, 14362–14363.
- 18 Substrate control: J. Hernández-Toribio, R. G. Arrayas and J. C. Carretero, *J. Am. Chem. Soc.*, 2008, **130**, 16150–16151. (*anti*-selective), compare to ref. 23c (*syn*-selective).



- 19 (a) B. Shen, D. M. Makley and J. N. Johnston, *Nature*, 2010, **465**, 1027–1032; (b) B. Shen and J. N. Johnston, *Org. Lett.*, 2008, **10**, 4397–4400.
- 20 T. A. Davis, J. C. Wilt and J. N. Johnston, *J. Am. Chem. Soc.*, 2010, **132**, 2880–2882.
- 21 *syn*-Selective α -iminyl glycine additions have been developed: (a) Z. L. Tao, A. Adele, X. Wu and L. Z. Gong, *Chin. J. Chem.*, 2014, **32**, 969–973; (b) A. Cayuelas, L. Serrano, C. Nájera and J. M. Sansano, *Tetrahedron: Asymmetry*, 2014, **25**, 1647–1653. (without simultaneous high dr/ee).
- 22 For *syn*-selectivity (but not enantioselective): L. Qiu, D. Wang, F. Lv, X. Guo, W. Hu, L. Yang and S. Liu, *Tetrahedron*, 2014, **70**, 1471–1477.
- 23 *syn*-Selective Mannich reaction using glycine Schiff base: (a) T. Arai, A. Mishiro, E. Matsumura, A. Awata and M. Shirasugi, *Chemistry*, 2012, **18**, 11219–11222; (b) L. Bernardi, A. S. Gothelf, R. G. Hazell and K. A. Jorgensen, *J. Org. Chem.*, 2003, **68**, 2583–2591; (c) J. Hernández-Toribio, R. Gómez Arrayás and J. C. Carretero, *Chem.–Eur. J.*, 2010, **16**, 1153–1157; (d) K. Imae, K. Shimizu, K. Ogata and S. Fukuzawa, *J. Org. Chem.*, 2011, **76**, 3604–3608.
- 24 (a) T. A. Davis, M. C. Dobish, K. E. Schwieter, A. C. Chun and J. N. Johnston, *Org. Synth.*, 2012, **89**, 380–393; (b) T. A. Davis, M. W. Danneman and J. N. Johnston, *Chem. Commun.*, 2012, **48**, 5578–5580.
- 25 The triflate salt afforded slightly inferior results; see Table 1, footnote *e*.
- 26 See ESI† for preparative details.

