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New Efficient Asymmetric Synthesis of Taranabant, a CB1R Inverse Agonist for the Treatment of Obesity

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Abstract:

Taranabant (1) is a cannabinoid-1 receptor (CB1R) inverse agonist that was recently in late-stage clinical development for the treatment of obesity. The previously employed synthesis exhibited a number of shortcomings for continuing development, and in this paper we report an improved synthesis of the target molecule that is suitable for large-scale implementation. Palladium-catalyzed amidation of an enol tosylate afforded a stereodefined tetrasubstituted enamide, and asymmetric hydrogenation thereof provided the target molecule.

Introduction

Sedentary lifestyles and easy access to high-energy foods has led to a sharp increase in obesity throughout the developed world during the past 20 years; currently over 65% of adults in the United States are overweight, with 30% classified as obese.[1] The cannabinoid receptor system has been implicated in the regulation of feeding behavior;[2] hence, selective cannabinoid-1 receptor (CB1R) inverse agonists are expected to be efficacious for suppression of food intake and thus weight reduction. Discovery efforts at Merck identified *taranabant* (**1**), as a potential selective CB1R inverse agonist,[3] for the treatment of obesity, necessitating development of a synthesis of **1** to support both preclinical and clinical trials.

Previous investigations from our laboratories had identified an efficient, asymmetric route to **1** which employed a dynamic kinetic resolution of racemic ketone **2** to set the stereochemistry, affording alcohol **3** (Scheme 1).[4] Alcohol **3** was converted to amine **4** via standard procedures including activation of the secondary alcohol, displacement with sodium azide, and reduction.[5] Coupling of amine **4** with pyridine acid **5** provided **1** in six steps and 41% overall yield.

Although this synthesis generated **1** in an efficient manner and was used on multikilogram scale during early development, as the project progressed, a number of shortcomings inherent with this approach became apparent. Of particular concern for potential manufacturing purposes was the use of sodium azide to introduce the nitrogen functionality, the hindered activated secondary alcohol being inert to displacement with other nitrogen nucleophiles. Additionally, the sequence suffered from lack of any suitable solid intermediates—a cornerstone of purification on larger scale—and also relied on the use of a proprietary catalyst in the kinetic resolution step. On the basis of these concerns a number of other approaches were investigated, and in this paper we report an alternate asymmetric synthesis of *taranabant* (**1**), which addresses the key issues above, and is suitable for large-scale implementation.

Results and Discussion

An attractive strategy for the synthesis of **1** was envisaged that utilized an asymmetric hydrogenation of tetrasubstituted enamide **6**, which would potentially allow the introduction of both stereocenters in a single, ideally catalytic step, starting from an achiral starting material (Scheme 2). However, although asymmetric hydrogenations of simpler enamides have been extensively developed,[6] the use of complex tetrasubstituted enamides such as **6** is still extremely rare. While the low reactivity of these sterically congested substrates towards hydrogenation[7] has contributed to the lack of development, a more serious barrier to their use has been the dearth of efficient

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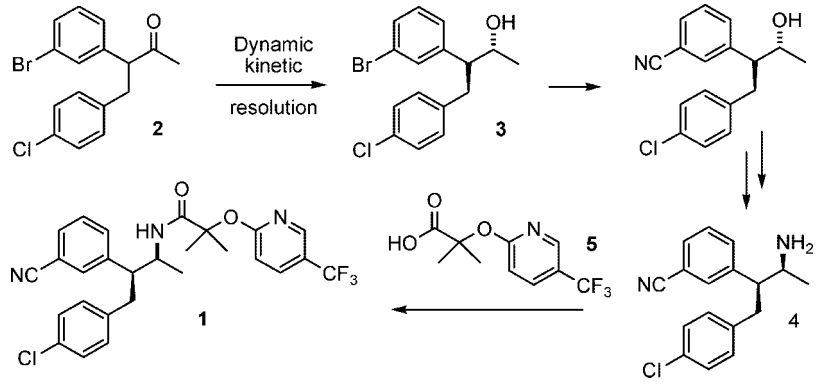
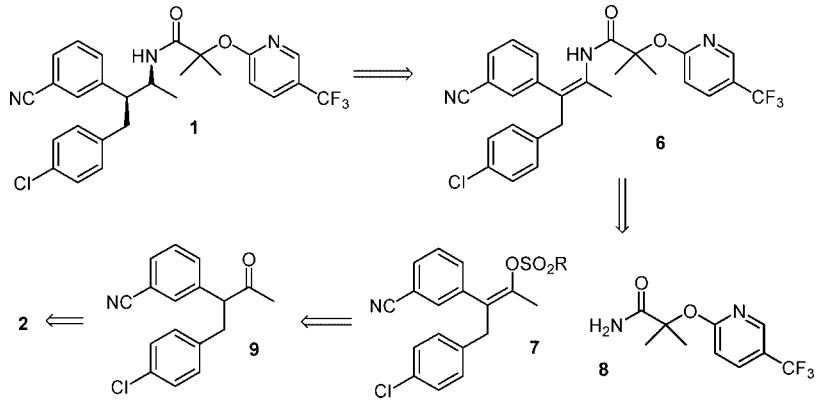
Scheme 1. **Structure and original synthesis of taranabant (1)**



Scheme 2. **Proposed preparation and hydrogenation of a tetrasubstituted enamide as a synthetic route to 1**



methods to prepare the desired acyclic tetrasubstitued enamides in a stereocontrolled manner.[8]

In recent years cross-coupling methodology has emerged as a viable method for enamide synthesis, and indeed there are a number of published protocols which employ palladium- or copper-catalyzed stereospecific amidations of vinyl halides.[9] However, in our case preparation of the desired vinyl halide *as a single isomer* would present a serious challenge. In contrast, the selective formation of a single enol sulfonate from a ketone may rely on simple kinetic vs thermodynamic control in the enolate formation step and can be tuned by judicious choice of base and solvent combination. Recent work by us[10] and others[11,12] has shown that enol triflates and tosylates are viable substrates for palladium-catalyzed amidation reactions, and hence the preparation of the desired tetrasubstituted enamide using an extension of this methodology was felt to be an achievable goal. Moreover, both the requisite enol sulfonate **7** and amide **8** were envisaged as resulting from common intermediates from our previous synthesis, namely the racemic ketone **2** and heterocyclic acid **5**.

The previously employed bromoketone **2** was subjected to a Pd-catalyzed cyanation which afforded the desired cyanoketone **9** in 94% yield as a crystalline solid.[13] Enolization of **9** with sodium hydride in THF followed by quench with $PhNTf_2$ afforded a ~1:1 mixture of enol triflates **10a** and **10b** in good yield. Subsequent optimization of the base and solvent led to the observation that use of DMPU as cosolvent (with THF) or use of amide solvents alone gave good selectivities for the desired *E*-isomer, and that *tert*-butoxide bases were suitable alternatives to the hazardous sodium hydride (Table 1).[14] While best selectivities were observed with KOtBu, the low solubility of the enolate led to volume inefficiency, and use of NaOtBu in DMAc was found to be optimum, leading to a 90:10 ratio in favor of the desired **10a**. The isomers could be separated by column chromatography affording an 85% yield of **10a**.

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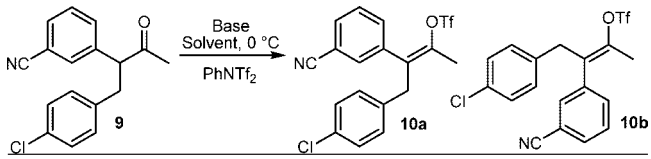
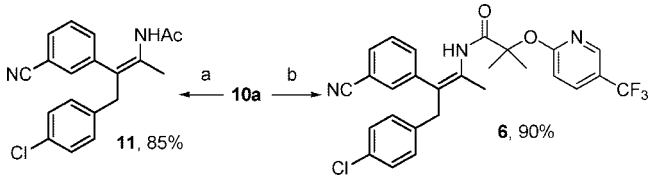
(14) The underlying factors controlling the enolization selectivity are not clear; however, it is felt that highly coordinating solvents (DMAC, DMF) could change the aggregation state of the enolate which in turn may contribute to selectivity. Additionally, potential coordination of the aryl nitrile group to the enolate metal is possible in the *E*-enolate (leading to **10a**) but not in the *Z*-enolate (leading to **10b**) which may also account for changes with metal and solvent.

Table 1. **Effect of base and solvent on enolization selectivity of 9**



entry	solvent	base	conversion	**10a:10b**
1	THF	NaH	95	50:50
2	THF/DMPU (80/20)	NaH	95	83:17
3	DME/DMPU (80/20)	NaH	95	74:26
4	MeCN	NaH	90	53:47
5	EtOAc	NaH	87	44:56
6	DMF	NaH	91	89:11
7	NMP	NaH	94	90:10
8	DMAc	NaH	98	90:10
9	DMAc	LiOtBu	98	84:16
10	DMAc	NaOtBu	98	90:10
11	DMAc	KOtBu	98	95:5

Scheme 3. **Amidations of enol triflate 10a**[a]



[a] Reagents and conditions: (a) CH_3CONH_2, Pd_2dba_3, Xantphos, Cs_2CO_3, dioxane, 30 °C. (b) Amide **8**, Pd_2dba_3, Xantphos, Cs_2CO_3, dioxane, 50 °C.

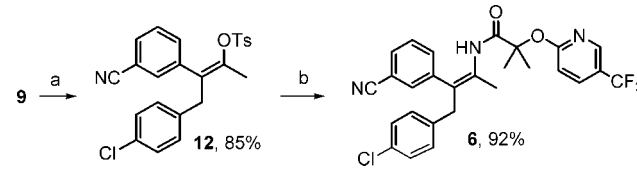
Encouragingly, enol triflate **10a** reacted readily with acetamide, under our previously optimized conditions to afford **11**. This tetrasubstituted enamide was found to be prone to partial *E*/*Z* double bond isomerization under the reaction conditions, leading to lower yields if time or temperature were not rigorously controlled. However, in line with previous observations[10a] that hindered enamides were more stable to isomerization, coupling with the heteroaromatic amide **8**[15] was found to afford the desired fully substituted enamide **6** with isolation as a crystalline solid in high yield and no loss of geometric integrity (Scheme 3).

The coupling of such a functionalized enol triflate and amide represented a significant extension of our previous coupling methodology and allowed for access of the desired enamide in good yield. However, use of the expensive triflating reagent $NPhTf_2$ coupled with its lack of bulk availability and the need for chromatographic purification to remove the minor enol triflate **10b** led us to once again push the boundaries of palladium-catalyzed C−N bond formations by considering the use of the less reactive enol tosylate.

Hence, generation of the sodium enolate of **9** followed by reaction with *p*-toluenesulfonic anhydride gave a 90:10 ratio of enol tosylates. Moreover, the crystalline nature of the product allowed for a crystallographic isolation of the desired tosylate **12**, *as a single isomer*, in 85% yield without recourse to chromatography. We were pleased to find that minor adjustments to our previously published protocol[10b] quickly led to

(15) The primary amide **8** is produced from pyridine acid **5** via formation of the acid chloride ($SOCl_2$, MeCN) followed by quenching with ammonium hydroxide.

Scheme 4. **Synthesis and coupling of the enol tosylate**[a]



[a] Reagents and conditions: (a) NaOtBu, DMAc, −20 °C, then Ts_2O. (b) $Pd_2(dba)_3$, dppb, K_2CO_3, *t*-AmOH, amide **8**, 100 °C.

viable conditions for the coupling of tosylate **12** with amide **8** using a cheap and readily available bis-phosphine ligand, 1,4-bis(diphenylphosphino)butane. The reaction conditions were optimized to afford clean coupling with only a slight excess of amide **8** (1.05 equiv) at 100 °C, using 5 mol % Pd_2dba_3/dppb catalyst, and *tert*-amyl alcohol as solvent.[16] Even under the high reaction temperature there was no detectable isomerization of either the tosylate or product enamide. Treatment of the reaction mixture with Darco KB-B followed by isolation of the product by crystallization afforded enamide **6** in 92% isolated yield-.(Scheme 4).

The asymmetric hydrogenation of tetrasubstituted enamide **6** was anticipated to be a challenging transformation, not only because of steric demands of the substrate and likely lower reactivity due to the presence of the pyridine substituent[17] but also because of potential aryl nitrile inhibition of cationic Rh catalysts typically used in enamide hydrogenations. Burk had observed such inhibitory effects during a study on the reduction of an α,β-unsaturated nitrile,[18] and furthermore, ^{31}P NMR evidence suggests that the preferred mode of coordination of **6** with the rhodium catalyst is via the nitrile.[19] Indeed, in initial studies the nitrile group of **6** was found to reduce preferentially under a range of hydrogenation conditions leading to aldehyde **13**, primary amine **14**, and reductive amination byproduct (Scheme 5) all of which acted as catalyst poisons in the reaction. In addition both the starting enamide and product had a deactivating effect when added to other enamide hydrogenations. In contrast hydrogenation of the structurally related enamide **15**, bearing an amide in place of the nitrile, led to complete and clean reduction of the enamide functionality. Under the same conditions less than 5% conversion of **6** to desired product was obtained. This experiment conclusively identified the nitrile group as the major detractor to the hydrogenation as all other structural attributes of the molecule were retained.

The challenge was then clearly defined to identify conditions that would preferentially reduce the enamide at both reasonable substrate concentrations and viable catalyst loadings and avoid

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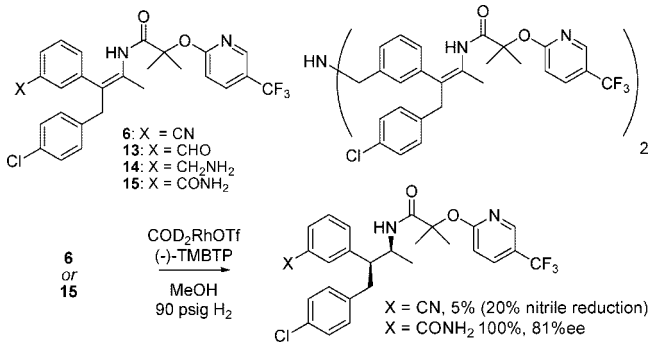
(19) Treatment of a 1:1 solution of **14** and $(COD)_2RhBF_4$ with either **6** or *m*-tolunitrile generates a new species with identical ^{31}P NMR spectra.

Scheme 5. **Problems associated with hydrogenations of enamides bearing an aryl nitrile group**



the poisoning properties of the nitrile group. A comprehensive screen of solvents, ligands, and additives was undertaken via high-throughput screening, and after significant experimentation we were pleased to discover a unique set of conditions whereby this could be realized. A catalyst derived from COD_2RhBF_4 and ligand **16** in 1,2-dichloroethane afforded nearly complete selectivity for enamide hydrogenation over nitrile reduction. Under optimized conditions enamide **6** was reduced directly to **1** in 85% ee and 90% yield using 2.5 mol % catalyst in 1,2-dichloroethane at 500 psi H_2 and 0.16 M (Scheme 6). Despite the modest enantioselectivity, results from our previous synthetic work had indicated that upgrade of enantiomeric purity was possible via preferential removal of the less soluble racemic material by crystallization.[4] In this manner, after a carbon treatment to achieve acceptable levels of residual rhodium, racemic **1** was crystallized, followed by subsequent isolation of **1** as a crystalline solid in 72% yield from **6**, and in 98.5% ee.

While the approach above constitutes the shortest synthesis of *taranabant* to date, environmental and regulatory concerns about the use of a chlorinated solvent in the final step, along with cost implications of the relatively high rhodium catalyst loading and hydrogenation pressure, remained concerns for large-scale implementation. On the basis of a promising preliminary result for hydrogenation of structurally related enamide **15** (*vide supra*), it was felt that temporary conversion of the nitrile group in **6** to an amide might allow for realization of a more facile hydrogenation at lower catalyst loadings and in more benign solvents than previously achieved. Given the anticipated ease of interconversion of the nitrile and amide groups, the feasibility of this approach was investigated (Scheme 7).

Straightforward hydrolysis of the nitrile group in **6** under basic peroxide conditions afforded **15** in high yield. Screening of hydrogenation conditions rapidly led to identification of conditions which allowed the desired hydrogenation to proceed at very low catalyst loadings and in nonchlorinated solvents. Optimal conditions involved use of 150 psi H_2 in trifluoroethanol as solvent and only 0.05 mol % of a catalyst derived from NBD_2RhBF_4 and ligand **17**. This protocol gave essentially quantitative conversion to amide **18** in 96% ee. Moreover, isolation of the product proceeded with an upgrade in enantiomeric purity leading to a 94% isolated yield of **18** as a crystalline solid in >99.5% ee. Final dehydration of the primary amide in **18** was achieved with cyanuric chloride to afford taranabant (**1**) in 79% over the three-step sequence. Despite the additional chemical steps, this alternate approach proceeds in higher overall yield than the hydrogenation of enamide **6** and offers advantages of lower catalyst loading, more environmentally acceptable conditions, and higher-purity final product.

Conclusion

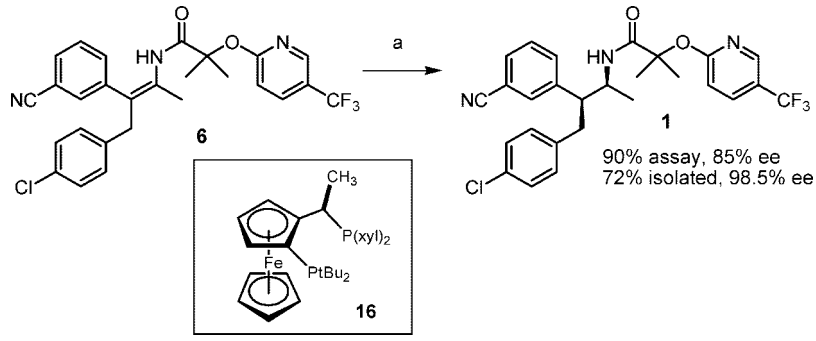
In summary, we have demonstrated two new syntheses of *taranabant* (**1**) which avoid the shortcomings of our previously employed route. Both utilize a selective enolization/tosylate formation followed by a Pd-catalyzed coupling of tosylate **12** with primary amide **8** to afford an enamide **6** containing all of the desired functionality for the final compound. The chirality was introduced by use of a Rh-catalyzed, asymmetric hydrogenation of tetrasubstituted enamide **6**, affording the desired compound directly, or by conversion to enamide **15** prior to hydrogenation. The syntheses proceeded in four or six steps from the previously described bromoketone **2** and 56% or 62% yield respectively. While both sequences are amenable to large-scale implementation, the cost and environmental benefits of the longer route render it more suitable for manufacturing-scale use. We believe that the technology described herein represents the state of the art in the stereoselective synthesis and asymmetric hydrogenation of highly functionalized, tetrasubstituted enamides, and efforts to demonstrate the generality of this novel methodology are ongoing.

Experimental Section

3-[1-(4-Chlorobenzyl)-2-oxopropyl]benzonitrile (9). *Catalyst Preparation.* A four-neck, 12 L round-bottom flask equipped with thermocouple, overhead stirrer, and N_2 inlet was charged with palladium acetate (12.8 g, 57 mmol), tri-*o*-tolylphosphine (69.9 g, 229 mmol), and dimethylformamide (2.8 L). The solution was degassed by subsurface nitrogen purge for 20 min at RT and then heated to 56 °C and stirred for 20 min. Diethylzinc (78.0 mL, 1.1 M in toluene, 85.8 mmol) was added via syringe, and the resulting yellow suspension was stirred at 56 °C for 45 min.

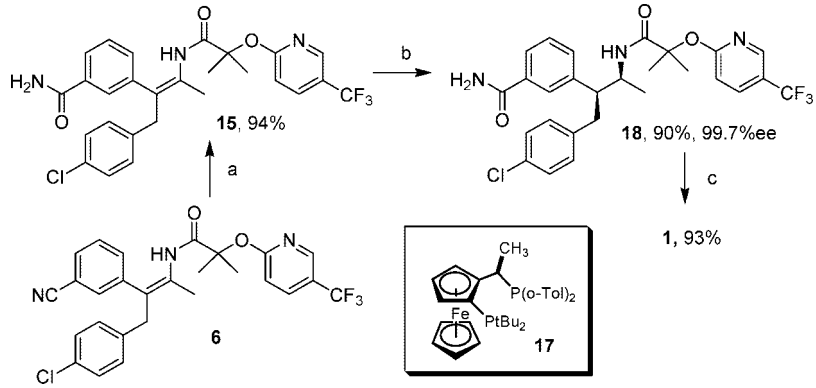
Cyanation. A four-neck, 12 L flask equipped with a thermocouple, overhead stirrer, and N_2 inlet was charged with **2** (966 g, 2.86 mol), zinc cyanide (201 g, 1.71 mol), and dimethylformamide (4.0 L). Nitrogen gas was bubbled through the suspension for 30 min at room temperature and for 1 h at 56 °C. The slurry of **2** and $Zn(CN)_2$ was transferred to the catalyst solution at 56 °C, and the reaction was aged at 56 °C for 4.5 h. The resulting suspension was cooled in an ice bath, and 30% ammonium hydroxide was added over 5 min, keeping the temperature below 30 °C. The reaction was warmed to room temperature, stirred for 60 min, and then filtered through a pad of Solka-Floc, eluting with toluene (5 L). The filtrate was added into a mixture of 20% aqueous ammonium hydroxide (6.9 L) and 5 L of toluene. The layers were separated, and the organic layer was washed with 7 L of half-saturated brine and then 7 L of water. The organic phase was concentrated under vacuum at 15−38 °C to a volume of 1.5 L, and then heptane (850 mL) was added. Once a seed bed formed, 6.5 L of heptane was added over 40 min, and the batch was cooled to 0 °C. The batch was filtered, and the filter cake was washed with heptane (2 L). The

Scheme 6. **Successful asymmetric hydrogenation of enamide 6[a]**



[a] Reagents and conditions: (a) H_2 (500 psi), 0.25 mol % CODRh(**16**)BF_4, 1,2-dichloroethane, 90 °C.

Scheme 7. **Efficient hydrogenation of enamide 15[a]**



[a] Reagents and conditions: (a) H_2O_2, K_2CO_3, DMSO, RT. (b) H_2 (150 psi), 0.05 mol % NBD_2Rh(**17**)BF_4, trifluoroethanol, 40 °C. (c) Cyanuric chloride, IPAc/DMF, RT.

resulting solid was dried under a stream of nitrogen to provide 755 g of **9** (98.9 LCAP 93% isolated yield). Mp 71.2−72.0 °C; IR (film) 3062, 3029, 2953, 2229, 1714, 1488, 1354, 1157, 1090, 1015 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.58 (dt, 1H, J = 7.0, 1.8 Hz), 7.49 (m, 1H), 7.42 (m, 2H), 7.19 m (2H), 6.95 (m, 2H), 3.93 (t, 1H, J = 7.5 Hz), 3.38 (dd, 1H, J = 13.9, 7.4 Hz), 2.87 (dd, 1H, J = 13.9, 7.7 Hz), 2.06 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 206.2, 139.5, 137.0, 132.7, 132.5, 131.9, 131.4, 130.3, 129.9, 128.7, 118.3, 113.3, 60.7, 38.0, 29.9; Anal. Calcd for $C_{17}H_{14}ClNO$: C, 71.96; H, 4.97; N, 4.94; Found: C, 71.86; H, 4.73; N, 4.86.

(1*Z*)-3-(4-Chlorophenyl)-2-(3-cyanophenyl)-1-methylprop-1-en-1-yl 4-methylbenzenesulfonate (12). A 4-neck, 12 L flask equipped with a mechanical stirrer, thermocouple, and nitrogen inlet was charged with DMAc (7.2 L) followed by **9** (744 g, 2.62 mol) and degassed by subsurface nitrogen purge. The mixture was cooled to −10 °C; NaOtBu (265 g, 2.76 mol) was added and then warmed to room temperature and stirred for 1 h. The mixture was cooled to −20 °C, and Ts_2O (893 g, 2.74 mol) was added as a solid, keeping the temperature below −5 °C. The mixture was aged at −10 °C for 1 h and then quenched with 1 M $NaHCO_3$ (1.9 L), and transferred into a mixture of 15 L IPAc and 13 L water. The layers were separated and the organic layer was washed twice with 7.5 L water. The organic layer was concentrated under vacuum (25 in Hg) at 55 °C to a volume of 2 L, and heated to 73 °C to produce a homogeneous solution. Heptane (6.6 L) was added while the mixture was allowed to slowly cool to room temperature. The resulting slurry was aged for 1 h, then filtered. The filter cake was washed with 3 L of heptane and dried under a stream of nitrogen to yield 974 g of **12** (>99.5 LCAP, 85% isolated yield). Mp 124.5−125.5 °C; IR (film) 3066, 2924, 2225, 1664, 1601, 1492, 1371, 1199, 1174, 1082 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36 (m, 3 H), 7.21 (m, 4H), 7.12 (m, 2H), 6.97 (m, 3H), 3.63 (s, 2H), 2.44 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 145.2, 144.1, 139.2, 135.7, 133.6, 133.3, 132.7, 131.9, 130.4, 129.6, 129.5, 128.9, 128.7, 127.7, 127.6, 118.5, 112.2, 38.3, 21.7, 18.4; Anal. Calcd for $C_{24}H_{20}ClNO_3S$: C, 65.82; H, 4.60; N, 3.20; Found: C, 65.72; H, 4.30; N, 3.10.

2-Methyl-2-{[5-(trifluoromethyl)pyridin-2-yl]oxy}propanamide (8). A 12 L, three-neck flask equipped with overhead stirrer, nitrogen inlet, and thermocouple was charged with acetonitrile (6.5 L) followed by **5** (772 g, 3.10 mol). Thionyl chloride (316 mL, 4.34 mol) was added over 30 min, keeping the temperature below 26 °C, and aged at room temperature for 2 h. A separate, 22 L, three-necked round-bottom flask equipped with overhead stirrer, nitrogen inlet, and thermocouple was charged with 30% $NH_4OH_{(aq)}$ (5 L) and cooled to −20 °C. The acid chloride solution was added to the solution of NH_4OH at such a rate that the internal reaction temperature was kept between −15 to −20 °C. The resulting slurry was warmed to room temperature, stirred for an additional 1 h, then transferred into a mixture of toluene (15 L) and water (15 L). The layers were separated, and the organic layer was washed with sat'd aq $NaHCO_3$ (5 L) and then water (5 L). The organic layer was concentrated under vacuum at 50 °C to a volume of

2 L, and heptane (5 L) was added. The batch was allowed to cool to RT, aged for 1 h, and the slurry was filtered. The filter cake was washed with heptane (1 L), and the resulting solid was dried under a stream of nitrogen to afford 626 g of **8** (99.6 LCAP, 81% isolated yield). mp 94.1−95.1 °C; IR (film) 3393, 3297, 3195, 1677, 1613, 1562, 1485, 1383, 1332, 1287, 1115 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 8.44 (s, 1H), 7.81 (d, 1H, $J = 8.7$ Hz), 6.86 (d, 1H, $J = 8.8$ Hz), 5.96 (br s, 1H), 5.53 (br s, 1H), 1.75 (s, 6 H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 176.8, 163.9, 144.6, 136.0, 127.9, 125.2, 122.5, 121.2, 120.9, 120.6, 120.2, 119.8, 112.3,81.6, 25.0; Anal. Calcd for $C_{10}H_{11}F_3N_2O_2$: C, 48.39; H, 4.47; N, 11.29; Found: C, 48.33; H, 4.17; N, 11.18.

(*N*-[(1*Z*)-3-(4-Chlorophenyl)-2-(3-cyanophenyl)-1-methylprop-1-en-1-yl]-2-methyl-2-{[5-(trifluoromethyl)pyridin-2-yl]oxy}propanamide (6). A three-neck, 5 L round-bottom flask fitted with a mechanical stirrer, reflux condenser, and a nitrogen inlet was charged with Pd_2dba_3 (27.5 g, 30 mmol), dppb (51.2 g, 120 mmol), **12** (526 g, 1.2 mol), **8** (313 g, 1.26 mol), and potassium carbonate (332 g, 2.4 mol). The flask was evacuated and backfilled with nitrogen three times, and then charged with *tert*-amyl alcohol (2.4 L, purged with nitrogen gas for 2 h). The flask was heated to 100 °C and stirred for 18 h. The resulting suspension was cooled to 25 °C, diluted with 7.2 L of MTBE, charged with Darco KB-B (250 g), and stirred for 2 h at RT. The batch was filtered over a pad of Solka-Floc, and the filter cake was washed with 7 L of MTBE. The batch was concentrated under vacuum at 40 °C to a volume of 1.5 L, and heptane (5 L) was added over 30 min. The batch was cooled to 20 °C and filtered. The filter cake was washed with 2 L of heptane/MTBE (10:1) and dried under a stream of nitrogen to provide 553 g of **6** (98.4 LCAP, 87% isolated yield). Mp 126.5−127.5 °C; IR (film) 3400, 3323, 3061, 2985, 2934, 2226, 1683, 1607, 1568, 1485, 1326, 1286, 1128, 1070 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.33 (m, 1H), 7.75 (dd, 1H, $J =$ 8.6, 2.5 Hz), 7.39 (dt, 1H, $J = 7.6$, 1.3 Hz), 7.25 (t, 1H, $J =$ 1.7 Hz), 7.18 (m, 3H), 7.12 (dt, 1H, $J = 7.8$, 1.5 Hz), 6.98 (d, 2H, 8.4 Hz), 6.62 (d, 1H, $J = 8.4$ Hz), 3.66 (s, 2H), 2.28 (s, 3H), 1.54 (s, 6H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 171.9, 163.5, 144.4, 141.3, 136.6, 136.2, 133.3, 132.3, 132.0, 131.5, 130.7, 129.7, 129.3, 128.7, 127.8, 126.4, 125.1, 122.4, 121.5, 121.1, 120.8, 120.5, 119.7, 118.3, 112.7, 112.4, 82.0, 38.4, 24.7, 16.7; Anal. Calcd for $C_{27}H_{23}ClF_3N_3O_2$: C, 63.10; H, 4.51; N, 8.18; Found: C, 63.20; H, 4.29; N, 8.02.

3-{(1*Z*)-1-(4-Chlorobenzyl)-2-[(2-methyl-2-{[5-(trifluoromethyl)pyridin-2-yl]oxy}propanoyl)amino]prop-1-en-1-yl}benzamide (15). A 5 L, 3-necked round-bottom flask equipped with overhead stirrer, thermocouple, and nitrogen inlet was charged with DMSO (2.7 L), **6** (524 g, 1.02 mol), and K_2CO_3 (112 g, 0.810 mol). Hydrogen peroxide (30% aqueous solution, 165 mL, 1.76 mol) was slowly added such that the temperature never rose above 25 °C. The reaction was aged for 1 h and then diluted with 1 L of isopropyl acetate and filtered over a bed of Solka-Floc. The bed was washed with 4.5 L of isopropyl acetate, and the resulting solution was washed with 5.5 L of water. The layers were separated, and the organic layer was washed twice with 3.1 L of water. The resulting organic layer was concentrated to a volume of 5 L, and then the solvent was switched to 5 L of toluene at 60 °C. Upon completion of the solvent switch, 500 mL of heptane was added, and the mixture was cooled to 20 °C. The batch was aged for 30 min, then filtered and washed with 1 L of toluene. The resulting solid was dried overnight under a stream of nitrogen to afford 522 g of **15** (99.4 LCAP, 94% isolated yield). mp 153.7−154.5 °C; IR (film) 3393, 3323, 3195, 2985, 2934, 2245, 1658, 1619, 1492, 1383, 1326, 1288, 1147, 1122, 1071, 1013 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 8.32 (m, 1H), 7.70 (dd, 1H, $J = 9.0$, 2.9 Hz), 7.58 (dt, 1H, $J = 7.9$, 1.5 Hz), 7.43 (t, 1H, $J = 1.7$ Hz), 7.15 (m, 4H), 7.02 (dt, 1H, $J = 7.6$, 1.4 Hz), 6.98 (m, 2H), 6.52 (d, 1H, $J = 8.5$ Hz), 6.10 (br s, 1H), 3.67 (s, 2H), 2.31 (s, 3H), 1.53 (s, 6H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 172.0, 168.8, 163.5, 144.36, 144.33, 144.29, 144.25, 140.3, 137.1, 136.09, 136.06, 136.03, 136.00, 133.7, 132.4, 132.1, 130.7, 129.9, 128.8, 128.6, 127.9, 127.5, 126.7, 126.1, 125.2, 122.5, 121.3, 121.0, 120.6, 120.3, 119.8, 112.4, 82.0, 38.5, 24.7, 16.5; Anal. Calcd for $C_{27}H_{25}ClF_3N_3O_3$: C, 60.96; H, 4.74; N, 7.90; Found: C, 60.94; H, 4.74; N, 7.83.

3-{(1*S*,2*S*)-1-(4-Chlorobenzyl)-2-[(2-methyl-2-{[5-(trifluoromethyl)pyridin-2-yl]oxy}propanoyl)amino]propyl}benzamide (18). *Catalyst Preparation.* In a N_2-filled glovebox, NBD_2RhBF_4 (105.5 mg, 0.28 mmol) and ligand **17** (170.5 mg, 0.30 mmol) were added to a 125 mL bottle and dissolved in 91 mL of degassed trifluoroethanol (TFE) with stirring at room temperature for 25 min. A partial quantity of the resulting solution, 86.5 mL, was added to a nitrogen-purged charging apparatus, and 46 mL of TFE was added to the rinse chamber of the charging apparatus. The complete charging apparatus was sealed and removed from the glovebox.

Hydrogenation. Substrate **15** (115 g, 216 mmol) was dissolved in 337 mL of TFE at room temperature and then was charged to a 1 L autoclave. An additional 100 mL of TFE was used to rinse the substrate solution bottle, and the combined solution was degassed three times with nitrogen. The catalyst was added via the charging apparatus connected to the autoclave and rinsed with the TFE in the rinse chamber. The reaction was heated to 40 °C, and pressure purged with hydrogen twice, followed by hydrogen introduction to 150 psi. The reaction was allowed to proceed for 17 h. The solution was cooled to room temperature, solvent switched to isopropyl acetate (∼1.3 L, containing 2.6% TFE), treated with Ecosorb C-941 (36 g), and aged for 16 h at 40 °C. The slurry was filtered over a bed of Solka-Floc and rinsed with IPAc (630 mL). The combined filtrate was concentrated to 850 mL, heated to 65 °C, and charged with *n*-heptane (490 mL). The solution was cooled to 45 °C, seeded with authentic **18** (1 g), and aged for 4 h at 45 °C. Additional *n*-heptane (2.7 L) was added over 15 h, the mixture was filtered at 45 °C, and the cake was washed with 600 mL of *n*-heptane at room temperature. The resulting solid was dried under vacuum to deliver **18** (106 g, 99.5% ee, 92% yield). Mp 154−155 °C; $[\alpha^{23}{}_D]$ +98.7 ($c = 0.0069$ g/mL, CH_2Cl_2); IR (film) 3417, 3317, 3202, 2978, 2934, 1658, 1607, 1524, 1492, 1396, 1326, 1288, 1141, 1122, 1077 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 8.33 (m, 1H), 7.80 (dd, 1H, $J = 8.7$, 2.6 Hz), 7.60 (m, 2H), 7.25 (dd, 1H, $J = 15.4$, 5.1 Hz), 7.10 (m, 1H), 7.02 (m, 2H), 6.85 (d, 1H, $J = 8.5$ Hz), 6.71 (m, 2H), 6.42 (br s, 1H), 6.22 (br s, 1H), 5.97 (d, 1H, $J = 9.1$ Hz), 4.38 (m, 1H), 3.07 (m, 1H), 2.82 (m, 2H), 1.75 (s, 3H), 1.71 (s,

3H), 0.86 (d, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 173.4, 169.4, 163.9, 144.52, 144.47, 141.42, 138.05, 136.23, 133.5, 132.3, 131.8, 130.2, 128.6, 128.3, 127.7, 125.9, 125.1, 122.4, 121.4, 121.1, 120.8, 120.5, 119.7, 112.7, 82.1, 72.9, 53.7, 49.4, 48.8, 38.4, 25.3, 25.1, 18.5; Exact mass calcd for $[C_{27}H_{27}ClF_3N_3O_3+H]^+$: 534.1771; Found: 534.1767. Separation of enantiomers by HPLC analysis (Chiralpak AD-H, 90% heptane, 10% EtOH, 0.8 mL/min, T_r = 11.5, 16.6 min).

***N*-[(1*S*,2*S*)-3-(4-Chlorophenyl)-2-(3-cyanophenyl)-1-methylpropyl]-2-methyl-2-{[5-(trifluoromethyl)pyridin-2-yl]oxy}propanamide (1).** In a 12 L, four-necked round-bottom flask equipped with mechanical stirrer, thermocouple, and a 2 L addition funnel, DMF (2.3 L) and isopropyl acetate (1.0 L) were combined, followed by addition of cyanuric chloride (124 g, 0.68 mol). A solution of **18** (469 g, 0.9 mol) in a mixture DMF (940 mL) and isopropyl acetate (465 mL) was added to the slurry over 30 min, keeping the temperature below 25 °C, and the reaction was aged for 1 h. The mixture was cooled to 5 °C and quenched with 5 wt % $NH_4Cl_{(aq)}$ (4.7 L) over the period of 1 h, keeping the temperature below 10 °C. The layers were separated, and the organic layer was washed twice with water (4.7 L). The organic layer was concentrated to ~1.5 L at ~75 Torr and 45 °C, and *n*-heptane (4.2 L) was added. The mixture was seeded with pure **1** (23 g) and aged for 12 h. The resulting slurry was charged with 8.4 L of *n*-heptane over 12 h at 45 °C and then cooled to 0 °C. The slurry was aged for 1 h, filtered, and washed with 1 L of *n*-heptane, and dried under vacuum to afford **1** (287 g, 99.5 LCAP, 99.2% ee, 90% isolated yield). Mp 106.0−106.3 °C; $[\alpha^{23}_D]$ +85.7 (c = 0.0074 g/mL, 99.2% ee, CH_2Cl_2); IR (film) 3412, 3342, 3023, 2978, 2934, 2226, 1664, 1613, 1524, 1485, 1319, 1287, 1141, 1122, 1071 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (m, 1H), 7.83 (dd, 1H, J = 8.9, 2.7 Hz), 7.45 (dt, 1H, J = 7.6, 1.5 Hz), 7.31 (t, 1H, J = 8.4 Hz), 7.24 (m, 2H), 7.07 (m, 2H), 6.88 (d, 1H, J = 8.8 Hz), 6.72 (m, 2H), 4.35 (m, 1H), 3.13 (dd, 1H, J = 12.8, 3.2 Hz), 2.83 (m, 2H), 1.76 (s, 3H), 1.72 (s, 3H), 0.88 (d, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 173.4, 163.9, 144.5, 142.4, 137.5, 136.3, 133.0, 132.2, 132.0, 130.7, 130.0, 129.3, 128.5, 127.8, 125.1, 122.4, 121.6, 121.2, 120.9, 120.6, 119.7, 118.7, 112.7, 112.6, 82.1, 53.6, 48.6, 38.2, 25.4, 25.1, 18.4; Anal. Calcd for $C_{27}H_{25}ClF_3N_3O_2$: C, 62.85; H, 4.88; N, 8.14; Found: C, 62.85; H, 4.60; N, 8.08. Separation of enantiomers by HPLC analysis (Chiralcel OD-H, 93% hexane, 7% EtOH, 0.7 mL/min, T_r = 10.5, 12.8 min).

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Supporting Information Available

Additional experimental procedures and copies of ^{1}H and ^{12}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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