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Development of an Enantioselective Hydrogenation Route to (*S*)-1-(2-(Methylsulfonyl)pyridin-4-yl)propan-1-amine

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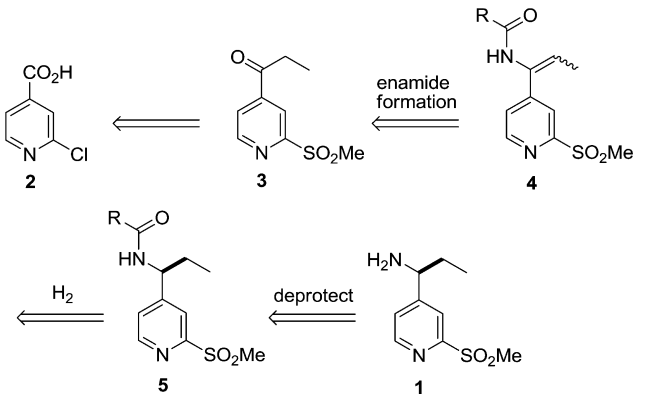
Supporting Information

ABSTRACT: A highly enantioselective enamide hydrogenation route to the title amine was developed. Highlights of the synthesis include an efficient two-step synthesis of a 2-sulfonyl 4-pyridyl ethyl ketone, a simple enamide synthesis by direct condensation of propionamide with a ketone, catalytic asymmetric enamide hydrogenation employing the in-house-developed ligand MeO-BIBOP, and a mild epimerization-free deprotection of a propionamide using Koenig's procedure.

INTRODUCTION

As part of a recent drug development program, we required an efficient synthesis of the intermediate chiral amine **1**. The retrosynthetic analysis of **1** is shown in Scheme 1. To set the stereocenter, asymmetric hydrogenation of an *N*-acylated enamide **4** was planned. Deacylation of the hydrogenation product **5** would provide the target amine **1**. The *N*-acylated enamide **4** was planned to derive from ketone **3**, which in turn would ideally be derived from an inexpensive starting material, such as 2-chloroisonicotinic acid **2**. It was also desired to install the sulfone moiety by an S_NAr reaction, thereby avoiding transition metal-catalyzed coupling processes.

Scheme 1. Retrosynthetic analysis of 1



DISCUSSION AND RESULTS

Installation of the Methyl Sulfone. The conversion of 2-chloroisonicotinic acid to the corresponding ethyl ketone **6** was accomplished by treatment of a cold THF solution of **2** with 2.2 equiv of EtMgCl (Scheme 2).[1] Warming of the solution from −20 to 20 °C effected complete consumption of the starting material. After quenching with aqueous HCl and extractive workup, the product was obtained in 72% yield. The synthesis of **6** from the analogous nitrile, 2-chloroisonicotinitrile, was also possible but proceeded in lower yield with formation of larger amounts of impurities.[2] The installation of the methyl sulfone group was initially accomplished by an S_NAr reaction of chloride **6** with aqueous NaSMe and catalytic Bu_4NBr in toluene to give an intermediate sulfide **7**, which was not isolated but directly oxidized by addition of AcOOH to give **3** in 69% yield after crystallization.[3] Other oxidants such as $NaBO_3 \cdot 4H_2O$/AcOH, MMPP, and H_2O_2/Na_2WO_4 were either less effective or required tedious workup and isolation procedures.

While this route effectively provided initial quantities of **3**, the use of NaSMe, even as the more convenient aqueous solution, was not desirable due to its potent stench, which proved difficult to eliminate even with the most rigorous containment procedures. A "stench-free" protocol was subsequently explored in which NaSMe was replaced with thiourea and iodomethane.[4] Thus, heating chloride **6** with thiourea in EtOH at 65 °C resulted in an S_NAr reaction to give the thiouronium salt **8** in 95% yield (Scheme 3). Conveniently, the thiouronium salt was isolated simply by direct filtration of the cooled reaction mixture. Treatment of a water solution of **8** with aqueous NaOH and MeI resulted in hydrolysis of the thiouronium salt to the 2-mercaptopyridine sodium salt and urea, with subsequent *S*-methylation to give the sulfide **7**. Again, **7** was not isolated but was directly oxidized by AcOOH to give sulfone **3** in 70% yield after crystallization. This process avoided the stench associated with the NaSMe process, as thiourea and the thiouronium salt **8** were odorless solids.

Although the thiouronium route to **3** solved the odor issue of the NaSMe route, it required two additional steps. Furthermore, the oxidation with AcOOH posed a safety concern for large-scale use.[5] The introduction of the sulfone group by an S_NAr reaction with $MeSO_2Na$ was therefore investigated.[6] The reaction was initially attempted by heating

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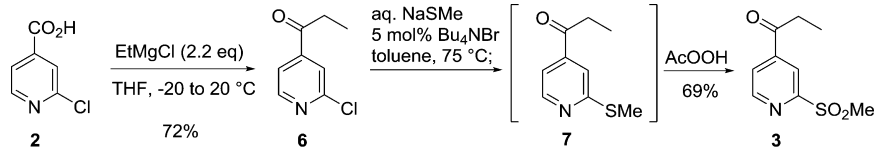
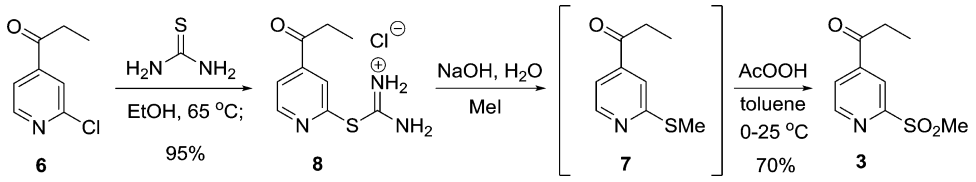
Scheme 2. Synthesis of ethyl ketone 6 and sulfone 3

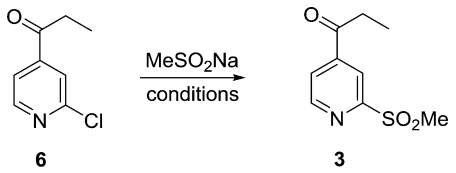


Scheme 3. Thiouronium route to methyl sulfone 3



chloride **6** and $MeSO_2Na$ in NMP. The conversion to sulfone **3** was slow under these conditions, however, reaching only 25% conversion after 24 h at 130 °C (Table 1, entry 1).

Table 1. S_NAr Reaction of 6 with $MeSO_2Na$



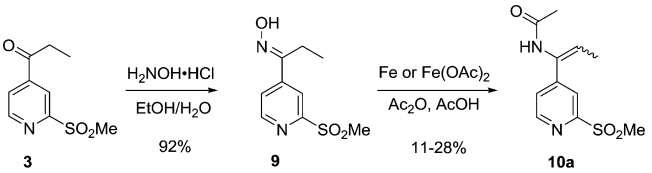
entry	conditions	conversion (%)[a]	yield (%)[b]
1	NMP, 130 °C, 24 h	25	–
2	CuI (1 equiv), NMP, 130 °C, 24 h	<5	–
3	Bu_4NCl (0.3 equiv), HCl (1 equiv), DMAc, 130 °C, 24 h	50	–
4	Bu_4NCl (0.3 equiv), DMAc, 130 °C, 48 h	95	52
5	H_2O/AcOH (5:1 v/v), 110 °C, 46 h	97	80
6	AcOH, 110 °C, 5 h	95	66

[a]Conversion of **6** to **3** as measured by HPLC analysis. [b]Isolated yield of **3** after crystallization from the reaction mixture.

Interestingly, the addition of stoichiometric CuI to the reaction resulted in almost complete suppression of the displacement (entry 2). Application of the conditions developed by Maloney and Kuethe (Bu_4NCl, DMAc, $MeSO_2Na$, HCl) gave an improved conversion of 50% after 24 h at 130 °C but with concomitant formation of several impurities (entry 3).[7] By omitting the HCl, however, the reaction proceeded more cleanly, and a 95% conversion was achieved after 48 h at 130 °C (entry 4). The product could be isolated in 52% yield by crystallization upon addition of water to the reaction mixture. The use of a water/AcOH (5:1 v/v) mixture as solvent led to a similar acceleration of the displacement compared to the Bu_4NCl conditions, and the product could be isolated in 80% yield after crystallization (entry 5). These conditions were optimal in terms of yield and also because they avoided the use of costly Bu_4NCl. Interestingly, switching to pure AcOH as solvent (entry 6) dramatically accelerated the reaction, but caused the formation of impurities which reduced the overall yield.

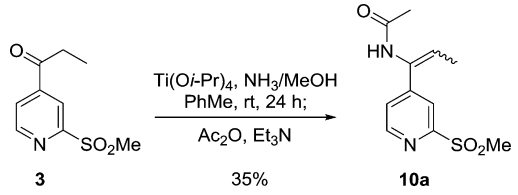
Enamide Preparation. With the ketone **3** in hand, the synthesis of the requisite enamide was investigated. The traditional approach to *N*-acetyl enamides from ketone starting materials involves the conversion of the ketone to a ketoxime, and subsequent reductive acylation, most commonly with Fe as the reductant.[8] While oxime formation from **3** proceeded smoothly, the reductive acetylation using either Fe powder or $Fe(OAc)_2$ proceeded in 11–28% yield with formation of significant impurities (Scheme 4).

Scheme 4. Formation of enamide 10a via oxime formation/reductive acylation



We recently developed a titanium-mediated enamide formation using ammonia in place of hydroxylamine.[9] Treatment of the ketone with $Ti(Oi\text{-}Pr)_4$ and methanolic NH_3 effects formation of an imine which is subsequently *N*-acetylated on addition of Et_3N and Ac_2O. This process unfortunately gave only a 35% yield of **10a**, consistent with our observation that highly electron-deficient ketones give decreased yields (Scheme 5).

Scheme 5. Titanium-mediated formation of enamide 10a with NH_3 and Ac_2O



The direct condensation of acetamide with ketones is perhaps the simplest and most direct route to *N*-acetyl enamides. Unfortunately, this reaction generally proceeds in very low yields for the majority of ketones.[10] Notable exceptions are 2-tetralone and 3-chromanone substrates, which have been shown to give the corresponding *N*-acetyl enamides in high yields.[11] Despite the discouraging precedent for efficient enamide formation via this avenue, the condensation of **3** with acetamide was explored. Refluxing a mixture of **3**, acetamide, and 0.1 equiv of TsOH in toluene with azeotropic removal of water, a 94% conversion to **10a** was achieved after 8 days. During this time, it was noted that

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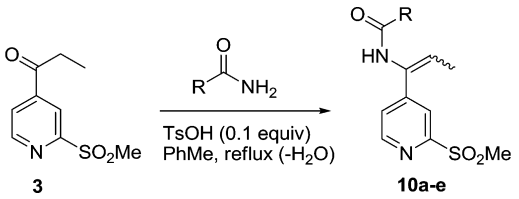
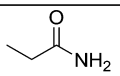
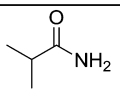
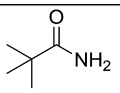
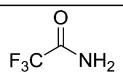
Table 2. Condensation of Amides with Ketone 3



entry	amide	product	time (h)	conversion (%)[a]	yield (%)[b]
1		**10a**	192	94	29[c]
2		**10b**	48	92	62
3		**10c**	24	86	57[c]
4		**10d**	48	90	57[c]
5		**10e**	24	0	-

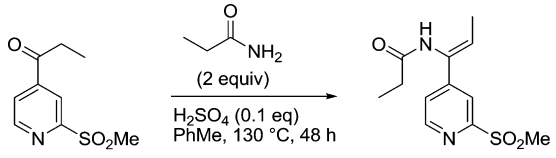
[a]Conversion of **3** to **10** as measured by HPLC analysis. [b]Isolated yield after crystallization. [c]Crystallization yield not optimized.

acetamide was collecting in the receiver. Consequently, additional acetamide was added to the reaction mixture periodically to compensate for the quantities lost by apparent sublimation or codistillation with toluene. While the reaction was very slow, it was nonetheless quite clean, and this encouraged further exploration of the reaction. It was reasoned that the use of higher-molecular weight amides might result in a faster reaction by avoiding the codistillation with toluene (Table 2). Thus, propionamide (entry 2), isobutyramide (entry 3), and pivalamide (entry 4) were tested in the enamide formation. All three of these amides gave much faster conversions to their respective enamides, reaching 86–92% conversion after 24–48 h. Propionamide gave a 62% isolated yield of **10b** after crystallization as a single *Z*-olefin isomer. Trifluoroacetamide (entry 5) gave no detectable product, presumably due to the low nucleophilicity of the amide.

Due to its superior performance in both the hydrogenation and deprotection reactions (*vide infra*), propionamide-derived **10b** was deemed the optimal substrate. A screen of alternative acid catalysts for the enamide formation (H_2SO_4, HCl, HBr, H_3PO_4, TfOH, Tf_2NH, Amberlyst 15 resin) showed H_2SO_4 to be most effective. The optimum process involved azeotropically distilling a mixture of **3**, propionamide (2 equiv), concentrated H_2SO_4 (0.1 equiv), and toluene for 24–48 h (85–94% conversion). On addition of *i*-PrOH, Et_3N (0.2 equiv) and water to the cooled reaction mixture, the product directly crystallized out in 70% yield (Scheme 6).

Enantioselective Hydrogenation of Enamide and Deprotection. The enamides were then subjected to catalytic asymmetric hydrogenation.[12] Selected screening results for the effects of different ligands, solvents, and catalyst loadings on enantioselectivity are shown in Table 3. The precatalyst rhodium bis(norbornadiene) tetrafluoroborate and a hydrogen

Scheme 6. Optimized conditions for synthesis of *N*-propionyl enamide 10b



pressure of 450 psi (31 bar) were employed for the screening studies. Using *N*-propionyl enamide **10b** as substrate, the patent-free ligands dipamp (**11**), skewphos (**12**), and norphos (**13**) (Figure 1) were examined in CH_2Cl_2 as solvent (entries 1–3), with dipamp providing the best selectivity (68% ee favoring the *R*-enantiomer). We have developed the BIBOP series of ligands and demonstrated their efficiency in the catalytic asymmetric hydrogenation of a variety of substrates, including *N*-acetyl enamides.[13] When MeO-BIBOP (**14**) was employed, a dramatic increase in ee to >99.9% in favor of the desired *S*-enantiomer was observed, keeping CH_2Cl_2 as solvent (entry 4). Application of the same conditions to the analogous *N*-acetyl (entry 5), *N*-isobutyryl (entry 6), and *N*-pivaloyl (entry 7) enamides resulted in high ee's for the acetyl and isobutyryl enamides, but a drop to 87% ee was observed for the more sterically demanding pivaloyl enamide.

Since the propionyl enamide **10b** was the optimal substrate for enamide formation, its hydrogenation was further optimized. On lowering the catalyst loading below 5 mol % with CH_2Cl_2 as solvent, the ee dropped significantly. We subsequently found that the catalyst loading could be reduced without sacrificing enantioselectivity by switching the solvent to MeOH. In this case, even at 0.05 mol % catalyst, a 97% ee was

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Table 3. Enamide hydrogenation screening results

10a: R = Me
10b: R = Et
10c: R = *i*-Pr
10d: R = *t*-Bu

15a: R = Me
15b: R = Et
15c: R = *i*-Pr
15d: R = *t*-Bu

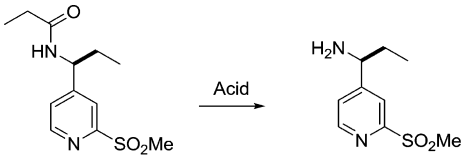
entry	R (substrate)	mol % $Rh(nbd)_2BF_4$	ligand[a]	solvent	ee (%) of product
1	Et (**10b**)	5	(*S*,*S*)-dipamp (**11**)	CH_2Cl_2	68[b]
2	Et (**10b**)	5	(*R*,*R*)-skewphos (**12**)	CH_2Cl_2	53[b]
3	Et (**10b**)	5	(*S*,*S*)-norphos (**13**)	CH_2Cl_2	37[b]
4	Et (**10b**)	5	MeOBIBOP (**14**)	CH_2Cl_2	>99.9
5	Me (**10a**)	5	MeOBIBOP (**14**)	CH_2Cl_2	97
6	*i*-Pr (10c)	5	MeOBIBOP (**14**)	CH_2Cl_2	96
7	*t*-Bu (10d)	5	MeOBIBOP (**14**)	CH_2Cl_2	87
8	Et (**10b**)	1	MeOBIBOP (**14**)	MeOH	98
9	Et (**10b**)	0.1	MeOBIBOP (**14**)	MeOH	98
10	Et (**10b**)	0.05	MeOBIBOP (**14**)	MeOH	97
11	Et (**10b**)	0.01	MeOBIBOP (**14**)	MeOH	94

[a]Ratio of ligand to catalyst = 1.1:1. [b]The *R*-enantiomer of **15b** was the major enantiomer.

achieved (entry 10). Further reduction of the loading to 0.01 mol % (entry 11) resulted in a 94% ee. Thus, for substrate **10b**, a loading of 0.05 to 0.1 mol % was deemed optimal.

The final step was the deprotection of the propionyl group to give the free amine. Traditionally this conversion is accomplished by acidic or basic hydrolysis at elevated temperatures.[14] Attempted hydrolysis of **15b** under basic conditions quickly led to hydrolytic displacement of the sulfone moiety under all conditions. Efforts were therefore focused on acidic conditions (Table 4). The use of 50% aqueous HCl at 90 °C led to complete decomposition of the starting material, due to hydrolysis of the sulfone group (entry 1). With 50% aqueous H_3PO_4, deprotection occurred but was accompanied by pronounced epimerization, with a 34% loss in enantiomeric excess (entry 2). Sulfuric acid also caused a significant amount of epimerization (entry 3). Aqueous HBr at 80 °C caused little loss in ee, but the reaction was quite slow,

Table 4. Deprotection of 15b under acidic conditions



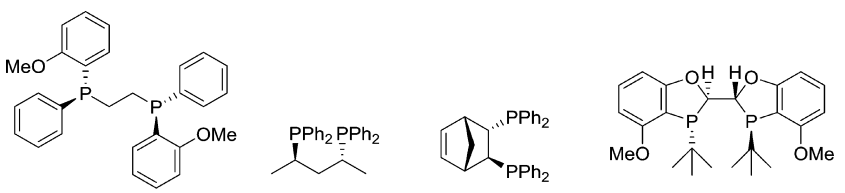
15b **1**

entry	conditions	time (h)	conversion (%)[a]	loss in ee (%)[b]
1	50% aq HCl, 90 °C	18	no product formation	–
2	50% aq H_3PO_4, 90 °C	24	>95	34
3	50% aq H_2SO_4, 90 °C	18	>95	22
4	48% aq HBr, 80 °C	67	92	2
5	MeOH, 50% aq HCl, 90 °C	29	97	8
6	*n*-PrOH, 50% aq HCl, 90 °C	16	95	20
7	*i*-PrOH, 50% aq HCl, 90 °C	22	93	13

[a]Conversion as measured by HPLC. [b][% ee of **15b**] − [% ee of **1**].

requiring 67 h to reach complete conversion (entry 4). The use of an alcohol cosolvent with HCl was explored. It was found that an equal volume of MeOH with 50% HCl gave a clean, albeit slow, conversion to **1** with about 8% loss in ee (entry 5). Using *n*-PrOH or *i*-PrOH, however, gave much more epimerization (entries 6–7).

The optimal conditions for deprotection still posed significant challenges. The product amine was highly water soluble, and recovering it from the aqueous solution was tedious. As a result, the isolated yield of **1** was low (25–30%). Furthermore, the loss of ee necessitated an upgrade in chiral purity. The HCl salt of **1** was a hygroscopic solid, however, and was not amenable to recrystallization. In 2009, Koenig and co-workers reported a mild deprotection of secondary acetamides via conversion to the corresponding imidoyl chlorides and subsequent *in situ* alcoholysis.[15] This procedure is run at mild temperatures (0 °C to rt) and was shown to avoid epimerization in sensitive substrates. Gratifyingly, application of Koenig's protocol to propionamide **15b** resulted in a fast (<20 min) and clean deprotection reaction. After addition of propylene glycol and warming to rt, the product crystallized out and was isolated by direct filtration in 86% yield (Scheme 7). Interestingly, the product **1a** was obtained as a 1:1 cocrystal with pyridinium hydrochloride. The stoichiometry of the cocrystal was consistent with elemental analysis data. In contrast to the hygroscopic HCl salt of **1** obtained by acid hydrolysis of **15b**, the pyridinium hydrochloride cocrystal **1a** was a nonhygroscopic white solid. Furthermore, the product was obtained with no loss in chiral purity: 98% ee starting propionamide provided 98% ee amine. Notably, application of



S,*S*-Dipamp (**11**) *R*,*R*-Skewphos (**12**) *S*,*S*-Norphos (**13**) *R*,*R*,*R*,*R*-MeOBIBOP (**14**)

Figure 1. Ligand structures.

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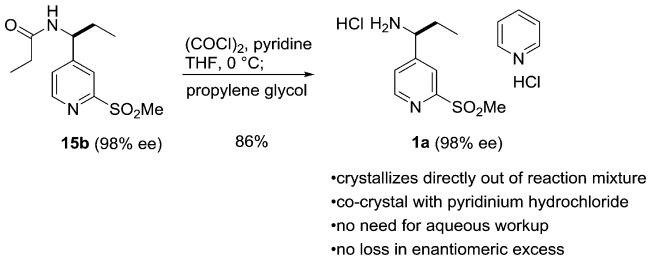
Scheme 7. Mild Deprotection of 15b using Koenig's Method



these deprotection conditions to isobutyramide **15c** and pivalamide **15d** gave **1** in 16% and 0% yield, respectively. The presence of at least two α-protons in the amide appears critical to the success of the imidoyl chloride formation. This is in concurrence with the observation of Koenig that benzamides were unchanged under the reaction conditions. The presence of the equivalent of pyridinium hydrochloride was tolerated in subsequent reactions.

CONCLUSION

The optimal route to **1a** is shown in Scheme 8. Highlights of the route are (1) the use of inexpensive 2-chloroisonicotinic acid as starting material; (2) a direct incorporation of the methyl sulfone via an S_NAr reaction of chloride **6** with sodium methanesulfinate; (3) a simple synthesis of enamide **10b** by direct condensation with propionamide; (4) a highly enantioselective hydrogenation of *N*-propionyl enamide **10b** using the novel in-house developed ligand **14**; (5) the efficient and epimerization-free deprotection of the propionyl group using Koenig's procedure. The use of propionamide or other primary amides instead of acetamide for enamide formation by direct condensation with ketones is a variation which may prove useful for other electron-poor ketone substrates.

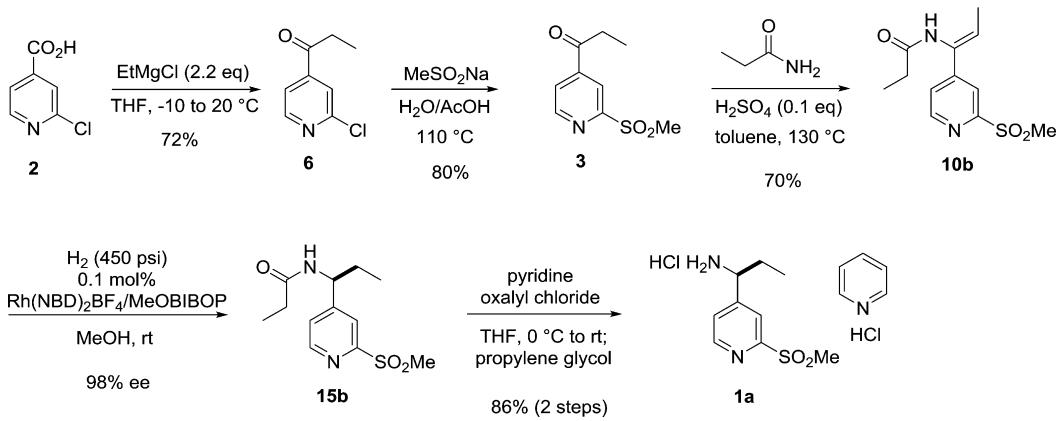
EXPERIMENTAL SECTION

General Information. HPLC analysis for reaction monitoring and purity determination was performed on an Agilent 1100 LC system with the following method: TSK-gel SuperODS column (ID 4.6 mm, length 5.0 cm), detection at 220 nm, run time 5 min, mobile phase A = water with 0.05% TFA, mobile phase B = MeCN with 0.05% TFA, ramp from 10% B to 90% B in 3.5 min, hold at 90% B until 5 min, column temperature 25 °C. Chiral purity determination of **15b** was done using the following method: Chiralpak AD-3 column, 4.6 mm × 150 mm, column temperature 25 °C, isocratic 90:10 heptane/1-propanol, 2 mL/min; (*R*)-enantiomer: 5.82 min, (*S*)-enantiomer: 8.83 min. Chiral purity determination of **1** was done using the following method: Chirosil SCA (−) column, 4.6 mm × 250 mm, 20 °C, 95:5 0.5% $HClO_4$/methanol, 1 mL/min; (*S*)-enantiomer: 4.68 min, (*R*)-enantiomer: 6.14 min.

1-(2-Chloropyridin-4-yl)propan-1-one (6). A slurry of 2-chloroisonicotinic acid **2** (115.0 g, 730.0 mmol) in THF (460 mL) was cooled to −20 °C. EtMgCl solution (800.0 mL, 2.0 M in THF, 1600 mmol, 2.2 equiv) was added at a rate to control the internal temperature at ≤5 °C. The reaction mixture was warmed to 20 °C and stirred for 4 h. The reaction mixture was cooled to 0 °C and treated over 10 min with EtOAc (75 mL) to quench residual EtMgCl (**CAUTION**: ethane gas evolution; explosion danger), followed by a solution of conc. HCl (230 mL) in water (460 mL). The resultant mixture was concentrated under vacuum at 45−50 °C to remove THF, and the residual aqueous phase was extracted with EtOAc (2 × 460 mL). The combined organic phases were concentrated under vacuum at 45−50 °C to give a solution of **6** in EtOAc (143.5 g, 62.3 wt % purity by assay, 72% yield) which was used directly in the next step. A pure sample of **6** was obtained by concentration to dryness of the EtOAc solution followed by crystallization from cold (0 °C) heptane to give **6** as an off-white solid. Mp 33−35 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (d, J = 5.1 Hz, 1 H), 7.69 (s, 1 H), 7.60 (dd, J = 1.3, 5.1 Hz, 1 H), 2.94 (q, J = 7.1 Hz, 2 H), 1.17 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.6, 152.8, 150.9, 145.6, 122.3, 119.9, 32.5, 7.7; HRMS: calcd for C_8H_9ClNO [M + H]: 170.0367. Found: 170.0374.

1-(2-(Methylsulfonyl)pyridin-4-yl)propan-1-one (3). A flask was charged with **6** (50.0 g, 294.8 mmol), Bu_4NBr (4.75 g, 14.7 mmol) and toluene (200 mL). To the resultant solution was added aqueous NaSMe solution (179.0 g, 15.0 wt % in water, 383.2 mmol, 1.3 equiv), and the reaction mixture was heated at 75 °C for 8 h. After cooling to rt, the lower aqueous phase was separated and discarded. The remaining toluene solution was cooled to 0 °C and treated slowly with AcOOH solution (136.4 mL, 32 wt % in AcOH, 648.6 mmol, 2.2 equiv). The reaction mixture was allowed to warm to rt and stirred at rt overnight. EtOAc (200 mL) and brine (200 mL) were added, and the lower aqueous phase was removed. The organic phase was washed with saturated aqueous $NaHCO_3$ (200 mL). The organic phase was concentrated by distillation under vacuum to a volume of about 200 mL. Water (50 mL) and heptane (250

Scheme 8. Optimized Route to 1a



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mL) were added, and the mixture was cooled to 0−5 °C. After 1 h, the resultant solid was filtered, washed with water and heptane, and dried under vacuum at 25 °C to give **3** (43.3 g, 69% yield) as white crystals. Mp 53−54 °C; ^{1}H NMR (400 MHz, DMSO *d*-6) δ 9.03 (dd, J = 0.7, 5.1 Hz, 1 H), 8.33−8.32 (m, 1 H), 8.19 (dd, J = 0.7, 4.9 Hz, 1 H), 3.35 (s, 3 H), 3.19 (q, J = 7.1 Hz, 2 H), 1.12 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (100 MHz, DMSO d_6) δ 199.2, 158.7, 151.7, 144.9, 125.4, 117.8, 39.8, 32.0, 7.4; HRMS: calcd for $C_9H_{12}NO_3S$ [M + H]: 214.0532. Found: 214.0543.

2-(4-Propionylpyridin-2-yl)isothiouronium Chloride (8). A flask was charged with **6** (100.0 g, 589.6 mmol), thiourea (47.1 g, 619.1 mmol), and absolute EtOH (300 mL). The mixture was heated at 65 °C for 18 h and cooled to rt. The solid was filtered, washed with EtOAc, and dried under vacuum at 25 °C to give **8** (137.5 g, 95% yield) as a tan solid. Mp 195−198 °C; ^{1}H NMR (400 MHz, DMSO d_6) δ 9.66 (br s, 4 H), 8.84 (dd, J = 0.7, 5.1 Hz, 1 H), 8.12−8.11 (m, 1 H), 7.90 (dd, J = 1.5, 5.1 Hz, 1 H), 3.11 (q, J = 7.1 Hz, 2 H), 1.08 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (100 MHz, DMSO d_6) δ 199.7, 166.7, 152.0, 150.4, 144.7, 125.6, 121.7, 32.0, 7.5; HRMS: calcd for $C_9H_{12}N_3OS$ [M − Cl]: 210.0696. Found: 210.0689.

1-(2-(Methylsulfonyl)pyridin-4-yl)propan-1-one (3) from 8. A flask was charged with **8** (100.0 g, 407.0 mmol) and water (250 mL). A solution of NaOH (34.18 g, 854.5 mmol, 2.1 equiv) in water (200 mL) was prepared. One half of this solution was charged to the reaction followed by MeI (27.9 mL, 447.7 mmol, 1.1 equiv). Then the remainder of the aqueous NaOH solution was charged dropwise. The reaction mixture was stirred at rt for 1 h, resulting in complete conversion of **8** to **7** as determined by HPLC analysis. Toluene (400 mL) was charged, and the lower aqueous phase was removed. The toluene solution was then cooled to about 0 °C. AcOOH solution (188.3 mL, 32 wt % in AcOH, 895.4 mmol, 2.2 equiv) was added slowly. The reaction mixture was allowed to warm to rt and stirred at rt for 3 h. A solution of Na_2SO_3 (50 g) in water (200 mL) was charged. After 30 min, a solution of NaOH (50 g) in water (50 mL) was added. The mixture was extracted with EtOAc (2 × 400 mL). The combined organic phases were concentrated by distillation under vacuum to a volume of about 400 mL. Water (50 mL) and heptane (400 mL) were added, and the mixture was cooled to 0−5 °C. After 1 h, the resultant solid was filtered, washed with water and heptane, and dried under vacuum at 25 °C to give **3** (60.8 g, 70% yield) as white crystals. Spectral data for **3** obtained by this route were consistent with those listed above.

1-(2-(Methylsulfonyl)pyridin-4-yl)propan-1-one (3) from 6. A flask was charged with **6** (10.0 g, 59.0 mmol), $MeSO_2Na$ (14.2 g, 85 wt %, 117.9 mmol, 2.0 equiv), AcOH (5.0 mL) and water (25 mL). The reaction mixture was heated at 110 °C for 46 h. After cooling to rt, water (40 mL) and heptane (5 mL) were added, and the mixture was cooled to 0 °C and held at this temperature for 1 h. The resultant solid was filtered, washed with water and heptane, and dried under vacuum at 25 °C to give **3** (10.1 g, 80% yield) as white crystals. Spectral data for **3** obtained by this route were consistent with those listed above.

(*E*)-1-(2-(Methylsulfonyl)pyridin-4-yl)propan-1-one oxime (9). A flask was charged with **3** (9.00 g, 42.2 mmol), NH_2OH·HCl (3.52 g, 50.6 mmol, 1.2 equiv) and EtOH (50 mL). To the resultant slurry was added 2 N aqueous NaOH solution (23.2 mL, 46.4 mmol, 1.1 equiv). The reaction mixture was stirred at rt for 20 h. The resultant slurry was filtered, and the solid was washed with water and dried under vacuum at 55 °C to give **9** (8.86 g, 92% yield) as a white solid. Mp 179−180 °C; ^{1}H NMR (400 MHz, DMSO d_6) δ 12.06 (br s, 1 H), 8.80 (d, J = 5.1 Hz, 1 H), 8.23−8.22 (m, 1 H), 7.91 (dd, J = 1.5, 5.1 Hz, 1 H), 3.30 (s, 3 H), 2.76 (q, J = 7.6 Hz, 2 H), 1.04 (t, J = 7.6 Hz, 3 H); ^{13}C NMR (100 MHz, DMSO d_6) δ 158.0, 155.5, 151.0, 145.5, 123.8, 116.3, 39.7, 17.6, 10.4; HRMS: calcd for $C_9H_{13}N_2O_3S$ [M + H]: 229.2735. Found: 229.2730.

(*Z*)-*N*-(1-(2-(Methylsulfonyl)pyridin-4-yl)prop-1-en-1-yl)acetamide (10a). A mixture of ketone **3** (10.0 g, 46.9 mmol), acetamide (5.50 g, 93.1 mmol), TsOH·H_2O (0.88 g, 4.64 mmol) and toluene (50 mL) was heated at 130 °C with azeotropic removal of water for 8 days (192 h). The reaction mixture was cooled to rt, diluted with CH_2Cl_2 (100 mL), and washed with a solution of saturated aqueous $NaHCO_3$ (50 mL). The organic phase was concentrated to dryness, and the resultant solid was recrystallized from EtOAc/hexanes to give **10a** (3.41 g, 29% yield, ∼95:5 mixture of *Z*: *E* isomers by ^{1}H NMR) as a white solid. Mp 141−144 °C; ^{1}H NMR (500 MHz, DMSO *d*-6) δ 9.44 (s, 1 H), 8.67 (d, J = 5.1 Hz, 1 H), 7.87 (s, 1 H), 7.68 (d, J = 5.1 Hz, 1 H), 6.38 (q, J = 6.9 Hz, 1 H), 3.28 (s, 3 H), 2.05 (s, 3 H), 1.77 (d, J = 6.9 Hz, 3 H); ^{13}C NMR (125 MHz, DMSO d_6) δ 168.5, 158.0, 150.2, 148.4, 132.4, 126.2, 123.2, 115.9, 39.7, 22.5, 13.8; HRMS: calcd for $C_{11}H_{15}N_2O_3S$ [M + H]: 255.0798. Found: 255.0807.

(*Z*)-*N*-(1-(2-(Methylsulfonyl)pyridin-4-yl)prop-1-en-1-yl)isobutyramide (10c). A mixture of ketone **3** (5.00 g, 23.4 mmol), isobutyramide (3.06 g, 35.2 mmol), TsOH·H_2O (445 mg, 2.34 mmol) and toluene (30 mL) was heated at 130 °C with azeotropic removal of water for 24 h. The reaction mixture was cooled to rt, and water (20 mL) was added dropwise. After stirring for 3 h at rt, the solid was filtered, washed with water and heptane, and dried under vacuum at 45 °C to give **10c** (3.77 g, 57% yield, ∼98:2 mixture of *Z*: *E* isomers by ^{1}H NMR) as a tan solid. Mp 169−170 °C; ^{1}H NMR (400 MHz, DMSO d_6) δ 9.36 (s, 1 H), 8.70 (d, J = 5.1 Hz, 1 H), 7.88 (d, J = 1.3 Hz, 1 H), 7.69 (dd, J = 1.7, 5.1 Hz, 1 H), 6.44 (q, J = 7.0 Hz, 1 H), 3.29 (s, 3 H), 2.69 (sept, J = 6.8 Hz, 1 H), 1.79 (d, J = 7.0 Hz, 3 H), 1.14 (d, J = 6.8 Hz, 6 H); ^{13}C NMR (100 MHz, DMSO d_6) δ 175.4, 158.1, 150.2, 148.4, 132.2, 126.4, 122.9, 115.9, 39.7, 33.9, 19.5, 13.7; HRMS: calcd for $C_{13}H_{19}N_2O_3S$ [M + H]: 283.1111. Found: 283.1127.

(*Z*)-*N*-(1-(2-(Methylsulfonyl)pyridin-4-yl)prop-1-en-1-yl)pivalamide (10d). A mixture of ketone **3** (5.00 g, 23.4 mmol), pivalamide (4.70 g, 46.5 mmol), TsOH·H_2O (445 mg, 2.34 mmol) and toluene (30 mL) was heated at 130 °C with azeotropic removal of water for 48 h. The reaction mixture was cooled to rt, and EtOAc (10 mL) was added followed by dropwise addition of water (20 mL). After stirring for 1 h at rt, the solid was filtered, washed with water and heptane, and dried under vacuum at 45 °C to give **10d** (3.95 g, 57% yield, >99:1 mixture of *Z*: *E* isomers by ^{1}H NMR) as a tan solid. Mp 174−176 °C; ^{1}H NMR (400 MHz, DMSO d_6) δ 9.01 (s, 1 H), 8.68 (d, J = 5.2 Hz, 1 H), 7.86 (d, J = 1.5 Hz, 1 H), 7.67 (dd, J = 1.7, 5.2 Hz, 1 H), 6.52 (q, J = 6.9 Hz, 1 H), 3.28 (s, 3 H), 1.75 (d, J = 6.9 Hz, 3 H), 1.24 (s, 9 H); ^{13}C NMR (100 MHz, DMSO d_6) δ 176.8, 158.1, 150.3, 148.7, 132.4, 127.3, 122.7, 115.7, 39.7, 38.6, 27.2, 13.7; HRMS: calcd for $C_{14}H_{21}N_2O_3S$ [M + H]: 297.1267. Found: 297.1286.

Optimized Process for Propionyl Enamide Formation. (*Z*)-*N*-(1-(2-(Methylsulfonyl)pyridin-4-yl)prop-1-en-1-yl)-propionamide (10b). A mixture of ketone **3** (100.0 g, 469.0 mmol), propionamide (63.1 g, 863.0 mmol), and toluene (500

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mL) was treated with concentrated H_2SO_4 (2.56 mL, 46.4 mmol) at rt. The reaction mixture was then heated at 130 °C with azeotropic removal of water for 48 h. The reaction mixture was cooled to 60 °C, and isopropanol (60 mL) and water (60 mL) were added successively. The reaction mixture was cooled to rt, stirred at rt for 1h, and the solid was filtered. The solid was washed with isopropanol followed by toluene, and dried under vacuum at 45 °C to give **10b** (88.1 g, 70% yield, >99:1 mixture of *Z*: *E* isomers by ^{1}H NMR) as a white solid. Mp 123.5−124.5 °C; ^{1}H NMR (400 MHz, DMSO d_6) δ 9.39 (s, 1 H), 8.69 (dd, J = 0.5, 5.1 Hz, 1 H), 7.89 (d, J = 1.2 Hz, 1 H), 7.69 (dd, J = 1.8, 5.1 Hz, 1 H), 6.44−6.39 (m, 1 H), 3.30 (s, 3 H), 2.37 (q, J = 7.6 Hz, 2 H), 1.79 (d, J = 7.0 Hz, 3 H), 1.11 (t, J = 7.6 Hz, 3 H); ^{13}C NMR (100 MHz, DMSO d_6) δ 172.3, 158.0, 150.2, 148.5, 132.3, 126.2, 123.1, 115.9, 39.7, 28.4, 13.8, 9.9; HRMS: calcd for $C_{12}H_{17}N_2O_3S$ [M + H]: 269.0954. Found: 269.0963.

(*S*)-*N*-(1-(2-(Methylsulfonyl)pyridin-4-yl)propyl)-propionamide (15b). A 100 mL hydrogenation vessel was charged with **10b** (10.0 g, 37.3 mmol) and MeOH (20 mL). In a glovebox, a vial was charged with rhodium bis-(norbornadiene) tetrafluoroborate (13.9 mg, 0.0373 mmol, 0.1 mol %) and ligand **14** (18.3 mg, 0.041 mmol, 0.11 mol %). MeOH (5 mL) was added to the vial, and the contents were stirred for 30 min. The resultant solution was charged to the hydrogenation vessel, and the vessel was then evacuated and filled with hydrogen. The reaction mixture was hydrogenated under 450 psi of hydrogen at 22 °C for 14 h. By HPLC analysis, the starting material was fully consumed to product **15b**. The product was formed in 98% ee by chiral HPLC analysis (Chiralpak AD-3 column, 4.6 mm × 150 mm, 25 °C, 90:10 heptane/1-propanol, 2 mL/min; (*R*)-enantiomer: 5.82 min, (*S*)-enantiomer: 8.83 min). The solution was filtered through a thin pad of Celite, and the pad was rinsed with additional MeOH. The combined MeOH filtrates were concentrated under vacuum to a thick oil (10.6 g, 95.0 wt %, quantitative yield), which was generally used directly in the next step. A pure sample of **15b** was obtained by crystallization of the crude oil from EtOAc/heptane. Mp 72−74 °C; ^{1}H NMR (400 MHz, DMSO d_6) δ 8.72 (d, J = 4.9 Hz, 1 H), 8.42 (d, J = 7.9 Hz, 1 H), 8.00 (s, 1 H), 7.66 (dd, J = 1.2, 4.9 Hz, 1 H), 4.83 (q, J = 7.6 Hz, 1 H), 3.30 (s, 3 H), 2.26−2.12 (m, 2 H), 1.78−1.62 (m, 2 H), 1.01 (t, J = 7.6 Hz, 3 H), 0.88 (t, J = 7.3 Hz, 3 H); ^{13}C NMR (100 MHz, DMSO d_6) δ 173.0, 158.0, 156.4, 150.1, 125.6, 117.9, 53.3, 39.6, 28.5, 28.4, 10.7, 9.9; HRMS: calcd for $C_{12}H_{19}N_2O_3S$ [M + H]: 271.1111. Found: 271.1120.

(*S*)-1-(2-(Methylsulfonyl)pyridin-4-yl)propan-1-amine Hydrochloride Pyridinium Hydrochloride Cocrystal (1a). A flask was charged with **15b** (10.0 g, 37.0 mmol), THF (60 mL), and pyridine (3.60 mL, 44.5 mmol, 1.2 equiv). The solution was cooled to 0 °C. Oxalyl chloride (3.60 mL, 40.4 mmol, 1.09 equiv) was added dropwise at a rate to control the batch temperature at not more than 5 °C. The reaction mixture (now a yellow slurry) was stirred at 0 °C for an additional 20 min. Propylene glycol (5.50 mL, 74.9 mmol, 2.0 equiv) was added at 0 °C, and the reaction mixture was allowed to warm to rt. Additional THF (30 mL) was added to dilute the thick white slurry. The slurry was stirred for 1 h and then filtered. The solid was washed with EtOAc followed by heptane and then dried under vacuum at rt to give **1a** (11.90 g, 98.3 wt % purity, 98.2% ee, 86% yield) as a white solid. The product was 98.2% ee by chiral HPLC analysis (Chirosil SCA (−) column, 4.6 mm × 250 mm, 20 °C, 95:5 0.5% $HClO_4$/methanol, 1 mL/min; (*S*)-enantiomer: 4.68 min, (*R*)-enantiomer: 6.14 min). Mp 184−185 °C; ^{1}H NMR (400 MHz, DMSO d_6) δ 9.19 (br s, 3 H), 8.98−8.96 (m, 2 H), 8.85 (d, J = 5.0 Hz, 1 H), 8.67−8.62 (m, 1 H), 8.30 (s, 1 H), 8.13−8.09 (m, 2 H), 8.04 (dd, J = 1.6, 5.0 Hz, 1 H), 4.45 (br s, 1 H), 3.32 (s, 3 H), 2.14−2.04 (m, 1 H), 1.94−1.83 (m, 1 H), 0.78 (t, J = 7.6 Hz, 3 H), 0.88 (t, J = 7.4 Hz, 3 H); ^{13}C NMR (100 MHz, DMSO d_6) δ 158.1, 150.5, 149.9, 146.2, 141.6, 127.3, 126.7, 119.5, 54.3, 39.8, 27.0, 9.7; HRMS: calcd for $C_9H_{15}N_2O_2S$ [M − pyridinium HCl − HCl + H]: 215.0849. Found: 215.0859. Anal. Calcd for $C_{14}H_{21}Cl_2N_3O_2S$: C, 45.90; H, 5.78; Cl, 19.36; N, 11.47; S, 8.75. Found: C, 45.67; H, 5.58; Cl, 19.24; N, 11.36; S, 8.60.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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