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Asymmetric Synthesis of a Potent, Aminopiperidine-Fused Imidazopyridine Dipeptidyl Peptidase IV Inhibitor

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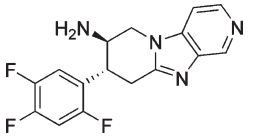

A practical asymmetric synthesis of a novel aminopiperidine-fused imidazopyridine dipeptidyl peptidase IV (DPP-4) inhibitor **1** has been developed. Application of a unique three-component cascade coupling with chiral nitro diester **7**, which is easily accessed via a highly enantioselective Michael addition of dimethyl malonate to a nitrostyrene, allows for the assembly of the functionalized piperidinone skeleton in one pot. Through a base-catalyzed, dynamic crystallization-driven process, the *cis*-piperidionone **16a** is epimerized to the desired *trans* isomer **16b**, which is directly crystallized from the crude reaction stream in high yield and purity. Isomerization of the allylamide **16b** in the presence of $RhCl_3$ is achieved without any epimerization of the acid/base labile stereogenic center adjacent to the nitro group on the piperidinone ring, while the undesired enamine intermediate is consumed to $< 0.5\%$ by utilizing a trace amount of HCl generated from $RhCl_3$. The amino lactam **4**, obtained through hydrogenation and hydrolysis, is isolated as its crystalline pTSA salt from the reaction solution directly, as such intramolecular transamidation has been dramatically suppressed via kinetic control. Finally, a Cu(I) catalyzed coupling-cyclization allows for the formation of the tricyclic structure of the potent DPP-4 inhibitor **1**. The synthesis, which is suitable for large scale preparation, is accomplished in 23% overall yield.

Introduction

Type 2 diabetes mellitus (T2DM) is a progressive disease. The worldwide prevalence of T2DM is growing at a continuous rate and could reach a total of 220 million cases by 2010.[1,2] Recently, protease dipeptidyl peptidase IV (DPP-4) inhibitors have emerged as a new class of antihyperglycemic agents for the treatment of T2DM[3,4] and offer several advantages such as lack of body weight gain and decreased incidence of hypoglycemic episodes over other existing antidiabetic agents. In addition, DPP-4 inhibitors could potentially alter the disease progress by restoring the β-cell function of the pancreas.[3]

The biological mechanism by which DPP-4 inhibitors operate involves stabilization of incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). GLP-1 and GIP are secreted by intestinal *L*-cells and *K*-cells in response to meal ingestion, respectively.[5] To date, it is well recognized that both GLP-1 and GIP can stimulate insulin secretion from β-cells. In addition, GLP-1 can also inhibit glucagon secretion and slow gastric emptying, which are all beneficial in controlling blood glucose and hemoglobin A_{1C}.[3,6] Unfortunately, the

(1) (a) International Diabetes Federation (IDF). *Diabetes Atlas*, 3rd ed.; December 2006, http://www.iotf.org/diabetes.asp. (b) Andrews, M. *U.S. News World Rep.*, **2009**, Feb 9.

(2) Zimmet, P.; Alberti, K. G. M. M.; Shaw, J. *Nature* **2001**, *414*, 782–787.

(3) For leading references, see: (a) Thornberry, N. A.; Weber, A. E. *Curr. Topics Med. Chem.* **2007**, *7*, 557–568. (b) Gwaltney, S. L. II; Stafford, J. A. *Annu. Rep. Med. Chem.* **2005**, *40*, 149–165. (c) Ahrén, B.; Landin-Olsson, M.; Jansson, P. A.; Svenson, M.; Holmes, D.; Schweizer, A. *J. Clin. Endocrinol. Metab.* **2004**, *89*, 2078–2084. (d) Weber, A. *J. Med. Chem.* **2004**, *48*, 4135–4141.

(4) (a) Florentin, M.; Liberopoulos, E. N.; Mikhailidis, D. P.; Elisaf, M. S. *Expert Opin. Pharmacother.* **2008**, *9*, 1705–1720. (b) Matikainen, N.; Mänttäri, S.; Schwizer, A. *Diabetologia* **2006**, *49*, 2049–2057.

(5) For review, see: Holst, J. J. *Diabetogoia* **2006**, *49*, 253–260.

(6) For lead references, see: (a) Chia, C. W.; Egan, J. M. *Drug Discovery Today: Disease Mech.* **2005**, *2*, 295. (b) Holst, J. J. *Curr. Opin. Endocrin. Diabetes Obesity* **2005**, *12*, 56–62.

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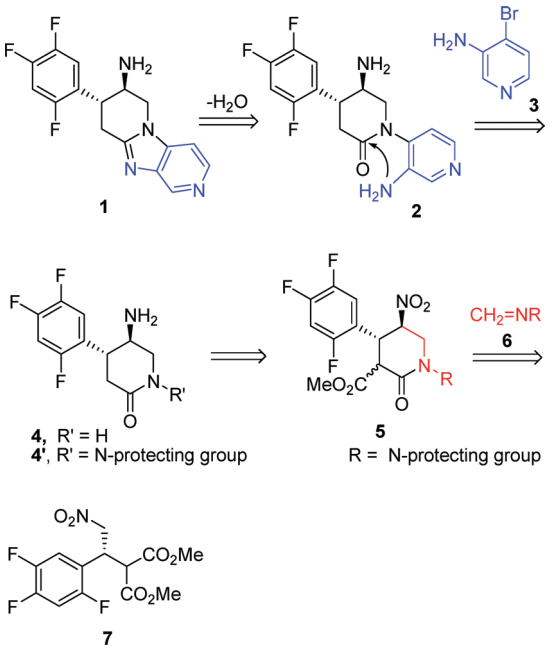
half-life of GLP-1 in human is very short (< 2 min) as the *N*-terminal amino acids are selectively clipped off by DPP-4. Therefore, inhibition of DPP-4 can stabilize GLP-1 and GIP and thus increase circulating levels of endogenous intact GLP-1 and GIP to allow their therapeutic benefits to be realized. This is a clinically proven, therapeutically novel approach to the treatment of T2DM.[2,3]

Aminopiperidine-fused imidazopyridine **1** is a potent, selective DPP-4 inhibitor and a drug candidate for the treatment of T2DM. The key challenge to synthesize **1** is to construct its piperidine moiety enantioselectively and efficiently. The piperidine ring is fused in a tricyclic system and has two adjacent stereogenic centers in a *trans* relationship. Asymmetric synthesis of this unique skeleton, as well as similar structures, was lacking at the inception of this work.[7] The previously described synthesis of **1** was racemic and required chromatographic resolution of a late-stage racemic intermediate.[7] Therefore, to develop a practical synthesis of **1** that is suitable for large-scale preparation to support the development of this drug candidate, we required an efficient asymmetric approach to the piperidine-fused imidazopyridine skeleton with the desired stereochemistry and functionality.

Application of multiple component couplings to synthesize organic molecules efficiently and practically is a desirable synthetic strategy,[8] since multiple transformations can be achieved through a series of cascade reactions in one-pot. The piperidine-fused imidazopyridine skeleton in **1** could be constructed via a convergent, transition-metal-assisted coupling[7a,9] of intermediates **3** and **4** (Scheme 1). We envisioned that the key intermediate **4**[10] could be derived from nitro piperidinone **5**. Through a cascade coupling[11] of **7** with a suitable imine species **6**, which arises from a condensation of a primary amine and formaldehyde, piperidinone **5** could in turn be accessed. Although at the time of this work the literature precedence for this type of cascade coupling transformation to build up intermediates such as **5** was unknown,[11] enantiomerically pure substrate **7** could be obtained in one-step by taking advantage of recent methodology for the asymmetric Michael addition of malonates to nitrostyrenes.[12] In this paper, we report a target-oriented, reaction mechanism-guided, asymmetric synthesis of **1** via a novel cascade coupling to realize the synthetic strategy described above.

SCHEME 1. Retrosynthetic Analysis of Aminopiperidine-Fused Imidazopyridine 1



Results and Discussion

Preparation of Coupling Precursor 7. Starting from commercially available 2,4,5-trifluorobenzaldehyde (**8**), nitrostyrene **10** was prepared through a Henry reaction.[13] Although the Henry alcohol **11** could be easily obtained in near-quantitative yield in the presence of a catalytic amount of base, dehydration of **11** through activation of the OH group under the reported conditions[14] resulted in formation of a dark product with decomposition, which led to a difficult isolation of the crystalline solid **10**.[15] After several attempts, we were glad to find that slowly quenching sodium *aci* salt[16] **9** into aqueous HCl−$ZnCl_2$ at 0 °C over 2−4 h could effectively yield the desired nitrostyrene **10** as the major product, which crystallized directly during the quench. The sodium *aci* salt **9** was easily obtained in almost quantitative yield by treating 2,4,5-trifluorobenzaldehyde

(7) (a) Edmondson, S. D.; Mastracchio, A.; Cox, J. M.; Eiermann, G. J.; He, H.; Lyons, K. A.; Patel, R. A.; Patel, S. B.; Petrov, A.; Scapin, G.; Wu, J. K.; Xu, S.; Zhu, B.; Thornberry, N. A.; Roy, R. S.; Weber, A. E. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4097–4101. (b) Cox, J. M.; Edmondson, S. D.; Harper, B.; Weber, A. E. *PCT Int. Appl.* WO2006039325, **2006**.

(8) For recent reviews, see: (a) Lelais, G.; MacMillan, D. W. C. *Aldrichim. Acta* **2006**, *39*, 79–87. (b) Palomo, C.; Mielgo, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 7876–7880.

(9) For a lead reference on metal-assisted coupling for the formation of amides, see: Klapars, A.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 7421–7428.

(10) In fact, piperidinones such as **4** are pharmaceutically useful intermediates. For examples, see: (a) Cox, J. M.; Harper, B.; Mastracchio, A.; Leiting, B.; Roy, R. S.; Patel, R. A.; Wu, J. K.; Lyons, K. A.; He, H.; Xu, S.; Zhu, B.; Thornberry, N. A.; Weber, A. E.; Edmondson, S. D. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4579–4583. (b) Pei, Z.; Li, X.; von Geldern, T. W.; Longenecker, K.; Pireh, D.; Stewart, K. D.; Backes, B. J.; Lai, C.; Lubben, T. H.; Ballaron, S. J.; Beno, D. W. A.; Kempf-Grote, A. J.; Sham, H. L.; Trevillyan, J. M. *J. Med. Chem.* **2007**, *50*, 1983–1987. (c) Edmondson, S. D.; Mastracchio, A.; Cox, J. M. *PCT Int. Appl.* WO2006058064, **2006**. (d) Ashwell, S.; Gero, T.; Ioannidis, S.; Janetka, J.; Lyne, P.; Su, M.; Toader, D.; Yu, D.; Yu, Y. *PCT Int. Appl.* WO2005066163, **2005**. (e) Cody, W. L.; Holsworth, D. D.; Powell, N. A.; Jalaie, M.; Zhang, E.; Wang, W.; Samas, B.; Bryant, J.; Ostroski, R.; Ryan, M. J.; Edmunds, J. J. *Bio. Med. Chem.* **2004**, *13*, 59–68.

(11) For a preliminary communication on cascade coupling, see: Xu, F.; Corley, E.; Murry, J. A.; Tschaen, D. M. *Org. Lett.* **2007**, *9*, 2669–2672.

(12) For examples, see: (a) Terada, M.; Ube, H.; Yaguchi, Y. *J. Am. Chem. Soc.* **2006**, *128*, 1454–1455. (b) Evans, D. A.; Seidel, D. *J. Am. Chem. Soc.* **2005**, *127*, 9958–9959. (c) Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X.; Takemoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 119–125. (d) Li, H.; Wang, Y.; Tang, L.; Deng, L. *J. Am. Chem. Soc.* **2004**, *127*, 9906–9907. (e) Watanabe, M.; Ikagawa, A.; Wang, H.; Murata, K.; Ikariya, T. *J. Am. Chem. Soc.* **2004**, *126*, 11148–11149. (f) Ji, J.; Barnes, D. M.; Zhang, J.; King, S. A.; Wittenberger, S. J.; Morton, H. E. *J. Am. Chem. Soc.* **1999**, *121*, 10215–10216. (g) Hynes, P. S.; Stupple, P. A.; Dixon, D. J. *Org. Lett.* **2008**, *10*, 1389–1391. (h) Zhu, Q.; Huang, H.; Shi, D.; Shen, Z.; Xia, C. *Org. Lett.* **2009**, *11*, 4536–4539.

(13) One-pot synthesis led to a low yield of fluoro-substituted styrenes; see: Jacobo, R.; Cota, A.; Rogel, E.; Garcia, J. D.; Rivero, I. A.; Hellberg, L. H.; Somanathan, R. *J. Fluorine Chem.* **1994**, *67*, 253–255.

(14) For examples, see: (a) Denmark, S. E.; Marcin, L. R. *J. Org. Chem.* **1993**, *58*, 3850–3856. (b) Saikia, A. K.; Barua, N. C.; Sharma, R. P.; Ghosh, A. C. *Synthesis* **1994**, 685–686.

(15) Attempts to accomplish the dehydration with TMSCl, MsCl, *t*-BuCOCl/Et_3N, *i*-Pr_2NEt, DBU, and tetramethylguanidine in various solvents resulted in unsatisfactory results.

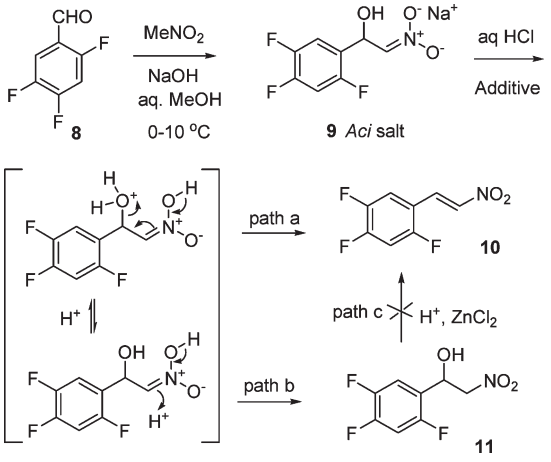
(16) (a) Anderson, W. K.; Dabrah, T. T.; Houston, D. M. *J. Org. Chem.* **1987**, *52*, 2945–2947. (b) Worrall, D. E. et al. *Organic Synthesis*; Wiley: New York, 1941; Collect. Vol. 1, p 413.

TABLE 1. Selected Results for the Preparation of Nitrostyrene 10 through *aci* Salt 9

entry	additives	equiv	ratio of **10**:**11**	isolated yield of **10**[a] (%)
1	None		2.5:1	63
2	$MgCl_2$	5	3.6:1	70
3	$ZnCl_2$	1	3:1	N/A
4	$ZnCl_2$	2	3.5:1	69
5	$ZnCl_2$	5	7:1	81

[a]The *aci* salt **9** was quenched with aq HCl at 5 °C over 2−4 h.

SCHEME 2. Preparation of Nitrostyrene 10 through *aci* Salt 9 and Plausible Pathways



(**8**) and nitromethane with NaOH in aqueous MeOH. The use of $ZnCl_2$[17] to significantly improve the ratio of **10** and **11** is unprecedented and proved to be robust and reproducible (Table 1, entry 5). Presumably, Lewis acid $ZnCl_2$ promoted the dehydration (Scheme 2, path a) of the initially quenched enolized intermediate rather than the Henry alcohol **11** since attempts to convert the isolated Henry alcohol **11** to nitrostryene **10** under acidic conditions such as in aq HCl or HCl/$ZnCl_2$ were unsuccessful (path c) and a good recovery of **11** was obtained under these conditions.

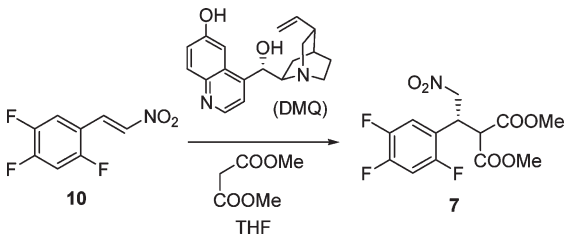
Thus, the desired **10** was directly obtained from the quenched reaction mixture as a yellowish crystalline solid in >80% yield and >98 area% purity (HPLC) through simple filtration, while the Henry alcohol **11** was effectively rejected in the mother liquors.

With nitrostyrene **10** secured, we turned our attention to enantioselective Michael addition of dimethyl malonate on nitrostyrene **10** to set up the desired tertiary stereogenic center of the key intermediate **7**. Several catalysts have been reported to achieve this type of Michael addition with high enantioselectivity.[12] Our studies on this step focused on the use of readily obtained demethyl quinidine (DMQ).[12d,18] After optimization, the desired product **7** was obtained in 99% conversion and ca. 95% ee between −20 and −15 °C in the presence of 1.1 equiv of dimethyl malonate and 0.5−1 mol % of catalyst (vs typical 10 mol % loading in literature). Our experimental results revealed that the enantioselectivity

(17) To the best of our knowledge, the use of Lewis acids such as $ZnCl_2$ to enhance the selectivity of the formation of nitro styrenes has not been reported.

(18) For an improved, practical preparation of DMQ without chromatographic purification, see the Supporting Information.

TABLE 2. Optimization of Michael Addition



temp (°C)	−20 °C	−15 °C	−10 °C	20 °C
ee[a,b] (%)	95.5	93	90	85.4
H_2O in THF (%)	0.05	0.2	0.4	1
ee[a,c] (%)	94	89.9	87.4	80.3

[a]Unless otherwise mentioned, the enantiomeric excess (ee) was determined by high-performance liquid chromatography (HPLC): Chiralcel OD-H column, 4.6 × 250 mm, 5 μm particle size, 20 °C, isocratic 10% *i*-PrOH in hexane; flow rate: 1.5 mL/min; UV detection: 215 nm. [b]In the presence of 2 mol % of DMQ in dry THF reaction solution. [c]In the presence of 1 mol % of DMQ at −15 °C.

of the reaction depends on both reaction temperature and water content (Table 2). Regarding the former, lower reaction temperatures resulted in higher ee. However, the reaction became sluggish below −25 °C. With respect to the latter, the presence of a small amount of water significantly decreased the enantioselectivity (Table 2), while keeping the reaction system dry at −20 °C yielded **7** in >95% ee reproducibly.

To isolate **7**, a straightforward process was developed. After the reaction was complete, the crude reaction solution was solvent-switched to *i*-PrOH. Water was then added to the reaction mixture and **7** directly crystallized from aq *i*-PrOH in 88% isolated yield with about 1% ee upgrade.

One-Pot Cascade Coupling. Various methods have been developed for the preparation of lactams and cyclic amines; however, efficient asymmetric synthesis of functionalized piperidinones with the stereochemistry setup such as **4**[19−21] has been lacking. Interestingly, the core structure of our retro-synthetic precursor piperidinone **4** also exists in a number of pharmaceutically important compounds.[10]

As shown in our retrosynthetic analysis (Scheme 1), we required the use of nitro malonate **7** to trap an active, unstable alkyl imine species in order to form the desired corresponding nitro piperidinone precursor. Condensation of a primary alkyl amine and formaldehyde led to instantaneous formation of the imine species **6** (Scheme 3), which could be masked as its corresponding trimer **12**[22] during the reaction. However, at the time of this work, the literature

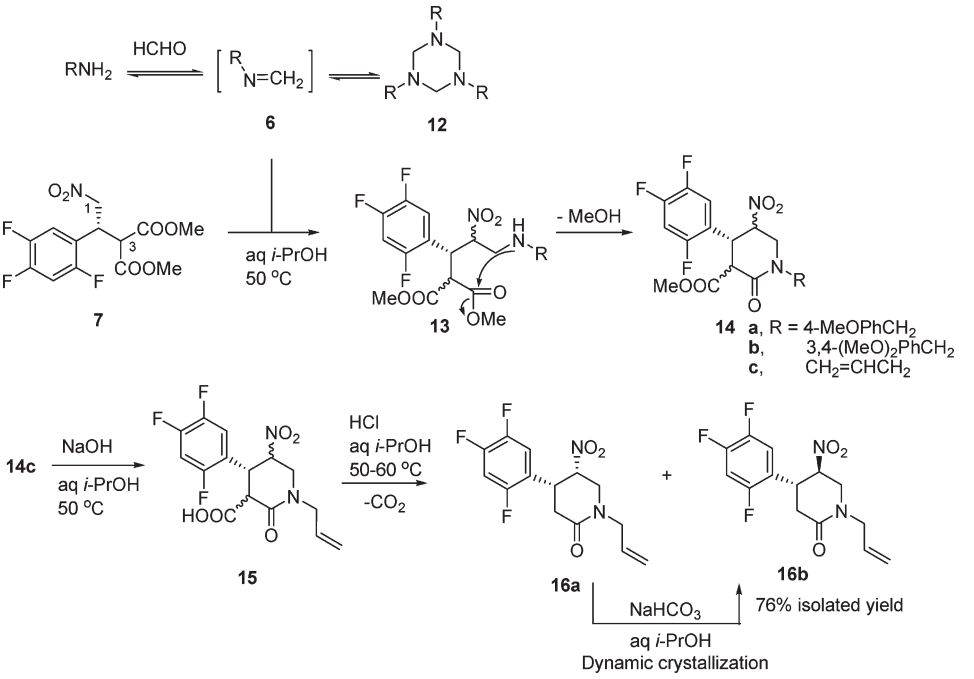
(19) For examples, see: Kumar, S.; Flamant-Robin, C.; Wan, Q.; Chiaroni, A.; Sasaki, N. A. *J. Org. Chem.* **2005**, *70*, 5946−5953 and references therein

(20) For similar three-component couplings, see: (a) Nara, S.; Tanaka, R.; Eishima, J.; Hara, M.; Takahashi, Y.; Otaki, S.; Foglesong, R. J.; Hughes, P. F.; Turkington, S.; Kanda, Y. *J. Med. Chem.* **2003**, *46*, 2467–2473. (b) Desai, M. C.; Lefkowitz, S. L. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 2083–2086. (c) Desai, M. C.; Thadeio, P. F.; Lefkowitz, S. L. *Tetrahedron Lett.* **1993**, *34*, 5831–5834. (d) Bhagwatheeswaran, H.; Gaur, S. P.; Jain, P. C. *Synthesis* **1976**, 615–616.

(21) For recent examples of multiple-component coupling involving nitroalkane or amine/formaldehyde, see: (a) Enders, D.; Hüttlm, M. R. M.; Grondal, C.; Raabe, G. *Nature* **2006**, *441*, 861–863. (b) Sundén, H.; Ibrahem, I.; Eriksson, L.; Cordova, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 4877−4880 and references therein.

(22) Overman, L. E.; Burk, R. M. *Tetrahedron Lett.* **1984**, *25*, 1635–1638.

SCHEME 3. Cascade Three-Component Coupling in One Pot



precedence for this type of cascade coupling transformation was unknown.[11] Other similar three-component coupling transformations were limited to the use of an aryl aldehyde to form a stable imine species that was then captured by an ester. The use of the nitro malonates such as **7** had not been reported.[20]

After several experiments,[23] we found that the use of alkyl amines, such as 4-methoxybenzylamine and 3,4-dimethoxybenzylamine, did give the desired corresponding coupling products **14a**,**b** (for more information, see the Supporting Information). However, taking into consideration the ease of operation as well as atom-economical efficiency to transform **14** into retro-synthetically desired precursor **4**, allylamine became our amine of choice for further development. The use of allylamine offered advantages over the use of other amines based on our recent studies on selective deprotection of the *N*-allylamide.[24] With further optimization, we were pleased to find that **14c** as a mixture of isomers could be obtained in 90% yield by treatment of malonate **7** with 1.3 equiv of allylamine and 1.05 equiv of aqueous HCHO in *i*-PrOH at 50 °C (Scheme 3). The stoichiometric utilization of formaldehyde was important in this cascade reaction. In fact, overcharging formaldehyde could lead to a lower yield, as the excess formaldehyde could further react with **14** to form bispidine derivatives.[11] Nevertheless, the formation of bispidine byproducts were easily suppressed under the above optimized conditions.

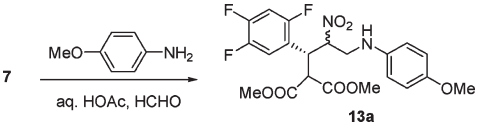
Scheme 3 also outlines a plausible mechanism for this cascade transformation.[25] The steric hindrance and pK_a differences between the C-1 H adjacent to the nitro group and the C-3 H adjacent to the two ester groups were believed to suppress the formation of potential competing products via Mannich reaction on C-3. These Mannich products were not observed under our reaction conditions. Without workup, the crude reaction mixture **14c** was treated with NaOH followed by decarboxylation of the resulting acid **15** upon acidification to give a mixture of *cis*/*trans* **16a,b** in one-pot.

However, our initial results showed that the *cis*/*trans* ratio (**16a**:**16b**) changed significantly as the decarboxylation conditions such as reaction time, pH, and temperature were varied. In order to further understand this observation, we screened various conditions to facilitate the epimerization of the nitro group. Interestingly, the *cis* **16a** isolated through chromatography purification can be partially converted to the *trans* isomer **16b** after several weeks at ambient temperature; in comparison, the isolated *trans* isomer is stable for several months under the same conditions, which also indicates that the *trans* isomer is the more thermodynamically stable form. More interestingly, the undesired *cis* piperidinone **16a**, is always the dominant product in a homogeneous reaction solution under acidic epimerization conditions.[26] The ratio of **16a**:**16b**[27] could be as high as 97:3 if the

(23) For an alternative synthesis as well as optimization of the cascade reaction using 4-methoxybenzyl amine, see the Supporting Information.

(24) For deprotection of *N*-allyl acyclic amides with cat. $RhCl_3$, see: Zacuto, M. J.; Xu, F. *J. Org. Chem.* **2007**, *72*, 6298−6300. However, deprotection of *N*-allyl lactams as described here gave a mixture of deprotected lactam **17** and *N*,*O*-acetal lactam **18**.

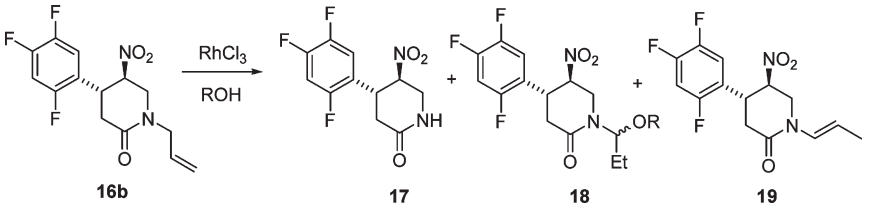
(25) Presumably due to the less nucleophilic aryl amine nitrogen, the cascade coupling stalled at intermediate **13** when aryl amines such as 4-methoxyphenylamine were used. The formation of **13a** thus further supports the stepwise reaction pathway (Scheme 3).



(26) It is not very clear why the *cis* isomer is the major product through acidic equilibrium. Presumably, the formation of the *cis* isomer is kinetically favored under acidic conditions.

(27) Unless otherwise mentioned, the ratio of *cis*/*trans* or diastereomers was determined by HPLC analysis (YMC Pack Pro C18, 5 μm particle size, 250 × 4.6 mm, mobile phase: 10 mM H_3PO_4/MeCN).

TABLE 3. Selected Results of $RhCl_3$-Catalyzed Isomerization



entry	solvents	$RhCl_3$ (mol %)	temp (°C)	time (h)	ratio of **17**:**18**:**19**
1	MeOH	2	64	10	no reaction
2	EtOH[a]	2	78	20	1:1: 9
3	*n-PrOH*	*2−3*	*95*	*17*	*1:4−6:0.03*
4	*n*-PrOH[b]	2	95	16	**19** + its epimer
5	80% aq *n*-PrOH	2.5	95	16	(**17** + its epimer):(**18** + its epimer) = 1:2.4
6	*i*-PrOH	2.5	95	20	1: 6: 1
7	H_2O−DMF	2.5	95	24	**19** only

[a]Sluggish reaction. [b]0.25 equiv of *i*-Pr_2NEt was used.

decarboxylation was carried out homogenously in aq HCl/*i*-PrOH at 55 °C. By contrast, epimerization of the *cis* isomer to its corresponding thermodynamically favored *trans* isomer could be realized upon exposure to weak bases; however, poor *cis*/*trans* ratios in favor of the *trans* isomer were obtained. For example, the ratio of **16a**:**16b** was only 1:2 after equilibrium between **16a** and **16b** was reached in aq $NaHCO_3$ in *i*-PrOH at 45 °C.

An efficient isolation of the desired *trans* isomer **16b** was eventually achieved by designing a base-catalyzed, dynamic crystallization-driven process. The desired *trans* isomer **16b** was allowed to crystallize from the reaction solution, as the *cis* isomer **16a** in the supernatant was continuously converted to the thermo-dynamically favored *trans* isomer **16b** through a base-promoted equilibrium of both isomers in the supernatant. In practice, without any aqueous workup, the one-pot cascade reaction mixture after decarboxylation was pH-adjusted to pH = 7−8 by simply adding aq $NaHCO_3$. Upon aging at 45 °C, the desired *trans* isomer of **16b** gradually crystallized and was isolated directly from crude aqueous *i*-PrOH solution by a simple filtration in 76% overall isolated yield and >98 area% purity (HPLC). Only about 1−2% of the undesired *cis* isomer of **16a** remained in the mother liquor.

Rh-Catalyzed Isomerization/Deallylation. With the desired *trans*-piperidinone **16b** in hand, we set forth to prepare the precursor **4** through reduction of the nitro group and removal of the *N*-allyl group. To realize this transformation, one of the challenges was to select the proper order of events. For example, reduction of the nitro group in **16b** prior to *N*-allyl group removal would have limited our options to those reduction methods that are not ideal for large scale preparation,[7,28] in order to prevent saturation of the *N*-allyl moiety. Alternatively, deprotection of *N*-allylamide prior to reduction of nitro group would have to avoid epimerization of the labile nitro-bearing stereogenic center in **16b**. While various methods can be applied to deprotect *N*-allylamines, the deprotection of *N*-allylamides is considerably more challenging,[29] and few methods are currently available.[30,31] However, our recent studies on the deprotection of *N*-allyl acyclic amides via isomerization/hydrolysis in the presence of a catalytic amount of $RhCl_3$ improved the attractiveness of the allyl protecting group for amide synthesis.[24]

After several experiments, we found that the reaction temperature of the rhodium-catalyzed isomerization of *N*-allylamide clearly played an important role[30b] to effectively convert **16b** to a mixture of **17** and *N*,*O*-acetal **18**. Table 3 depicts some selected results. The rhodium-catalyzed isomerization and deprotection in refluxing EtOH gave the undesired enamine **19**[32] as a major product (Table 3, entry 2). By contrast, no reaction was observed in refluxing MeOH (Table 3, entry 1). However, when the reaction temperature was increased to 95 °C in dry *n*-PrOH, two major products, the desired amino acetal **18** (R = *n*-Pr) and deallylated lactam **17**, were formed in high yield in the presence of 2 mol % of $RhCl_3$, while the undesired enamine **19** was reduced to <0.5% (Table 3, entry 3). Similar results were obtained when the reaction was carried out in MeOH or EtOH in a sealed-tube between 90 and 95 °C.

Reaction of $RhCl_3$ with an alcohol not only provides a rhodium hydride species, which is believed to be the active species that catalyzes the isomerization of *N*-allylamide **16b**, but also generates a crucial catalytic amount of HCl.[33,34]

(28) Hudlický, M. *Reductions in Organic Chemistry*, 2nd ed.; ACS Monograph 188; American Chemical Society: Washington, DC, 1996.

(29) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley & Sons, Inc.: New York, 1999.

(30) (a) Stille, J. K.; Becker, Y. *J. Org. Chem.* **1980**, *45*, 2139–2145. (b) Nemeto, H.; Jimenez, H. N.; Yamamoto, Y. *Chem. Commun.* **1990**, 1304–6. (c) Kanno, O.; Miyauchi, M.; Kawamoto, I. *Heterocycles* **2000**, *53*, 173–181. (d) Cainelli, G.; Giacomini, D.; Galetti, P. *Synthesis* **2000**, 289–294. (e) Cainelli, G.; DaCol, M.; Galetti, P.; Giacomini, D. *Synlett* **1997**, 923–924. (f) Chiusoli, G. P.; Costa, M.; Fiore, A. *Chem. Commun.* **1990**, 1303–1304.

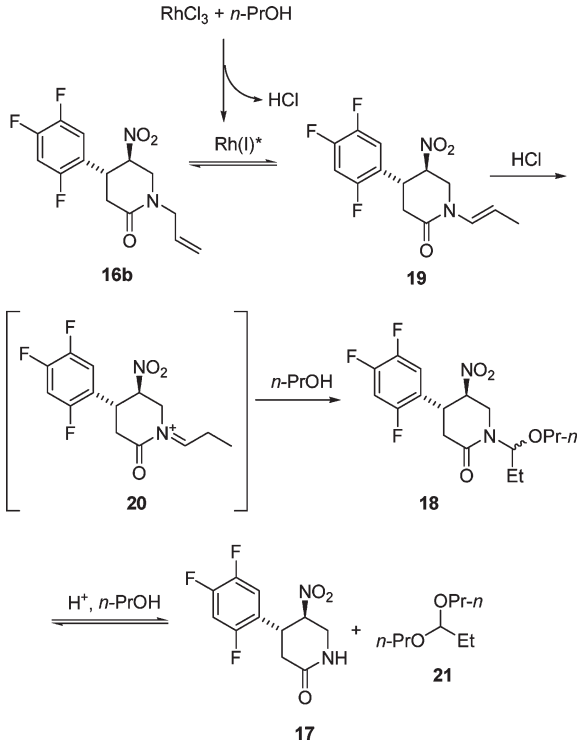
(31) (a) Alcaide, B.; Almendros, P.; Alonso, J. M.; Aly, M. F. *Org. Lett.* **2001**, *3*, 3781–3784. (b) Alcaide, B.; Almendros, P.; Alonso, J. M. *Tetrahedron. Lett.* **2003**, *44*, 8693–8695. (c) For a report on the Ru-catalyzed isomerization but not applied to *N*-allyl deprotection, see: Krompiec, S.; Pigulla, M.; Krompiec, M.; Baj, S.; Mrowiec-Bialon, J.; Kasperczyk, J. *Tetrahedron Lett.* **2004**, *45*, 5257–5261.

(32) Attempts to hydrolyze **19** under acidic conditions resulted in epimerization of the stereogenic center adjacent to nitro group. In addition, subsequent hydrogenation would also reduce enamine **19** to the undesired corresponding *n*-propyl lactam.

(33) For relevant observations, see: (a) Cramer, R. *J. Am. Chem. Soc.* **1967**, *89*, 1633−1639 and references therein. (b) Trebellas, J. C.; Olechowski, J. R.; Jonassen, H. B.; Moore, D. W. *J. Organomet. Chem.* **1967**, *9*, 153. (c) Hirai, H.; Sawai, H.; Ochiai, E.-I.; Makishima, S. *J. Catal.* **1970**, *17*, 119. (d) Su, A. C. *Adv. Organomet. Chem.* **1979**, *17*, 269. These mechanistic studies, including deuterium labeling experiments, suggest a Rh(I) hydride species is likely the active catalyst, since Rh(III) is reduced to Rh(I) in the presence of olefins and alcohol solvents.

(34) Liberation of HCl by treating $RhCl_3$ with alcohol solvents was also observed in our previous communication, cf. ref 24.

SCHEME 4. Plausible Pathways of the $RhCl_3$-Promoted Isomerization



The existence of such a trace amount of HCl in the reaction solution should not cause any epimerization of the labile stereogenic center adjacent to the nitro group, and indeed, the apparent pH of the reaction solution was observed experimentally to be pH = 4. However, the catalytic amount of HCl does play a pivotal role in converting the undesired enamine intermediate **19**, to the desired *N*,*O*-acetal intermediates **18** via a plausible iminium intermediate **20** (Scheme 4). Enamine **19** is believed to be formed first[24,31] through rhodium-catalyzed isomerization. Furthermore, the trace amount of HCl present in the reaction solution also promotes the partial exchange of the *N*,*O*-acetal **18** to dipropyl acetal **21** as the deprotected lactam **17** is liberated. The formation of acetal **21** was observed during the reaction. The plausible reaction pathways are depicted in Scheme 4. Although a mixture of deallylated lactam **17** and *N*,*O*-acetal **18** was obtained, hydrogenation reduction of the mixture of **17** and **18** followed by aqueous acid treatment would result in the desired precursor **4** without any epimerization.

Evidence to confirm the important role of HCl in this transformation are also shown in Table 3. When Hunig's base (Table 3, entry 4) was introduced to the reaction solution to neutralize the trace amount of HCl generated from $RhCl_3$ and keep the reaction under basic conditions, the pathways to form the lactam **17** as well as *N*,*O*-acetal **18** through HCl promoted acetal formation and exchange were shut down. This observation also confirmed that the pathways to form **17** and **18** are clearly not catalyzed by the active rhodium species. In addition, epimerization of the labile stereogenic center adjacent to the nitro group was also observed in the presence of base. Increasing the steric bulkiness of the alcohol, which acted as a nucleophile during these transformations, resulted in more unconsumed enamine **19** (Table 3, entry 6), as expected. Replacing an alcohol with other solvents (Table 3, entry 7) also made the isomerization stall at the enamine stage. In summary, under our optimization conditions, the formation of enamine **19** can be reproducibly reduced to $< 0.5\%$ (Table 3, entry 3) *without epimerization of the acid/base labile stereogenic center adjacent to the nitro group*.

Hydrolysis and Isolation of 4. At this point, acidic deprotection of *N*,*O*-acetal **18** to nitro piperidinone **17** was not practical, because hydrolysis of *N*,*O*-acetal **18** under acidic conditions resulted in formation of the corresponding undesired, epimerized *cis*-piperidionone. This fully agrees with our previous observation: the *cis*-nitropiperidinones such as **16a** always become the dominant products upon exposure of the corresponding *trans* isomers to acidic conditions.

Thus, without any workup, the crude rhodium-catalyzed isomerization reaction mixture of **17**/**18** was subjected to hydrogenation (Raney Ni, 90 psi, 40 °C, MeOH/*n*-PrOH) to give a mixture of the corresponding amines cleanly. The presence of $RhCl_3$ did not have any adverse effects on hydrogenation. After completion of the reduction of nitro intermediates **17**/**18**, the reaction mixture was then solvent switched to aq *n*-PrOH and treated with *p*-toluenesulfonic acid (pTSA) to hydrolyze acetal **22** to **4**. The choice of using a combination of *n*-PrOH/water (5:1) and pTSA was carefully selected after evaluating several acids in various solvents, so that the desired amine pTSA salt **4** crystallized directly from the reaction mixture as the hydrolysis proceeded.

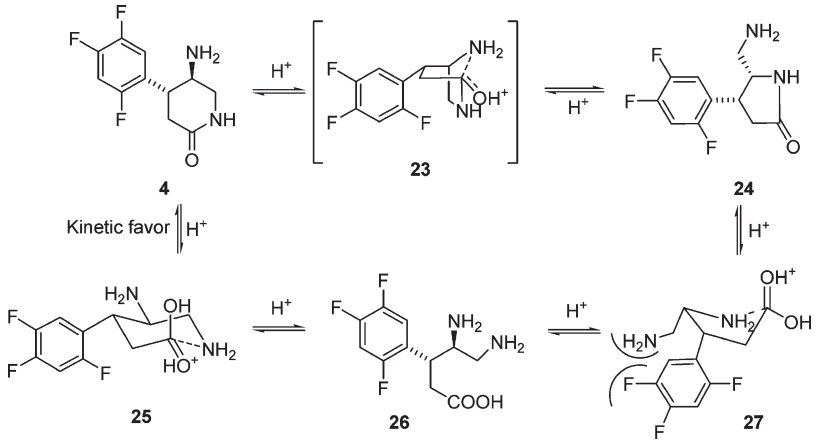
It is worthwhile to note that the direct crystallization of **4** as its pTSA salt from the crude reaction mixture allows for further harnessing the reaction pathways of hydrolysis of **22** to suppress formation of the rearranged byproduct **24** (Table 4). The formation of transamidation byproduct **24** was presumably formed through intermediate **23** via intramolecular nucleophilic attack of the amide carbonyl group by the amino group in **4** and/or **22**.[35] The undesired side reactions to form **24** was kinetically minimized/controlled by maintaining a low concentration of **4** in the supernatant as the pTSA salt **4** precipitated from the reaction mixture during the hydrolysis. By contrast, if the hydrolysis was carried out in a *homogeneous* solution in the presence of strong acids such as HCl or $MeSO_3H$ in aqueous alcohol or DMSO, the formation of a significant amount of rearranged pyrrolidinone **24** accompanied with small amount of hydrolyzed acid **26** was inevitable.[36]

To understand the kinetic/dynamic equilibrium profile of the intramolecular transamidation between **4** and **24** and, therefore, to determine optimal reaction conditions to suppress the formation of byproducts, the isolated free base **4** was treated with excess of HCl (~3.5 equiv) in aqueous *n*-PrOH, as such the reaction could be carried out in a homogeneous solution. After 24 h at 56 °C, a ratio of **4** to **24** (1:1.85 in favor of pyrrolidinone **24**) at equilibrium was achieved (Table 4, entry 5 and the Supporting Information). The kinetic rate differences of the interconversion at different concentrations of the free acid (H^+) and the protonated **4**

(35) For examples of intramolecular transamidation, see: (a) Tanaka, K.-I.; Nemoto, H.; Sawanishi, H. *Tetrahedron: Asymmetry* **2005**, *16*, 809–815. (b) Langlois, N. *Org. Lett.* **2002**, *4*, 185–187. (c) Langlois, N. *Tetrahedron. Lett.* **2002**, *43*, 9531–9533.

(36) Although isolation of **24** and **26** from the reaction mixture was difficult, their structures could be unambiguously characterized by applying NMR techniques.

TABLE 4. Selected Results of the Interconversion between 4, 24, and 26



entry	substrate	reaction conditions	conc (M)	products/results
1	**4**	MeOH/*n*-PrOH (1:1), 55 °C, 24 h	0.137[a,b]	2% **24**
2	**4**	1.2 equiv of pTSA, 83% aq *n*-PrOH, 53 °C, 24 h	0.27[a,c]	6.4% **24**, < 0.5% **26**
			0.137[a,c]	3.5% **24**, < 0.5% **26**
			0.02[a,b]	2.4% **24**, < 0.5% **26**
3	**4**	1.5 equiv of pTSA, 83% aq *n*-PrOH, 53 °C 24 h	0.02[a,b]	10.6% **24**, < 0.5% **26**
4	**4**	1.0 equiv of pTSA, 2.5 equiv of HCl, 83% aq *n*-PrOH, 53 °C 24 h	0.02[a,b]	15.3% **24**, < 0.5% **26**
5	**4**	3.66 equiv of HCl, 50% aq *n*-PrOH, 56 °C, 24 h	0.082[a,b]	43% **24**, < 0.5% **26**
			0.137[a,b]	64.9% **24**, < 0.5% **26**
6	**4/24/26** (1:1:1)	1.1 equiv of pTSA, DMSO-d_6, rt, 7 days		by NMR: **4/24/26** = 2:1:0.1; 90% of **26** consumed.
7	**26**	pH ~2, 85% aq *n*-PrOH, rt, overnight		**4**, 95% conversion; **24**, not detected.

[a]Unless otherwise mentioned, the product distribution profile was arbitrarily compared after 24 h under varied reaction conditions and did not necessarily reach the equilibrium. For more information, see the Supporting Information. [b]Homogenous solution. [c]Slurry, 1 g of **4** in 9 mL of 85% *n*-PrOH in water.

in the solution or supernatant are also depicted in Figure 1. In comparison with the kinetic profile of a HCl treated homogeneous reaction solution, the profile of a pTSA-treated reaction slurry (Figure 1, plot 1, line a vs lines b and c; plot 2, line d vs lines e and f) clearly shows that the intramolecular transamidation of **4** to **24** becomes significantly slower as the majority of **4** is precipitated to maintain lower concentration of **4** in the supernatant, while the concentration of the free acid (H^+) unneutralized by amine **4** and **24** also maintains low. The concentration of the H^+ in the reaction mixture remained unchanged and no consumption of acid was observed, as the concentration of acid unneutralized by amine **4** or **24** could affect the reaction rate. This kinetics observation is in line with the results of the concentration effects on transamidation (Table 4, entries 2−5). The more dilute the reaction is, the slower the formation of **24**. In addition, as expected, the less amount the acid (Table 4, entries 2 and 3) used, the slower the conversion to **24**. In the absence of an acid, treatment of the free base **4** in MeOH/*n*-PrOH at 55 °C for 24 h only resulted in ~2% of **24** (Table 4, entry 1).

Interestingly, NMR studies showed that after a mixture of **4/24/26** (~1:1:1) was aged in the presence of 1.2 equiv of pTSA in DMSO-d_6 at ambient temperature for a week, the ratio was changed to **4/24/26** = 2:1:0.1. Pyrrolidinone **24** remained unchanged while the open acid **26** was cyclized to **4** presumably via intermediate **25**, which is favored in terms of steric hindrance in contrast to **27** (Table 4, entry 6). Exposure of crude **26**, which could be generated by treating **4** with NaOH at 80 °C, in aq HCl/*n*-PrOH (pH = 2) at ambient temperature overnight also gave kinetic favored cyclized **4** (Table 4, entry 7). These results are consistent with the observation that the formation of hydrolyzed **26** was always low when **4** was treated with an acid (Table 4 and the Supporting Information).

Nevertheless, with a good understanding of the reaction pathways, an easily operated, three-step through process was finally developed (Scheme 5). Therefore, via direct crystallization of **4** as its pTSA salt during the hydrolysis, a kinetic control of the product distribution was gained and the formation of undesired **24** was minimized. The hydrolysis of the *N*,*O*-acetal **22** was observed to be faster than the intramolecular transamidation. Typically, under our optimized conditions, after 3−5 h age at 55 °C the hydrolysis of *N*,*O*-acetal **22** is completed in the presence of 1.2 equiv of pTSA and **4** was then isolated as its pTSA salt in 62% yield over three steps (>99% purity and >98% ee). A significant ee upgrade (e.g., upgrade from 93% ee to 98% ee) was also achieved during the isolation of the pTSA salt **4**.

Cu-Assisted Coupling and Endgame. Several options were explored to finish the synthesis of **1**. 4-Bromo-3-aminopyridine (**3**)[37] did undergo Cu-mediated coupling with the free base amine **4** to give **1** directly. However, isolation and purification of **1** from this reaction was challenging and it was difficult to meet the pharmaceutical industry purity

(37) (a) Stockmann, V.; Fiksdahl, A. *Tetrahedron* **2008**, *64*, 7626–7632. (b) Tjosaas, F.; Kjerstad, I. B.; Fiksdahl, A. *J. Heterocycl. Chem.* **2008**, *45*, 559−562 and references cited therein.

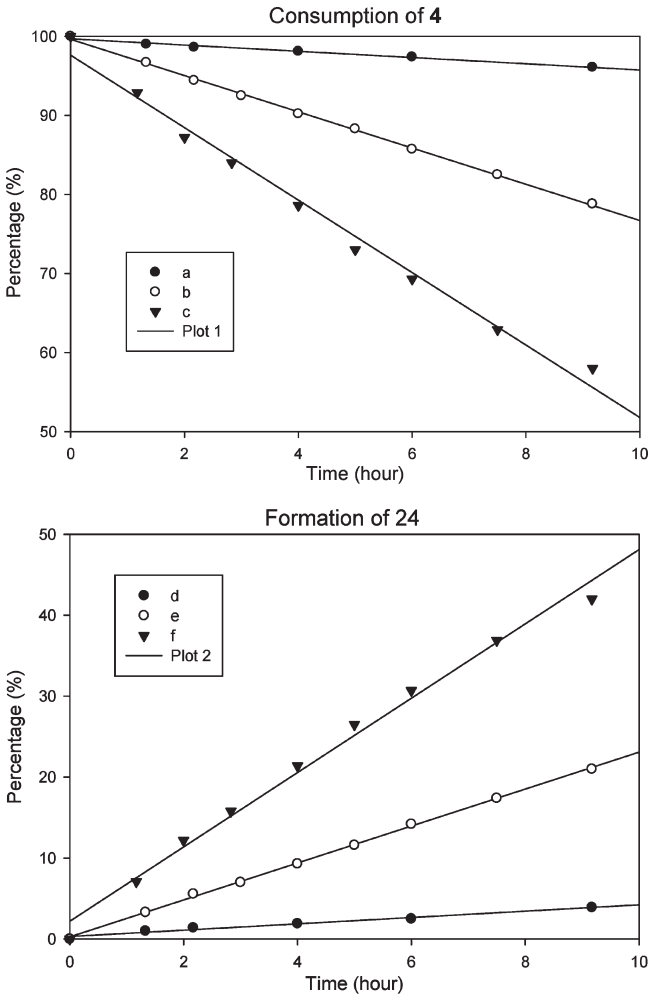


FIGURE 1. Selected kinetic profile of transamidation. For a full picture of the reaction kinetic profile, see the Supporting Information. Note the use of pTSA or HCl did result in a significant difference of the concentration of the protonated **4** in the reaction supernatant/solution, as the corresponding HCl salt did not result in any precipitation. Plot 1, line a, and plot 2, line d: a slurry of free base **4** in *n*-PrOH/H_2O (5:1, 0.137 M) in the presence of 1.2 equiv of pTSA was aged at 56 °C. Plot 1, line b, and plot 2, line e: a homogeneous solution of free base **4** in *n*-PrOH/H_2O (1:1, 0.082 M) in the presence of 3.5 equiv of HCl was aged at 56 °C. Plot 1, line c, and plot 2, line f: a homogeneous solution of free base **4** in *n*-PrOH/H_2O (1:1, 0.137 M) in the presence of 3.5 equiv of HCl was aged at 56 °C.

standards as a final product. In comparison, use of the Boc-protected lactam **28** led to higher conversions and an improved assay yield. The ~20% increase in yield was presumably due to the suppression of side reactions as the free amino moiety was protected with a Boc group. In addition, commercially available 4-chloro-3-aminopyridine as a coupling partner was also extensively evaluated under various conditions. Although the copper catalyst, base, solvents, ligands and additives were varied, no conditions were identified that could give the coupled product **29** in a yield comparable to that obtained with **3**.

Thus, **4** was treated with Boc_2O in the presence of Et_3N in aq THF to afford **28** in 95% isolated yield and >99.5% purity (Scheme 6). Finally, the Boc lactam **28** was coupled with pyridine **3** in the presence of CuI, K_2CO_3, and *N*,*N*′-dimethylethylenediamine. The crude reaction product **29**, obtained in 88% assay yield after removal of the inorganic salts, was directly subjected to the final deprotection step.

Treatment of the crude **29** with concd HCl in EtOH at 50 °C afforded **1**. The tris-HCl salt **1** gradually crystallized from the reaction solution as the deprotection proceeded. In practice, this salt was conveniently isolated from EtOH/*i*-PrOH (1:1) in 77% yield over two steps with >99.7% purity and >97% ee. After a salt break of the tris HCl salt with NaOEt, the free base **1** hydrate was crystallized from aq EtOH, which further converted to the desired anhydrous crystalline free base **1** upon drying at 60 °C overnight in 82% yield (>99% purity).

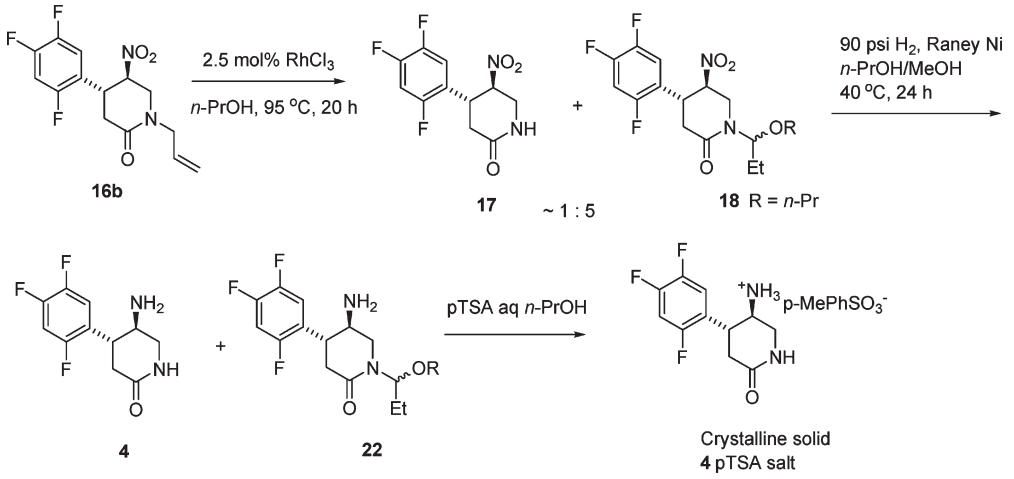
Conclusion

We have developed a practical asymmetric synthesis of potent, selective DPP-4 inhibitor **1**, a drug candidate for the treatment of T2DM. To achieve this target-oriented synthesis, a novel three-component cascade coupling was developed. Through a highly enantioselective malonate addition to nitrostryene the first stereogenic center was set up efficiently. Applying a selective cascade coupling allowed for the effective assembling of the key piperidinone skeleton with the desired stereochemistry setup. A simple base-catalyzed, dynamic crystallization-driven process was developed to isolate the *trans*-piperidinone intermediate in one-pot in high yield and purity, while the undesired *cis* piperdinone was fully utilized and converted to the desired *trans* isomer. Further mechanistic studies on the rhodium-catalyzed isomerization of allylamide led to an efficient synthetic strategy for the preparation of the lactam **4**. With a good understanding of the kinetics of hydrolysis/intramolecular transamidation, the desired hydrolyzed amine lactam **4** was directly isolated as its crystalline pTSA salt from the crude reaction solution. Finally, construction of the tricyclic core structure of **1** was hence finished by a Cu(I)-catalyzed coupling-cyclization in one step. Starting from commercially available 2,4,5-trifluorobenzaldehyde, the overall yield for the synthesis of aminopiperidine-fused imidazopyridine **1** was 23%. The success of our synthesis, as an example of target-oriented and mechanism-guided development, clearly demonstrated the powerful impact of the integration of synthetic and physical organic chemistry.

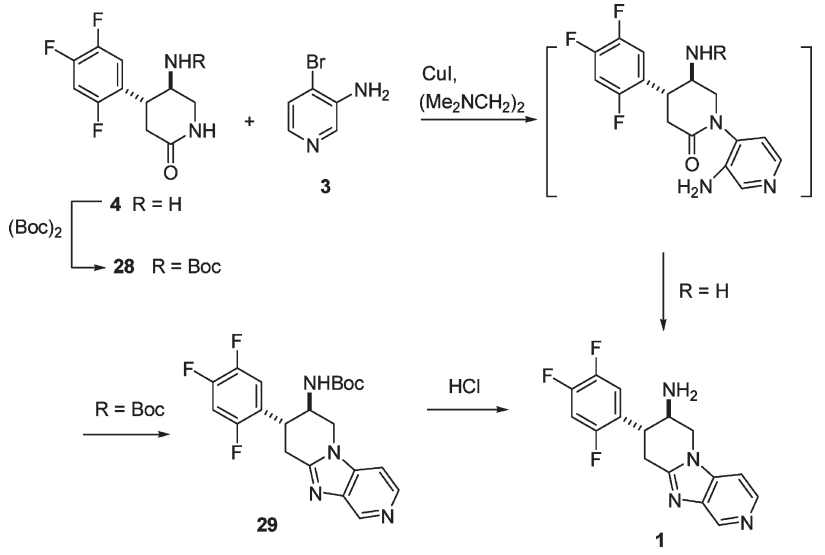
Experimental Section

1,2,4-Trifluoro-5-((*E*)-2-nitrovinyl)benzene (10). To a solution of MeOH (600 mL), water (300 mL), and 2.5 N NaOH (300 mL) at 5 °C was added a solution of 2,4,5-trifluorobenzyaldehyde (**8**, 100 g, 0.6246 mol) and $MeNO_2$ (40 mL, 0.7495 mol) in MeOH (100 mL) dropwise over 30−60 min, while the internal temperature was maintained between 5 and 10 °C with external cooling. The reaction solution was then agitated between 0 and 5 °C for an additional 30 min, maintained between 0 and 5 °C, and added dropwise to a solution of $ZnCl_2$ (426 g, 3.123 mol) in concd HCl (130 mL, 1.5615 mol) and water (170 mL) at 0−10 °C with vigorous agitation over 2−4 h. The light yellow product precipitated during the addition. After addition, the slurry was allowed to warm to ambient temperature and aged for 1 h before filtration. The wet cake was washed with 40% MeOH in water (3 × 300 mL). The wet cake was suction dried at ambient temperature to give 103 g of light yellow product **10**. 81% yield: >98% purity. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J = 13.8 Hz, 1 H), 7.65 (d, J = 13.8 Hz, 1 H), 7.37 (m, 1 H), 7.09 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.6 (ddd, J = 243.5, 9.2, 2.5 Hz), 152.5 (ddd, J = 259.8, 14.7, 12.9 Hz), 147.5

SCHEME 5. Through Process To Prepare pTSA Salt 4



SCHEME 6. Preparation of 1 via Cu-Assisted Coupling



(ddd, J = 248.0, 13.0, 3.1 Hz), 140.0 d, J = 11.7, 2.4 Hz), 130.6, 118.4 (ddd, J = 20.3, 4.3, 1.9 Hz), 115.1 (ddd, J = 14.3, 5.8, 4.4 Hz), 107.2 (dd, J = 27.9, 21.3 Hz). Anal. Calcd for $C_8H_4F_3NO_2$: C, 47.31; H, 1.98; N, 6.90. Found: C, 47.27; H, 1.74; N, 6.86.

2-[(*R*)-2-Nitro-1-(2,4,5-trifluorophenyl)ethyl]malonic Acid Dimethyl Ester (7). To a solution of nitrostyrene **10** (100 g, 0.4923 mol), dimethyl malonate (91 g, 0.6842 mol), and THF (400 mL) at −15 to −20 °C was added demethylquinidine (DMQ)[18] (1.5 g, 4.9 mmol) in one portion, and the solution was stirred overnight (about 15 h) at −20 °C. The reaction solution was then solvent switched to *i*-PrOH (final volume: about 400 mL) in vacuum. The batch was seeded with crystalline **7** (0.5 g) and agitated for 2−3 h at ambient temperature. Water (107 mL) was then added dropwise over 2−3 h. After addition, the slurry was aged for additional 1 h at ambient temperature. Then, the slurry was slowly cooled to 5 °C and aged for 3 h before filtration. The wet cake was displacement washed with cold 70% *i*-PrOH in water (120 mL, 0−5 °C) followed by a displacement wash (50% *i*-PrOH in water 150 mL, 0−5 °C). Suction dry at ambient temperature afforded 145 g of off-white solid **7**: 88% yield; >98% purity; 95% ee; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.11 (m, 1 H), 6.96 (m, 1 H), 4.90 (m, 2 H), 4.38 (m, 1 H), 3.93 (d, J = 9.4 Hz, 1 H), 3.79 (s, 3 H), 3.63 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 167.0, 156.2 (ddd, J = 247.3, 10.4, 2.8 Hz), 150.3 (dt. J = 255.1, 12.7 Hz), 147.0 (ddd, J = 246.6, 12.4, 3.4 Hz), 119.7 (dt, J = 14.8, 4.8 Hz), 118.6 (dd, J = 19.4, 6.3 Hz), 106.6 (dd, J = 28.5, 20.8 Hz), 75.8, 53.5, 53.3, 52.9, 37.9. Anal. Calcd for $C_{13}H_{12}F_3NO_6$: C, 46.58; H, 3.61; N, 4.18. Found: C, 46.62; H, 3.37; N, 4.08.

(4*R*,5*R*)-1-Allyl-5-nitro-4-(2,4,5-trifluorophenyl)piperidin-2-one (16b). To a solution of nitro malonate **7** (100 g, 0.2983 mol) and allylamine (22.14 g, 0.3878 mol) in *i*-PrOH (500 mL) and water (100 mL) at 50 °C was added 37% HCHO (25.42 g, 0.3132 mol) dropwise over 1−2 h. The reaction solution was stirred for additional 2−3 h at 50 °C. NaOH (5 N, 104.4 mL, 0.522 mol) was added in one portion at 50 °C. The reaction solution was stirred additional 1−2 h at 50 °C. Concentrated HCl (54.2 mL, 0.6563 mol) was added dropwise over 30 min between 50 and 60 °C. The reaction solution was stirred at 55−60 °C for 2−3 h and then cooled to 45 °C, and 5% $NaHCO_3$ (ca. 100 mL) was added dropwise to pH = 7−8. Then, water (100 mL) was added dropwise over 30 min. The resulting slurry was stirred at 45 °C for 1−2 h and cooled to ambient temperature slowly. After aging overnight, the slurry was filtered. The wet cake was displacement washed with 50% aq *i*-PrOH (2 × 150 mL) and

suction dried at ambient temperature to give 72 g of off-white to yellowish solid **16b**: 76% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.04 (m, 1 H), 7.01 (m, 1 H), 5.76 (m, 1 H), 5.26 (m, 2 H), 5.07 (m, 1 H), 4.13 (dd, J = 14.9, 6.2 Hz, 1 H), 4.02 (m, 2 H), 3.91 (dd, J = 13.2, 6.9 Hz, 1H), 3.72 (dd, J = 13.2, 5.1 Hz, 1 H), 2.84 (dd, J = 17.5, 6.2 Hz, 1 H), 2.72 (dd, J = 17.5, 9.8 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 156.0 (ddd, J = 245.0, 10.0, 2.5 Hz), 150.1 (td, J = 251.3, 13.6 Hz), 147.3 (ddd, J = 246.3, 12.5, 3.8 Hz), 131.7, 121.6 (td, J = 15.0, 5.0 Hz), 119.6, 117.1 (ddd, J = 20.0, 6.3, 1.3 Hz), 106.9 (dd, J = 27.5, 21.3 Hz), 83.1 (d, J = 1.3 Hz), 49.4, 47.7, 36.7, 35.0. Anal. Calcd for $C_{14}H_{13}F_3N_2O_3$: C, 53.51; H, 4.17; N, 8.91. Found: C, 53.59; H, 4.12; N, 8.90.

(3*R*,4*R*)-6-Oxo-4-(2,4,5-trifluorophenyl)piperidin-3-ylammonium Toluene-4-sulfonate (4). A N_2-degassed solution of nitropiperidinone **16b** (100 g, 0.3182 mol) and $RhCl_3$ (1.8 g, 7.96 mmol) in *n*-PrOH (800 mL) was agitated at 90−95 °C for 17 h. The reaction solution was then concentrated to a volume of ca. 500 mL in vacuo. MeOH (350 mL) and Raney Ni (50 g) were charged, and the reaction mixture was hydrogenated (90 psig) at 40 °C for 5 h. The reaction mixture was cooled to ambient temperature and filtered through a pad of Solka Floc to remove the catalyst. The catalyst was washed with MeOH (300 mL). The combined filtrate was solvent switched to *n*-PrOH in vacuo (final volume: 750 mL). A solution of *p*-toluenesulfonic acid (pTSA, 78.7 g of pTSA monohydrate, 0.4137 mol) in water (150 mL) was added in one portion. The reaction solution was seeded with aminopiperidinone pTSA salt **4** (0.1 g), and the resulting slurry was agitated for 30 min at ambient temperature and an additional 3−5 h at 55−60 °C. The batch was slowly cooled to ambient temperature. The slurry was filtered, and the wet cake was washed with 90% aq *n*-PrOH (2 × 120 mL, displacement wash followed by a slurry wash) and *n*-PrOH (100 mL). Suction drying at ambient temperature gave 82.2 g of white solid **4**: 62% yield over three steps; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.02 (s, 3H), 7.78 (d, J = 2.6 Hz, 1 H), 7.61 (m, 2H), 7.48 (d, J = 8.1 Hz, 2 H), 7.12 (d, J = 8.1 Hz, 2 H), 3.80 (m, 1 H), 3.49 (m, 2H), 3.23 (dd, J = 12.1, 9.2 Hz, 1 H), 2.48 (d, J = 1.4 Hz, 1 H), 2.46 (s, 1 H), 2.29 (s, 3 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.5, 155.9 (ddd, J = 244.1, 10.4, 2.4 Hz), 148.7 (dt, J = 247.8, 13.7 Hz), 146.5 (ddd, J = 241.7, 16.1, 3.2 Hz), 144.9, 138.2, 128.3, 125.5, 123.1 (dt, J = 16.1, 4.8 Hz), 117.8 (dd, J = 20.1, 5.0 Hz), 106.4 (dd, J = 29.7, 21.7 Hz), 48.0, 43.0, 36.0, 35.3, 20.8. Anal. Calcd for $C_{18}H_{19}F_3N_2O_4S$: C, 51.92; H, 4.60; N, 6.73. Found: C, 51.67; H, 4.27; N, 6.62.

Intermediates **17**, **18**, and **19** could be isolated by silica gel column chromatography (gradient 20% to 90% EtOAc in hexane). **(4*R*,5*R*)-5-Nitro-4-(2,4,5-trifluorophenyl)piperidin-2-one (17):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (m, 1 H), 7.01 (m, 1 H), 6.65 (s, 1 H), 5.05 (m, 1 H), 4.04 (m, 1 H), 3.98 (td, J = 6.0, 2.0 Hz, 1 H), 3.80 (ddd, J = 13.3, 4.8, 2.8 Hz, 1 H), 2.83 (dd, J = 17.7, 6.4 Hz, 1 H), 2.70 (dd, J = 17.7, 9.6 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 156.0 (ddd, J = 246.5, 9.6, 3.2 Hz), 150.2 (dt, J = 253.5, 14.2 Hz), 147.4 (ddd, J = 243.8, 12.8, 3.5 Hz), 121.6 (dt, J = 15.3, 4.8 Hz), 117.3 (ddd, J = 19.9, 4.8 Hz), 107.0 (dd, J = 28.3, 21.0 Hz), 82.4, 77.4, 43.4, 37.4, 34.4. Anal. Calcd for $C_{11}H_9F_3N_2O_3$: C, 48.18; H, 3.31; N, 10.22. Found: C, 48.06; H, 3.16; N, 10.08.

(4*R*,5*R*)-5-Nitro-1-(1-propoxypropyl)-4-(2,4,5-trifluorophenyl)-piperidin-2-one (18): ^{1}H NMR (500 MHz, $CDCl_3$) (the ratio of two isomers is about 1.5:1) for the major isomer, δ 7.07 (m, 1 H), 7.01 (m, 1 H), 5.63 (m, 1 H), 4.99 (m, 1 H), 4.00 (m, 1 H), 3.81 (dd, J = 13.5, 6.8 Hz, 1 H), 3.76 (dd, J = 13.5, 5.0 Hz, 1 H), 3.34 (m, 2 H), 2.87 (t, J = 6.4 Hz, 1 H), 2.76 (dd, J = 17.4, 9.2 Hz, 1 H), 1.71 (m, 1 H), 1.57 (m, 2 H), 1.50 (m, 1 H), 0.92 (m, 6 H); for the major isomer, δ 7.07 (m, 1 H), 7.01 (m, 1 H), 5.63 (m, 1 H), 4.99 (m, 1 H), 4.11 (dd, J = 14.9, 7.2 Hz, 1 H), 4.00 (m, 1 H), 3.55 (dd, J = 14.1, 5.0 Hz, 1 H), 3.41 (m, 1 H), 3.34 (m, 1 H), 2.90 (t, J = 6.4 Hz, 1 H), 2.72 (m, 1 H), 1.71 (m, 1 H), 1.57 (m, 2 H), 1.50 (m, 1 H), 0.92 (m, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.4, 168.3, 156.2 (ddd, J = 245.5, 9.6, 3.1 Hz), 156.1 (ddd, J = 245.5, 9.6, 3.1 Hz), 150.4 (dt, J = 253.5, 13.5 Hz), 147.5 (ddd, J = 247.3, 9.8, 3.1 Hz), 147.4 (ddd, J = 247.3, 9.8, 3.1 Hz), 122.4 (dt, J = 16.0, 4.9 Hz), 122.2 (ddd, J = 16.0, 4.9 Hz), 117.5 (dd, J = 19.7, 6.2 Hz), 117.3 (dd, J = 28.3, 20.9 Hz), 107.3 (dd, J = 28.3, 20.9 Hz), 107.1 (dd, J = 28.3, 20.9 Hz), 84.40, 84.39, 83.9 (d, J = 1.8 Hz), 83.5 (d, J = 1.8 Hz), 77.9, 71.1, 71.0, 41.8, 41.2, 37.7, 36.7, 35.7, 35.1, 26.0, 25.8, 23.2, 23.0, 11.0, 10.9, 10.4, 9.90, 9.88. Anal. Calcd for $C_{17}H_{21}F_3N_2O_4$: C, 54.54; H, 5.65; N, 7.48. Found: C, 54.47; H, 5.52; N, 7.42.

(4*R*,5*R*)-5-Nitro-1-((*E*)-propenyl)-4-(2,4,5-trifluorophenyl)piperidin-2-one (19): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (dd, J = 14.4, 1.0 Hz, 1 H), 7.03 (m, 1 H), 7.01 (m, 1 H), 5.16 (m, 1 H), 5.13 (m, 1 H), 4.05 (dd, J = 12.9, 7.6 Hz, 1 H), 3.99 (dd, J = 9.6, 6.0 Hz, 1 H), 3.90 (dd, J = 12.9, 5.6 Hz, 1 H), 2.91 (dd, J = 18.1, 6.0 Hz, 1 H), 2.79 (dd, J = 18.1, 10.0 Hz, 1 H), 1.77 (dd, J = 6.4, 1.5 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6, 156.0 (ddd, J = 245.7, 9.6, 2.4 Hz), 150.2 (dt, J = 254.0, 14.4 Hz), 147.4 (ddd, J = 247.5,12.8, 4.0 Hz), 126.4, 121.1 (dt, J = 15.4, 4.9 Hz), 117.1 (ddd, J_1 = 20.0, 5.7, 1.5 Hz), 108.7, 107.0 (dd, J_1 = 28.2, 20.9 Hz), 82.6 (d, J = 1.8 Hz), 77.4, 46.1, 37.1, 35.1, 15.5. Anal. Calcd for $C_{14}H_{13}F_3N_2O_3$: C, 53.51; H, 4.17; N, 8.91. Found: C, 53.42; H, 3.92; N, 8.73.

[(*R*)-6-Oxo-4-(2,4,5-trifluorophenyl)piperidin-3-yl]carbamic Acid *tert*-Butyl Ester (28). To a slurry of tosylate salt **4** (5.5 kg, 13.2 mol) in THF/water (33 L/16.5 L) at ambient temperature was added Et_3N (5.5 L, 39.6 mol) in one portion. Then, di-*tert*-butyl dicarbonate (3.45 kg, 15.84 mol) was added to the resulting clear solution over 30 min in portions. After aging for 15 h at room temperature, the reaction mixture was extracted with toluene (50 L). The organic phase was washed with water (2 × 25 L) and azetropically concentrated to a volume of 25 L. The resulting slurry was aged at ambient temperature for 2−4 h before filtration. The wet cake was washed with *n*-heptane (8 L) and dried under vacuum to afford 4.236 kg of white solid **28** (97% ee): 95% yield; ^{1}H NMR (400 MHz, $CDCl_3$) major rotomer[38] δ 7.13 (m, 1 H), 7.07 (m, 1 H), 6.96 (m, 1 H), 4.83 (d, J = 6.7 Hz, 1 H), 4.18 (s, br 1 H), 3.57 (m, 1 H), 3.41 (m, 1 H), 3.22 (dd, J = 11.7, 9.9 Hz, 1 H), 2.72 (dd, J = 17.8, 5.8 Hz, 1 H), 2.58 (dd, J = 17.8, 10.8 Hz, 1 H), 1.33 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 155.2, 156.1 (ddd, J = 244.5, 9.6, 2.4 Hz), 149.3 (dt, J = 252.2, 13.2 Hz), 147.2 (ddd, J = 245.4, 12.2, 2.8 Hz), 123.8 (m), 116.7 (dd, J = 20.1, 5.1 Hz), 105.9 (dd, J = 28.1, 21.0 Hz), 80.3, 48.4, 46.1, 37.5, 36.4, 28.3. Anal. Calcd for $C_{16}H_{19}F_3N_2O_3$: C, 55.81; H, 5.56; N, 8.14. Found: C, 55.95; H, 5.49; N, 8.43.

(*R*)-7-(2,4,5-Trifluorophenyl)-5,6,7,8-tetrahydro-2,4b-diazafluoren-6-ylamine (1). To a slurry of Boc piperidinone **28** (3.993 kg, 11.6 mol), 4-bromo-3-aminopyridine (**2**, 2.81 kg, 16.24 mol), and potassium carbonate (3.527 kg, 25.52 mol) in toluene (30 L) at ambient temperature was charged *N*,*N*′-dimethylethylenediamine (1.25 L, 11.6 mol) dropwise. The resulting thick slurry was degassed with nitrogen purge, and then CuI (221 g, 1.16 mol) and toluene (8 L) were charged. The reaction mixture was agitated at 100 °C until > 96% conversion was achieved. Then, the reaction mixture was cooled to 60 °C, and THF (40 L) was added. The slurry was filtered through 10 kg of silica gel and rinsed with 40 L of warm THF (60 °C). The combined filtrate was solvent-switched to ethanol to a volume of 36 L in vacuum. The assay yield of coupled product **29** was 88.4% (4.29 kg).

To the above ethanol solution of **29** at 50 °C was added concd HCl (96 mol, 8 L) dropwise at such a rate as to maintain the internal temperature between 50 and 60 °C. The tris-HCl salt **1**

(38) For this specific compound, the sample concentration would also affect the observed chemical shifts.

started to crystallize at the completion of the HCl addition. *i*-PrOH (32 L) was added dropwise, and the slurry was allowed to cool to ambient temperature slowly and stirred overnight prior to filtration. The wet cake was washed successively with *i*-PrOH (2 × 4 L), *i*-PrOH/*i*-PrOAc (2:1, 8 L), and *i*-PrOAc (8 L). Suction drying gave 3.8 kg of the tris-HCl salt **1** (99.78% purity, 97.2% ee) in 87% yield.

To a slurry of the tris-HCl salt **1** (3.8 kg, 8.89 mol) in anhydrous ethanol (48 L) was added a solution of sodium ethoxide (2.178 kg, 32 mol) in ethanol (24 L) dropwise. The resulting sodium chloride was removed by filtration. The ethanol filtrate was concentrated to a volume of 16 L in vacuum. The slurry of the free base **1** was then warmed to 50 °C. Water (30 L) was added dropwise over 1 h. The slurry was stirred overnight at ambient temperature before filtration. The wet cake was washed with 10% aqueous ethanol (2 × 3 L) followed by water (5 L). Vacuum oven drying at 60 °C gave the anhydrous free base **1** (2.327 kg) in 82% yield: 99.2% purity; 98.6% ee; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.84 (d, J = 0.8 Hz, 1 H), 8.31 (d, J = 5.5 Hz, 1 H), 7.60 (m, 1 H), 7.56 (dd, J = 5.5, 0.8 Hz, 1 H), 7.53 (m, 1 H), 4.45 (dd, J = 12.0, 5.3, 1 H), 3.79 (dd, J = 12.0, 9.8 Hz, 1 H), 3.58 (m, 1 H), 3.42 (m, 1 H), 3.27 (m, 2 H), 1.67 (s, 2 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 155.9 (ddd, J = 242.5, 9.4, 2.2 Hz), 152.4, 147.8 (dt, J = 247.9, 14.5 Hz), 146.7 (ddd, J = 241.4, 12.5, 3.2 Hz), 140.8, 140.4, 140.2, 138.9, 125.9 (dt, J = 16.8, 4.9 Hz), 117.1 (dd, J = 19.5, 6.2 Hz), 105.8 (dd, J = 30.0, 20.9 Hz), 105.5, 49.3, 48.8, 38.8, 30.0. Anal. Calcd for $C_{16}H_{13}F_3N_4$: C, 60.37; H, 4.12; N, 17.60. Found: C, 60.24; H, 3.98; N, 17.37.

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Supporting Information Available: Alternative synthesis, experimental procedure, and kinetic profiles of intramolecular transamidation. This material is available free of charge via the Internet at http://pubs.acs.org.