

# A Highly Diastereoselective and Enantioselective Synthesis of Polysubstituted Pyrrolidines via an Organocatalytic Dynamic Kinetic Resolution Cascade

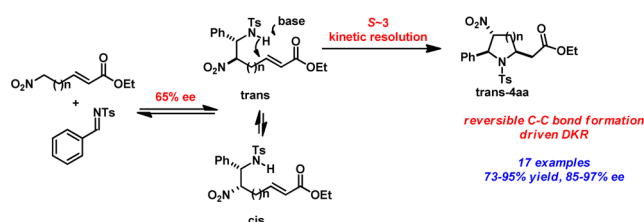
Tao Cheng, Sixuan Meng, and Yong Huang\*

Key Laboratory of Chemical Genomics, School of Chemical Biology and Biotechnology, Shenzhen Graduate School of Peking University, Shenzhen, China

huangyong@pkusz.edu.cn

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## ABSTRACT



Highly functionalized pyrrolidine and piperidine analogues, with up to three stereogenic centers, were synthesized in good yield (50–95%), excellent dr (single isomer), and high ee (>90%) using a *Cinchona* alkaloid-derived carbamate organocatalyst. High stereoselective synergy was achieved by combining a reversible aza-Henry reaction with a dynamic kinetic resolution (DKR)-driven aza-Michael cyclization. Whereas both reactions proceed with moderate enantioselectivities (50–60% for each step), high enantioselectivities are obtained for the overall products devoid of dr sacrifice.

Dynamic kinetic asymmetric transformations (DYKATs) have now emerged as powerful tools for the construction of stereogenic centers.<sup>1</sup> Using this strategy, products of high optical purity can be synthesized via reaction cascades that no longer necessitate overwhelmingly selective steps. In addition, ee enrichment of the overall products does not come at the cost of sacrificing either yields or diastereoselectivities. Since the discovery of organocatalytic cascade reactions,<sup>2</sup> DYKAT has enjoyed remarkable advances that have led to a number of efficient organocatalytic domino processes<sup>3</sup> and synergistic catalysis cascades, a process in which two distinct catalytic

mechanisms are merged into a single reaction.<sup>2a</sup> In particular, cascades that take advantage of a first reversible step and a second dynamic kinetic resolution step (DKR) have led to one-pot syntheses of chiral cyclic compounds with particularly high ee and dr in excellent yield. For example, Wang reported a cascade featuring a reversible thio-Michael and a DKR Michael reaction for his synthesis of substituted thiochromans.<sup>4</sup> Córdova, Jørgensen, Wang and others

(1) (a) Parsons, A. T.; Johnson, J. S. *Dynamic Kinetic Asymmetric Transformations Involving Carbon–Carbon Bond Cleavage*, in *Asymmetric Synthesis II: More Methods and Applications*; Christmann, M., Bräse, S., Eds.; Wiley-VCH: Weinheim, Germany, 2012. (b) Steinreiber, J.; Faber, K.; Griengl, H. *Chem.—Eur. J.* **2008**, *14*, 8060. (c) Trost, B. M.; Fandrick, D. R. *Aldrichimica Acta* **2007**, *40*, 59.

(2) (a) Allen, A. E.; MacMillan, D. W. C. *Chem. Sci.* **2012**, *3*, 633. (b) Patil, N. T.; Shinde, V. S.; Gajula, B. *Org. Biomol. Chem.* **2012**, *10*, 211. (c) Pellissier, H. *Adv. Synth. Catal.* **2012**, *354*, 237. (d) Albrecht, L.; Jiang, H.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2011**, *50*, 8492. (e) Ruiz, M.; López-Alvarado, P.; Giorgi, G.; Menéndez, J. C. *Chem. Soc. Rev.* **2011**, *40*, 3445. (f) Grondal, C.; Jeanty, M.; Enders, D. *Nat. Chem.* **2010**, *2*, 167.

(3) For recent examples of organocatalytic cascade reactions, see: (a) Zhang, X.; Song, X.; Li, H.; Zhang, S.; Chen, X.; Yu, X.; Wang, W. *Angew. Chem., Int. Ed.* **2012**, *51*, 7282. (b) Takizawa, S.; Nguyen, T. M.; Grossmann, A.; Enders, D.; Sasai, H. *Angew. Chem., Int. Ed.* **2012**, *51*, 5423. (c) Rajkumar, S.; Shankland, K.; Brown, G. D.; Cobb, J. A. *Chem. Sci.* **2012**, *3*, 584. (d) Maciver, E. E.; Knipe, P. C.; Cridland, A. P.; Thompson, A. L.; Smith, M. D. *Chem. Sci.* **2012**, *3*, 537. (e) Albrecht, L.; Ransborg, L. K.; Lauridsen, V.; Overgaard, M.; Zweifel, T.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2011**, *50*, 12496. (f) Celebi-Oelcuem, N.; Lam, Y.-H.; Richmond, E.; Ling, K. B.; Smith, A. D.; Houk, K. N. *Angew. Chem., Int. Ed.* **2011**, *50*, 11478. (g) Ozboya, K. E.; Rovis, T. *Chem. Sci.* **2011**, *2*, 1835. (h) Cai, Q.; Zheng, C.; Zhang, J.-W.; You, S.-L. *Angew. Chem., Int. Ed.* **2011**, *50*, 8665. (i) Tan, B.; Candeias, N. R.; Barbas, C. F., III. *Nat. Chem.* **2011**, *3*, 473. (j) Zhang, S.-L.; Xie, H.-X.; Zhu, J.; Li, H.; Zhang, X.-S. *Nat. Commun.* **2011**, *2*, 1214.

(4) Wang, J.; Xie, H.-X.; Li, H.; Zu, L.-S.; Wang, W. *Angew. Chem., Int. Ed.* **2008**, *47*, 4177.

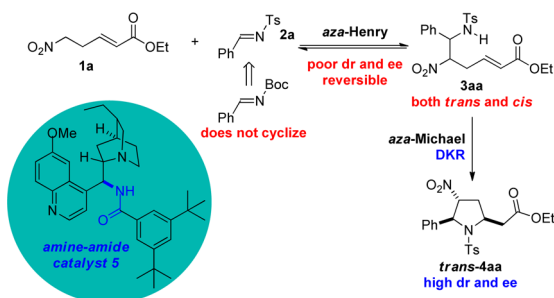
disclosed a series of “organo-metal cooperative catalysis” utilizing reversible Michael reactions and transition metal catalyzed diastereoselective carbocyclization to access five-membered carbo- and heterocycles.<sup>5</sup> Very recently, Zhao reported a chiral cyclohexane synthesis that combined a reversible Henry reaction and a subsequent selective Michael cyclization.<sup>6</sup> In this report, we describe the highly diastereo- and enantioselective synthesis of polysubstituted pyrrolidines using a parallel DYKAT strategy. In this cascade, a reversible *aza*-Henry reaction was combined with an *aza*-Michael cyclization to yield N-containing heterocycles. Among recent organocatalytic chiral syntheses of pyrrolidine analogues, most reactions have relied on aldehydes as a key component.<sup>7</sup> Processes free of aldehydes primarily reside in the Lewis acid and the organometallic paradigm.<sup>8</sup> Noteworthy, most strategies only permit access to pyrrolidines with specific substitution patterns, as restricted by their individual reaction mechanisms. Our *aza*-Henry/*aza*-Michael cascade (Table 1) offers a solution to the 2,3,5-trisubstituted pyrrolidine scaffold. One advantage of this method is that it does not require the common usage of a gem-diester like substrates.<sup>7c-g</sup>

The NO<sub>2</sub> substrate **1a** was readily available in two steps following literature procedures.<sup>3c</sup> The racemic reaction

proceeded smoothly at rt with DBU as the catalyst, yielding the desired trisubstituted pyrrolidine in quantitative yield. In order for the second step *aza*-Michael cyclization to proceed, the N—H acidity of the *aza*-Henry product had to be strong enough to be deprotonated by DBU. Aldimines other than TsN=C stalled at the initial *aza*-Henry stage, with no heterocyclization typically observed, as documented previously.<sup>9</sup> A single diastereomer (*trans*-**4aa**) was isolated. NMR experiments revealed that the initial *aza*-Henry reaction was modestly diastereoselective, giving a mixture of *trans/cis* products in a *ca.* 2:1 ratio. It was observed that only the *trans* *aza*-Henry adduct *trans*-**3aa** underwent subsequent cyclization.

The need to employ NTs aldimines posted a challenging task for the development of an asymmetric synthesis. There is no successful organocatalytic *aza*-Henry reaction involving this quite reactive imine functionality.<sup>10</sup> Dual functional H-bond/base catalysts were examined for asymmetric induction.<sup>11</sup> Moderate yields and enantioselectivities were observed with the popularly used Takemoto–Jacobsen amine/thiourea.<sup>12</sup> Attempts to improve ee through thiourea modification were fruitless. The corresponding amine/squaramide, developed by Rawal et al.,<sup>13</sup> afforded a nearly racemic product (Figure 1).

**Table 1.** Cascade Design and Initial Condition Screening<sup>a</sup>



entry	solvent	additive	yield (%) <sup>b</sup>	ee (%) <sup>c</sup>
1	DCM	—	50	83
2	toluene	—	33	91
3	THF	—	23	65
4	Et <sub>2</sub> O	—	46	91
5	CH <sub>3</sub> CN	—	26	25
<b>6</b>	<b>toluene</b>	<b>5 Å M.S.</b>	<b>72</b>	<b>91</b>
7	toluene	5 Å M.S.	>99	80 <sup>d</sup>

<sup>a</sup> Reactions were carried out on a 0.1 mmol scale using 10 mol % catalyst at rt; **1a/2a** = 1:1.5 at 0.2 M. <sup>b</sup> Isolated yields after flash column chromatography. <sup>c</sup> Ee's were determined by chiral HPLC analysis. <sup>d</sup> After stirring at rt for 1 d, heated to 100 °C for 8 h.

(5) For reviews on “organo-metal cooperative catalysis”, see: (a) Shao, Z.; Zhang, H. *Chem. Soc. Rev.* **2009**, *38*, 2745. (b) Du, Z.; Shao, Z. *Chem. Soc. Rev.* **2013**, *42*, 1337. For recent examples of DYKATs in this paradigm, see: (c) Deiana, L.; Afewerki, S.; Palo-Nieto, C.; Verho, O.; Johnston, E. V.; Córdova, A. *Sci. Rep.* **2012**, *2*, 851. (d) Sun, W.; Zhu, G.; Hong, L.; Wang, R. *Chem.—Eur. J.* **2011**, *17*, 13958. (e) Zhao, G.-L.; Ullah, F.; Deiana, L.; Lin, S.; Zhang, Q.; Sun, J.; Ibrahim, I.; Dziedzic, P.; Córdova, A. *Chem.—Eur. J.* **2010**, *16*, 1585. (f) Jensen, K. L.; Franke, P. T.; Arróniz, C.; Kobbelgaard, S.; Jørgensen, K. A. *Chem.—Eur. J.* **2010**, *16*, 1750.

(6) Dai, Q.; Arman, H.; Zhao, J. C.-G. *Chem.—Eur. J.* **2013**, *19*, 1666.

(7) For the synthesis of chiral pyrrolidine derivatives using asymmetric organocatalysis, see: (a) Jui, N. T.; Garber, J. A. O.; Finelli, F. G.; Macmillan, D. W. C. *J. Am. Chem. Soc.* **2012**, *134*, 11400. (b) Kumar, I.; Mir, N. A.; Gupta, V. K.; Rajnikant *Chem. Commun.* **2012**, *48*, 6975. (c) Lin, S.-Z.; Deiana, L.; Zhao, G.-L.; Sun, J. L.; Córdova, A. *Angew. Chem., Int. Ed.* **2011**, *50*, 7642. (d) He, L.; Chen, X.-H.; Wang, D.-N.; Luo, S.-W.; Zhang, W.-Q.; Yu, J.; Ren, L.; Gong, L.-Z. *J. Am. Chem. Soc.* **2011**, *133*, 13504. (e) Shi, F.; Luo, S.-W.; Tao, Z.-L.; He, L.; Yu, J.; Tu, S.-J.; Gong, L.-Z. *Org. Lett.* **2011**, *13*, 4680. (f) Li, H.; Zu, L.-S.; Xie, H. X.; Wang, J.; Wang, W. *Chem. Commun.* **2008**, 5636. (g) Vicario, J. L.; Reboredo, S.; Badia, S.; Carrillo, L. *Angew. Chem., Int. Ed.* **2007**, *46*, 5168. (h) Xu, X.-N.; Furukawa, T.; Okino, T.; Miyabe, H.; Takemoto, Y. *Chem.—Eur. J.* **2006**, *12*, 466.

(8) (a) Wang, M.; Wang, Z.; Shi, Y.-H.; Shi, X.-X.; Fossey, J. S.; Deng, W.-P. *Angew. Chem., Int. Ed.* **2011**, *50*, 4897. (b) Yamashita, Y.; Imaizumi, T.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2011**, *50*, 4893. (c) Oura, I.; Shimizu, K.; Ogata, K.; Fukuzawa, S. *Org. Lett.* **2010**, *12*, 1752. (d) Kuwano, P.; Kashiwabara, M.; Ohsumi, M.; Kusano, H. *J. Am. Chem. Soc.* **2008**, *130*, 808. (e) Fukuzawa, S.; Oki, H. *Org. Lett.* **2008**, *10*, 1747. (f) Saito, S.; Tsubogo, T.; Kobayashi, S. *J. Am. Chem. Soc.* **2007**, *129*, 5364. (g) Zeng, W.; Chen, G.-Y.; Zhou, Y.-G.; Li, Y.-X. *J. Am. Chem. Soc.* **2007**, *129*, 750.

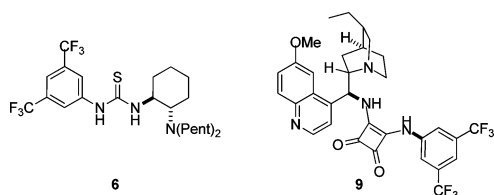
(9) (a) Gu, Q.; You, S.-L. *Chem. Sci.* **2011**, *2*, 1519. (b) Scherrer, R. A.; Donovan, S. F. *Anal. Chem.* **2009**, *81*, 2768. (c) Gimbert, C.; Moreno-Mañas, M.; Pérez, E.; Vallribera, A. *Tetrahedron* **2007**, *63*, 8305.

(10) Generally, <10% ee was observed using N-Ts aldimines; see: (a) Gomez-Bengoia, E.; Linden, A.; López, R.; Múgica-Mendiola, I.; Oiariabarri, M.; Palomo, C. *J. Am. Chem. Soc.* **2008**, *130*, 7955. (b) Wang, C.; Zhou, Z.; Tang, C. *Org. Lett.* **2008**, *10*, 1707. N-Ts aldimines was only demonstrated successfully in transition metal catalyzed *aza*-Henry reactions; see: (c) Zhou, H.; Peng, D.; Qin, B.; Hou, Z.; Liu, X.; Feng, X. *J. Org. Chem.* **2007**, *72*, 10302.

(11) For detailed catalyst and condition screening, see Supporting Information for details.

(12) (a) Takemoto, Y. *Chem. Pharm. Bull.* **2010**, *58*, 593. (b) Connon, S. J. *Chem. Commun.* **2008**, 2499. (c) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1520.

(13) For recent reviews on chiral squaramides as organocatalysts, see: (a) Aleman, J.; Parra, A.; Jiang, H.; Jørgensen, K. A. *Chem.—Eur. J.* **2011**, *17*, 6890. (b) Storer, R. I.; Aciro, C.; Jones, L. H. *Chem. Soc. Rev.* **2011**, *40*, 2330. For pioneering references by Rawal et al., see: (c) Konishi, H.; Lam, T. Y.; Malerich, J. P.; Rawal, V. H. *Org. Lett.* **2010**, *12*, 2028. (d) Zhu, Y.; Malerich, J. P.; Rawal, V. H. *Angew. Chem., Int. Ed.* **2010**, *49*, 153. (e) Malerich, J. P.; Hagihar, K.; Rawal, V. H. *J. Am. Chem. Soc.* **2008**, *130*, 14416.



**Figure 1.** Takemoto–Jacobsen amine/thiourea and Rawal amine/squaramide chiral bifunctional catalyst.

Surprisingly, switching to a single point amine/amide catalyst **5** allowed excellent cascade stereoselectivity.<sup>14</sup> Interestingly, stronger H-bond analogues, such as sulphonamides, were much less selective, which indicated that the H-bond strength of the catalyst ought to be finely tuned within a narrow range for optimal results. The enantioselectivity of this cascade was in direct inverse proportion to the polarity of solvents. In order to improve the overall conversion of this cascade, several additives were screened and 5 Å molecular sieves were found to significantly accelerate the *aza*-Michael cyclization without eroding the product ee. The desired **trans-4aa** was isolated in 72% yield with 91% ee. Heating to 100 °C accelerated the cyclization, and a quantitative yield of **trans-4aa** could be achieved with 80% ee. Both the relative and absolute configuration of **trans-4aa** was unambiguously determined by single-crystal X-ray diffraction.<sup>15</sup>

The substrate scope was examined, and the results are summarized in Table 2. The substrate tolerance for aldimines was particularly broad. Both aromatic and aliphatic aldimines with various substitutions were well suited to this cascade, and high enantioselectivities (>90%) were obtained uniformly, regardless of electronics and the substitution pattern. Heterocyclic aldimines derived from pyridines were particularly selective (>99% ee). The rate of the *aza*-Michael cyclization for this substrate, on the other hand, proved very slow, and only a 30% isolated yield was obtained after 2 days at rt. The overall yield could be improved by heating at 100 °C upon completion of the initial step, while still maintaining 90% enantioselectivity. This observation is worth noting, as relatively loose H-bonding catalysis rarely shows high selectivity at such elevated temperatures. This might be the result of amplified rate differences between the rate of reversibility of the *aza*-Henry vs the *aza*-Michael cyclization. The conversion to pyrrolidine was noticeably slower for aliphatic substrates, and the reaction time increased to 2 days.

(14) For literature examples employing amide derived Cinchona alkaloids as chiral organocatalysts, see: (a) Liu, X.-H.; Lin, L.-L.; Feng, X.-M. *Chem. Commun.* **2009**, 6145. (b) Seitz, T.; Baudoux, J.; Bekolo, H.; Cahard, D.; Plaquevent, J.-C.; Lasne, M.-C.; Rouden, J. *Tetrahedron* **2006**, *62*, 6155. (c) Brunner, H.; Baur, M. A. *Eur. J. Org. Chem.* **2003**, 2854. (d) Baur, M. A.; Riahi, A.; Héning, F.; Muzart, J. *Tetrahedron: Asymmetry* **2003**, *14*, 2755. (e) Drees, M.; Kleiber, L.; Weimer, M.; Strassner, T. *Eur. J. Org. Chem.* **2002**, 2405. (f) Brunner, H.; Schmidt, P. *Eur. J. Org. Chem.* **2000**, 2119.

(15) CCDC 905204, <http://www.ccdc.cam.ac.uk>. See Supporting Information for details.

**Table 2.** Substrate Scope<sup>a</sup>

entry	R <sub>1</sub>	yield (%)	ee (%)	entry	R <sub>1</sub>	yield (%)	ee (%)
1		72	91	7		76	97
	<b>trans-4aa</b>				<b>trans-4ag</b>		
2		72	90	8		73	90
	<b>trans-4ab</b>				<b>trans-4ah</b>		
3		80	91	9		72	94
	<b>trans-4ac</b>				<b>trans-4ai</b>		
4		73	95	10		95	94
	<b>trans-4ad</b>				<b>trans-4aj</b>		
5		76	93	11 <sup>b</sup>		95	90
	<b>trans-4ae</b>				<b>trans-4ak</b>		
6		73	92	12 <sup>c</sup>		67	90
	<b>trans-4af</b>				<b>trans-4al</b>		

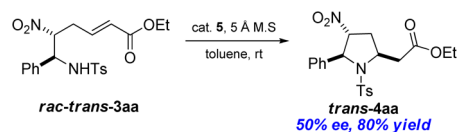
	X:	OMe 70% (90% ee)	<b>trans-4am</b>		73% (85% ee)	<b>trans-4an</b>
		OBu 65 (90% ee)	<b>trans-4an</b>			
		OBn 90% (88% ee)	<b>trans-4ao</b>			
		Ph 65% (86% ee)	<b>trans-4ap</b>			

<sup>a</sup>The absolute stereochemistry of the products was derived from the single X-ray diffraction of **trans-4aa**. <sup>b</sup>Stirred at rt for 24 h and heated at 100 °C for 8 h. Results for rt 48 h: 30% yield, >99% ee. <sup>c</sup>Reaction time: 2 d.

Nitroalkenes bearing various esters and ketones readily engaged in the cyclization cascade. Both pyrrolidines and piperidines were synthesized in good-to-excellent yields and selectivities. It was evident that, for groups which allowed faster cyclization, lower ee's were observed. This is in consistent with our reversible-DKR cascade model.

The DKR *aza*-Michael cyclization step was confirmed by an independent experiment using racemic **trans-3aa** (Scheme 1). **Trans-3aa** did not cyclize in the absence of a base. Pyrrolidine **trans-4aa** was isolated in 50% ee in 80% yield after 24 h, revealing a modestly selective kinetic resolution. With *aza*-Henry reversibility omitted, this result correlated to an *S* factor of 3. Standing pure *cis*-**3aa** in DCM solution led to the emergence of starting materials, a process which could be accelerated by the addition of organic bases.

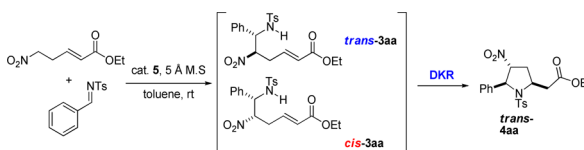
**Scheme 1.** DKR *aza*-Michael Cyclization Using Racemic **3aa**



Real time NMR experiments showed that the first *aza*-Henry reaction proceeded rather quickly (completed within 4 h), generating a 2.3:1 mixture of **trans-3aa** and **cis-3aa** (Table 3). The rate determining step was evidently the cyclization step, as the primary *aza*-Henry adduct could be isolated by column chromatography on SiO<sub>2</sub>.

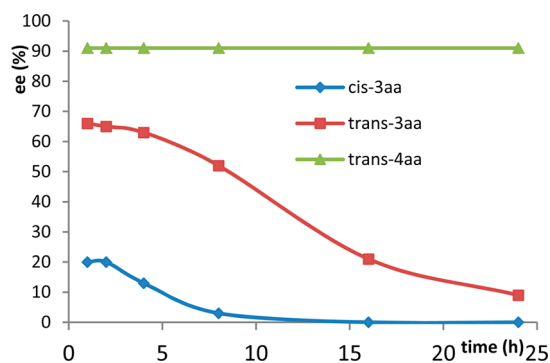
Under standard reaction conditions, the *trans/cis* ratio of the thermodynamic equilibrium of the *aza*-Henry adduct was

**Table 3.** Real Time Conversion, dr, and ee for the Intermediates and Product



entry	time (h)	trans/cis ( <b>3aa</b> )	yield (%)	ee (%)
1	4	2.3	10	91
2	8	2.5	24	91
3	16	2.7	40	91
4	24	3.1	72	91
5 <sup>a</sup>	6	2.3	quant.	80

<sup>a</sup> The *aza*-Michael cyclization was carried at 100 °C.

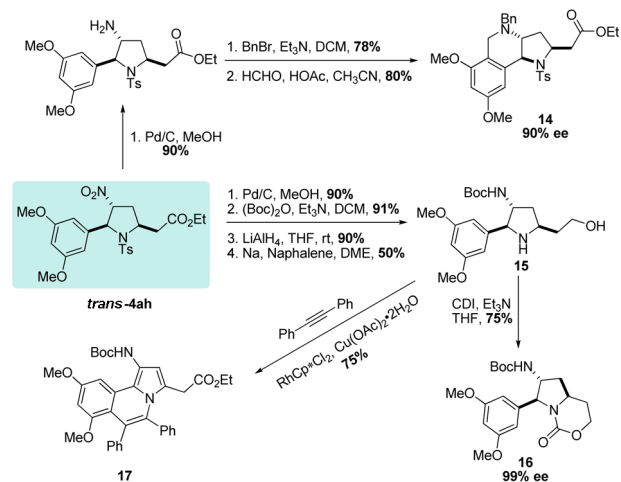


2.3:1 (*trans-3aa* vs *cis-3aa*). A stand alone *aza*-Henry experiment between nitropropane and N-Ts benzaldimine using catalyst **5** yielded similar levels of dr and ee. While *trans-3aa* was formed with modest ee (65%), the optical purity of the *cis* isomer was merely 20% ee initially. Ee's of *trans-3aa*, *cis-3aa*, and the product were monitored over time. Ee's of both intermediate isomers gradually decreased over time, accompanied by a steady accumulation of the cascade product *trans-4aa* of constantly high optical purity. Eventually, both *cis-3aa* and *trans-3aa* became racemic. Factoring a 3:1 kinetic resolution efficiency ( $S = 3$ ), the initial moderate 65% enantioselectivity for *trans-3aa* ( $er = 6.6:1$ ) was enhanced by the subsequent DKR step to a theoretical enantiomeric ratio of  $6.6 \times 3 = 19.8/1$ , compared to the 91% observed ee, for the pyrrolidine product *trans-4aa*. Based on the above analysis, the low ee of *cis-3aa* is direct evidence that the *cis*-to-*trans* isomerization is primarily due to reaction reversibility (C–C bond cleavage), not NO<sub>2</sub> group epimerization under basic conditions. Due to the modest selectivity of the kinetic resolution step, direct epimerization of *cis-3aa* of 20% ee would result in a theoretical ee of 83% ( $er = 3.7 \times 3 = 11.1$ ) for the final product.

The rich functionalities surrounding this scaffold allowed a number of chemical manipulations (Scheme 2). For example, an isoquinoline fused pyrrolidine skeleton could be accessed through a three-step sequence.

The appending side chain could be engaged in additional cyclization reactions with the pyrrolidine nitrogen. Interestingly, attempts to tether the aromatic ring and pyrrolidine via dehydrogenative annulation resulted in a fully aromatized compound due to *in situ* oxidation.<sup>16</sup>

**Scheme 2.** Product Derivatization



In summary, we have developed a highly diastereo- and enantioselective organocatalytic cascade that provides heavily substituted pyrrolidines with up to three stereogenic centers. This domino reaction relies on a reversible *aza*-Henry reaction and a subsequent DKR *aza*-Michael cyclization, both catalyzed by an amine/amide *Cinchona* alkaloid derivative, to ensure overall stereoselectivity. The unique features of this reaction and the further utility of amide derived H-bond catalysts are being investigated in detail and will be reported in due course.

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**Supporting Information Available.** Experimental procedures, characterization data, and NMR spectra for all new compounds, and X-ray data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

(16) (a) Ackermann, L.; Wang, L.; Lygin, A. V. *Chem. Sci.* **2012**, *3*, 177. (b) Morimoto, K.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2010**, *12*, 2068. (c) Ueura, K.; Satoh, T.; Miura, M. *Org. Lett.* **2007**, *9*, 1407.

The authors declare no competing financial interest.