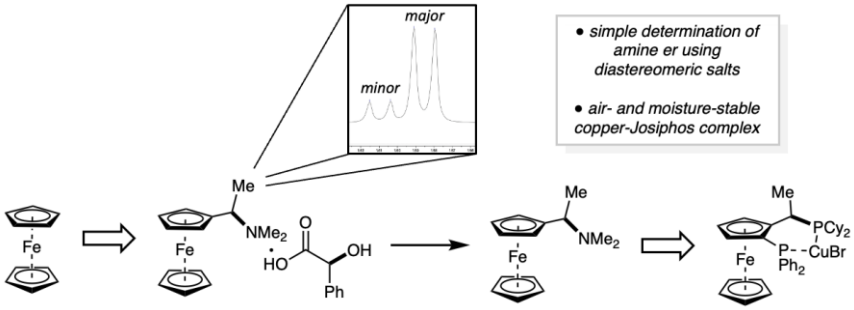
Simplified Synthesis of Air-stable Copper-complexed Josiphos Ligand via Ugi's Amine: Complete Preparation and Analysis from Ferrocene

Emma C. Murphy[a]
Jeffrey S. Johnson*[a]

[a]Department of Chemistry, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27514-3290, United States

jsj@unc.edu



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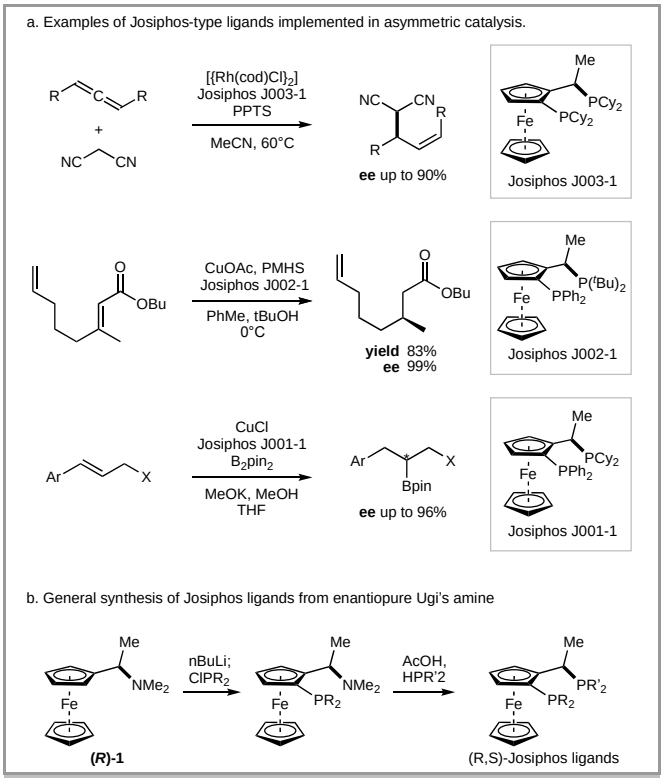
Abstract Ligands containing ferrocene backbones often feature both planar chirality and asymmetric centers, making them attractive options for asymmetric catalysis. Ugi's amine is a ubiquitous ferrocene-based chiral building block that can be functionalized to form a variety of tunable Josiphos ligands; however; few sources lay out the route from start to finish. Starting from ferrocene, we have compiled a synthetic route to an air- and moisture-stable copper(I)-Josiphos complex via enantiopure Ugi's amine, providing a one-stop shop for the synthesis of a wide range of Josiphos ligands.

Key words chiral phosphine ligands, Ugi's amine, Josiphos

Introduction

Josiphos-type ligands are commonly implemented in asymmetric catalysis due to their tunability and effectiveness. By altering the alkyl and aryl substituents on phosphorus, both steric hindrance and electronic effects of the ligand can be manipulated to optimize the performance of the catalyst.[1] One feature of these ligands is that they contain stereocenters close to the metal center, which helps impart chirality to the reactive substrate.[2] Josiphos-type ligands are widely used across different reaction types, including asymmetric allylation,[3] hydrosilylation,[4] and hydroboration(Scheme 1a).[5]

The chiral building block that is used as starting material for Josiphos-type ligands is [1-(dimethylamino)ethyl]ferrocene (**(*R*)-1**), also known as Ugi's amine. Starting from enantiopure Ugi's amine, a wide range of ligands can be achieved in two steps, through directed lithiation of the cyclopentadienide ring and a substitution of the amine group that proceeds via an S_N1-type mechanism (Scheme 1b).[6,7] In these substitutions, the carbocation is stabilized by backside metal participation or interactions between the iron d-orbitals and the empty p-orbital of the carbon, which leads to stereoretention.[8]



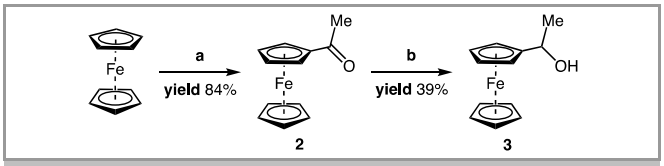
Scheme 1. Applications and general synthesis of Josiphos-type ligands.

Following the S_N1-type step, the purification of the crude mixture poses a challenge as Josiphos slowly oxidizes in air. One way to avoid this issue is by complexing the crude Josiphos to copper bromide, which results in an air- and moisture-tolerant complex.[9] The complexed Josiphos can then be purified via flash chromatography or recrystallization methods without concern of oxidation. The pure (Josiphos)CuBr can be decomplexed using ethylenediamine.[9]

The synthesis of Ugi's amine is well-known and widely used, but there are few sources that lay out the full synthetic route from ferrocene to Josiphos-type ligands. In this report, we aim to provide a one-stop shop for the synthesis of these commonly used ligands, and we discuss a cost-effective synthetic pathway to Josiphos starting from ferrocene, including a ^{1}H NMR spectroscopic method to determine the enantiomeric excess of Ugi's amine. The purification of Josiphos after complexation with copper(I) bromide is also investigated.

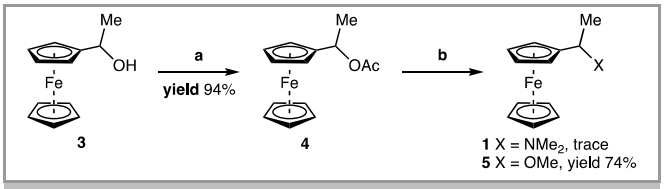
Results and Discussion

The route to Ugi's amine begins with the synthesis of acetylferrocene (**2**), which was achieved through the addition of acetyl chloride and aluminum trichloride to ferrocene (Scheme 2) in excellent yield (84%) on 30-gram scale.[3] Acetylferrocene was then reduced to 1-ferrocenylethanol (**3**, 39%) using Red-Al in benzene.[3]



Scheme 2. Synthesis of racemic 1-ferrocenylethanol. Reagents and conditions: (a) AcCl (1.2 equiv), $AlCl_3$ (1.2 equiv), DCM; (b) Red-Al (0.55 equiv), benzene.

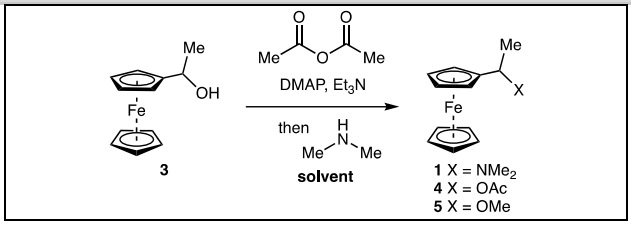
Two different acetylation/amination steps were then attempted to afford Ugi's amine. The first route used acetic acid in refluxing cyclohexane to reach 1-ferrocene ethyl acetate (**4**, Scheme 3) in excellent yield (94%).[3] The resulting acetate was then subjected to a substitution reaction with dimethylamine in methanol. Trace amounts of Ugi's amine (**1**) were isolated; however, the major product formed was 1-ferrocenyl ethyl methyl ether (**5**).



Scheme 3. First synthetic route attempted to reach racemic Ugi's amine. Reagents and conditions: (a) HOAc (3.5 equiv), cyclohexane, Dean-Stark trap; (b) Dimethylamine (40 wt% in H_2O, 10 equiv), MeOH.

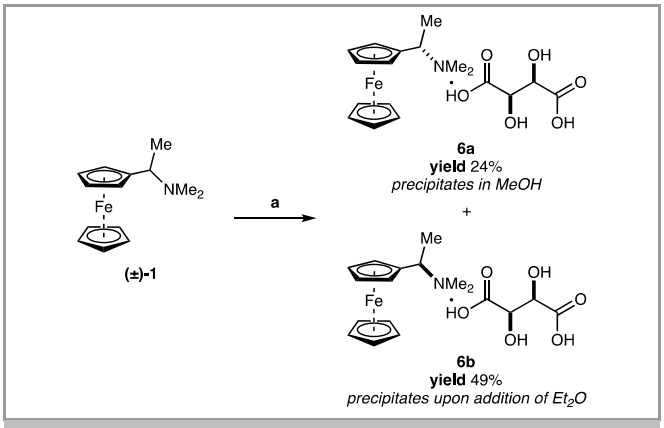
In attempt to avoid the formation of the unwanted ether, an alternate acetylation/amination step was performed in a one-pot fashion (Table 1).[10] 1-Ferrocenylethanol (**3**) was combined with triethylamine, acetic anhydride, and a catalytic amount of DMAP, followed by addition of MeOH and dimethylamine, affording only the undesired methyl ether (**5**, Table 1, Entry 1). When THF was used as the reaction solvent, the acetate was unreactive with the dimethylamine (Table 1, Entry 2). It was determined that MeOH must be present for the desired substitution reaction to occur, as using a mixture of THF and MeOH afforded Ugi's amine (**1**) in good yield (70%, Table 1, Entry 3).

Table 1 Acetylation/amination conditions to reach racemic Ugi's amine.



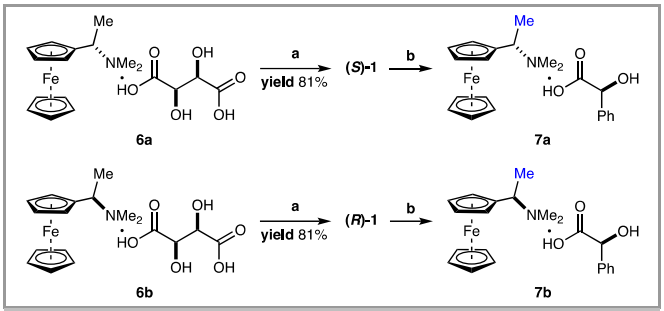
Entry	Solvent(s) Used	Yield **1** (%)	Yield **4** (%)	Yield **5** (%)
1	MeOH	0	0	79
2	THF	0	100	0
3	THF:MeOH (3:1)	70	13	0

The racemic Ugi's amine was then resolved using *L*-tartaric acid and slow cooling of the resulting salt in MeOH (Scheme 4).[11] The (*S*)-diastereomeric salt (**6a**) precipitated during the slow recrystallization and was resubjected to the reaction conditions. The addition of Et_2O to the mother liquor afforded the (*R*)-diastereomeric salt (**6b**), which was then recrystallized to afford diastereopure material.



Scheme 4. Resolution of Ugi's amine. Reagents and conditions: (a) *L*-tartaric acid (1.0 equiv), MeOH, 55 °C → rt.

The diastereomeric tartrate salts could then be free-based using aqueous NaOH (Scheme 5), affording (*S*)-**4** and (*R*)-**4** (81%). To determine the er of the amine and if another round of resolution was needed, it was reacted with *L*-mandelic acid to form diastereomeric mandelate ammonium salts which have distinct signals by ^{1}H NMR spectroscopy, unlike the tartrate salts.[12] The resulting dr was determined using the integration of the methyl protons (highlighted in blue); the (*S*)-diastereomeric salt (**7a**) has a doublet centered at 1.61, while the signal for the (*R*)-diastereomeric salt (**7b**) is centered at 1.59 (Figure 1), with slight chemical shift variation based on concentration of the sample. This method constitutes a simple and attractive alternative for HPLC analysis, as Ugi's amine requires expensive or uncommon columns, such as OA or Cyclabond I 2000 SN, as well as tri-solvent elution systems.[13,14] It is also more reliable than polarimetry, as enantiopurity and optical purity may not be the exact same, and varied optical rotation values appear throughout the literature.[11,15]



Scheme 5. Free-basing and ^{1}H NMR spectroscopy method to determine dr of mandelate ammonium salts. Reagents and conditions: (a) NaOH (1 equiv, 20 wt% in H_2O); (b) *L*-mandelic acid (1.0 equiv), $CDCl_3$.

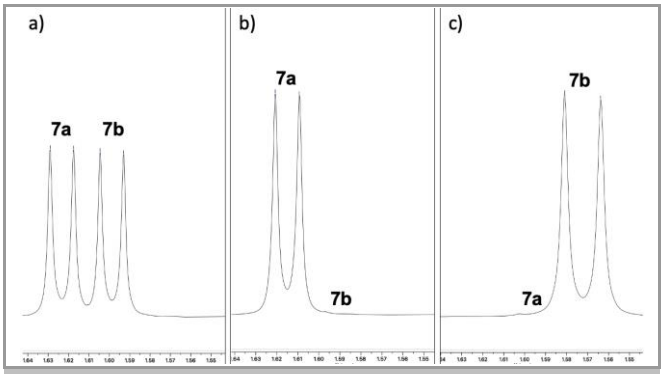


Figure 1. ^{1}H NMR (600 MHz) spectroscopy signals of methyl protons (highlighted in blue) of compounds **7a** and **7b**; (a) mixture of both diastereomeric salts; (b) **7a** (>20:1 dr); (c) **7b** (>20:1 dr).

A few comments around the NMR method are warranted. A limit of detection study was performed. Using a 1 M solution of **7a** and a 0.1 M solution of **7b**, various ratios of the diastereomeric salts were made (1:1, 50:1, 100:1). The 0.02 ppm difference in chemical shift translates to a small amount of peak overlap and results in slight differences in peak integration relative to actual charged amounts. The racemic mixture (Figure 2a) thus displayed a 1.00:0.94 ratio with respect to peak integrations. As the ratio of the diastereomers diverges from unity, the integration of the signal from the minor diastereomer becomes less reliable as it is on the shoulder of the major diastereomer doublet. We have found it most useful to integrate the outermost peaks of the symmetric doublets. The integrations of the 50:1 mixture (Figure 2b) resulted in a 96:4 dr, versus the charged 98:2 dr. Similarly, the integrations of the 100:1 mixture (Figure 2c) produced a 98:2 dr rather than 99:1 dr. Most importantly, a spectrum of diastereopure **7a** (Figure 2d) shows no detectable signal upfield of the doublet. We concluded that, although this analysis does not portray the exact dr, it is nonetheless able to effectively assay the presence of low amounts (<1%) of either diastereomer, and is a reliable and time-efficient way to confirm if another round of resolution is needed to reach enantiopure Ugi's amine.

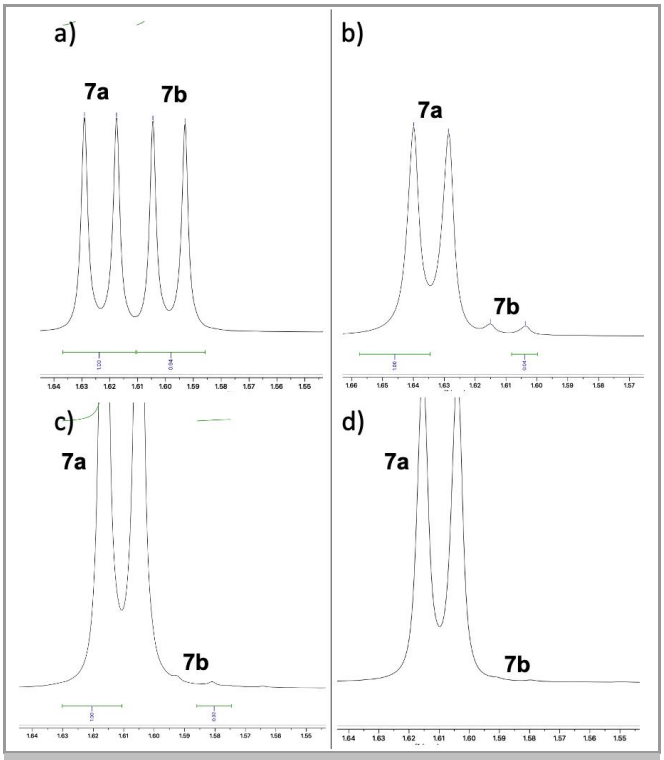
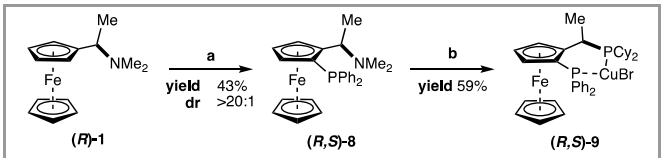


Figure 2. Limit of detection study using a) 1:1 **7a**:**7b**; b) 50:1 **7a**:**7b**; c) 100:1 **7a**:**7b**; d) **7a**.

With enantiopure Ugi's amine in hand, a chiral Josiphos ligand was then targeted (Scheme 5). The directed lithiation of **(*R*)-1** using ^{n}BuLi and chlorodiphenylphosphine afforded dimethyl{(*R*)-1-[(*S*)-2-(diphenylphosphanyl)ferrocenyl]ethyl} amine (**(*R,S*)-8** , (*R,S*)-PPFA, 43%) as a single diastereomer.[7] **(*R,S*)-8** and dicyclohexylphosphine were then heated at reflux in acetic acid to perform an acetylation and substitution step.[15] Due to oxidation of Josiphos during purification attempts via flash chromatography and recrystallization, the crude mixture was combined with copper bromide dimethyl sulfide complex in DCM to afford the bromocopper-(*R*)-l-[(*S*)-2-(diphenylphosphino)ferrocenyl]ethyldicyclo-hexylphosphine complex (**(*R,S*)-9**, 59% over two steps).[9]



Scheme 5. Synthesis of (*R,S*)-Josiphos-copper Complex. Reagents and conditions: (a) ^{n}BuLi (1.2 equiv), chlorodiphenylphosphine (2 equiv), Et_2O; (b) dicyclohexylphosphane (1.1 equiv), AcOH; then CuBr DMS (1.0 equiv), DCM (0.07 M).

Conclusion

Starting from ferrocene, Ugi's amine was reached in three steps, the racemic amine was then resolved using *L*-tartaric acid to form diastereomeric salts, which selectively crystallized. Through a ^{1}H NMR spectroscopy method, the resolved amines were both found to have >99:1 er. The enantiopure (*R*)-Ugi's amine was used as starting material to synthesize a chiral phosphine ligand, which was complexed to provide an air- and moisture-stable copper(I)-

Josiphos complex. The (Josiphos)CuBr complex was synthesized in eight steps from ferrocene, with an overall yield of 6.3%.

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General Methods: Unless otherwise stated, all reactions were carried out open to air. Thin layer chromatography (TLC) was performed on Sorbent Technologies 0.20 mm Silica Gel TLC plates. Visualization was accomplished using UV light and either $KMnO_4$ solution or cerium ammonium molybdate (CAM) stain. Flash chromatography was performed under positive air pressure using Siliaflash-P60 silica gel (40-63 μm) purchased from Silicycle.

Instrumentation and Data Acquisition: Proton (^1H) magnetic resonance spectra were obtained on Bruker NEO Avance 400 MHz or Bruker NEO Avance 600 MHz instruments, using solvent resonances for internal chemical shift calibration (^1H NMR: $CDCl_3$ at δ 7.26 ppm, D_2O at δ 4.79 ppm).

Data Reporting: The following format is used for the presentation of ^1H NMR spectroscopic data: magnet strength, analysis solvent, chemical shift (ppm), multiplicity (s = singlet, br s = broad singlet, app s = apparent singlet, d = doublet, bd = broad doublet, t = triplet, app t = apparent triplet, q = quartet, app q = apparent quartet, dd = doublet of doublets, td = triplet of doublets, app td = apparent triplet of doublets, ddd = doublet of doublet of doublets, ddt = doublet of doublet of triplets, app ddt = apparent doublet of doublet of triplets, dddd = doublet of doublet of doublet of doublets, m = multiplet), *J*-coupling constants (Hz), and integration.

Materials: Unless otherwise stated, technical grade solvents were used as received. Anhydrous tetrahydrofuran (THF), diethyl ether (Et_2O), methylene chloride (CH_2Cl_2), toluene (PhMe), and triethylamine (TEA, NEt_3) were obtained by passage of the respective solvents through a neutral alumina column under nitrogen. Solvent ratios are reported as volume ratios.

Ferrocene (Sigma), aluminum chloride (Sigma), acetyl chloride (Sigma), Red-Al (60 wt% in toluene, Sigma), dimethylamine (40 wt% in H_2O, Sigma), *L*-(+)-tartartic acid (Sigma), and *L*-(+)-mandelic acid (Oakwood) were obtained from commercial sources and used as received.

Procedures

Acetylferrocene (2). A flame-dried 2 L round-bottomed flask was taken into a glovebox and charged with aluminum chloride (25.8 g, 1.2 equiv., 193.5 mmol) and anhydrous DCM (350 mL, [$AlCl_3$] = 0.55 M) under N_2. The resulting mixture was cooled to 0 °C. In a separate flame-dried 500 mL round-bottomed flask equipped with a stir bar, ferrocene (30.00 g, 1.0 equiv., 161.3 mmol) was dissolved in anhydrous DCM (350 mL, [ferrocene] = 0.45 M) under N_2. The ferrocene solution was added via cannula transfer to the round-bottomed flask containing aluminum chloride. Acetyl chloride (5.06 g, 4.59 mL, 1.2 equiv., 64.5 mmol) was added dropwise and the solution was allowed to warm to room temperature and stirred for 3 h. The reaction was then cooled to 0 °C and ice water (400 mL) was slowly added, resulting in an exotherm. The biphasic mixture was allowed to warm to room temperature and transferred to a separation funnel. The aqueous layer was extracted with DCM (3 x 200 mL) and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and the volatiles removed under vacuum to afford acetylferrocene (**2**, 30.73 g, 134.7 mmol, 84% yield) as a brown solid. ^1H NMR data matched those reported in the literature.[3]

^1H NMR ($CDCl_3$, 600 MHz): δ 4.77 (t, *J* = 2.0 Hz, 2H, Cp-*H*), 4.50 (t, *J* = 2.0 Hz, 2H, Cp-*H*), 4.20 (s, 5H, Cp-*H*), 2.40 (s, 3H, C(O)-C*H*$_3$).

1-ferrocenylethanol (3). A flame-dried two-necked 500 mL round-bottomed flask, equipped with an addition funnel and stir bar was charged with acetylferrocene (**2**, 25.81 g, 1 equiv, 113.2 mmol) and anhydrous benzene (165 mL, [**2**] = 0.8 M) under N_2. Red-Al (60% in toluene, 20.97 g, 20.30 mL, 0.55 equiv, 62.24 mmol) was syringed into the addition funnel, then benzene (20 mL, [Red-Al] = 0.7 M) was added via syringe. The solution was slowly added to the round-bottomed flask via addition funnel, resulting in the evolution of H_2. The reaction was stirred for 1.5 h at room temperature, monitored by TLC (20% EtOAc/hexanes). Under N_2, EtOAc (4 mL) was added dropwise via syringe, followed by the slow addition of saturated aqueous NH_4Cl (120 mL) via syringe. The biphasic mixture was transferred to a separation funnel and the aqueous phase was extracted with Et_2O (3x100 mL). The combined organic layers were washed with water, dried over Na_2SO_4, filtered and the volatiles removed under vacuum. The resulting oil was purified via column chromatography (20% EtOAc/hexanes) to afford 1-ferrocenylethanol (**3**, 10.13 g, 44.0 mmol, 39% yield) as an orange solid. ^1H NMR data matched those reported in the literature.[3]

^1H NMR ($CDCl_3$, 600 MHz): δ 4.54 (q, *J* = 6.2 Hz, 1H, -C*H*-OH), 4.20 (m, 9H, Cp-*H*), 1.82 (br s, 1H, -O*H*), 1.44 (d, *J* = 6.4 Hz, 3H, -C*H*$_3$).

[1-(dimethylamino)ethyl]ferrocene ((±)-1, "Ugi's amine"). To a two-necked 2 L round-bottomed flask equipped with an addition funnel and stir bar, 1-ferrocenylethanol (**3**, 10.13 g, 1 equiv, 44.0 mmol) and NEt_3 (7.5 mL) were added. DMAP (0.323 g, 0.06 equiv, 2.64 mmol) was added in one portion, followed by the addition of acetic anhydride (44.95 g, 41.6 mL, 10 equiv, 440.3 mmol), and the mixture was stirred at room temperature and monitored by TLC (50% EtOAc/hexanes). Upon consumption of the starting material, THF:MeOH (3:1, 275 mL, [**3**] = 0.16 M) was added, and dimethylamine (40% in H_2O, 99.26 g, 41.6 mL, 880.5 mmol, 20 equiv) was added dropwise via an addition funnel to prevent exotherm. The reaction was stirred overnight at room temperature. Et_2O (100 mL) and water (100 mL) were each added in one portion, and the biphasic mixture was transferred to a separation funnel. The aqueous layer was extracted with Et_2O (3x100 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and the volatiles removed under vacuum. The crude product was purified via column chromatography (2% NEt_3 in 50% EtOAc/hexanes) to afford Ugi's amine (**(±)-1,** 11.22 g, 43.63 mmol, 99% yield) as a red oil. ^1H NMR data matched those reported in the literature.[3]

^1H NMR ($CDCl_3$, 600 MHz): δ 4.08-4.19 (m, 9H, Cp-*H*), 3.81 (q, *J* = 7.0 Hz, 1H, -C*H*-NMe_2), 2.17 (s, 6H, N(C*H*$_3$)$_2$), 1.53 (d, *J* = 6.5 Hz, 3H, -C*H*$_3$).

Resolution (S,S)- and (R,S)-Ugi's amine tartrate salts (6a, 6b). In a 100 mL round-bottomed flask equipped with a stir bar, racemic Ugi's amine (**(±)-1** 6.69 g, 1 equiv, 26.03 mmol) was dissolved in MeOH (13 mL, [(±)-**1**] = 2 M) and heated to 55 °C. *L*-tartaric acid (3.91 g, 1 equiv, 26.03 mmol) was dissolved in MeOH (13 mL, [*L*-tartaric acid] = 2 M) in a 20-mL scintillation vial and heated to 55 °C before being added dropwise via syringe to the amine solution. A seeding crystal was added, and the temperature was decreased by 3 °C/h, then stirred overnight at room temperature. The resulting orange precipitate was filtered and washed with cold EtOH, then free-based (see below) and resubjected to the resolution conditions to reach (*S*,*S*)-Ugi's amine tartrate salt (**6a**, 2.59 g, 6.34 mmol, 24% yield). The combined mother liquor of both resolutions was concentrated to ¼ of the original volume and Et_2O was added until white precipitate stopped forming. The solid was filtered, washed with Et_2O, and recrystallized twice in acetone:H_2O (10:1, 200 mL) to afford (*R*,*S*)-Ugi's amine tartrate salt (**6b**, 5.30 g, 13.01 mmol, 49% yield). ^1H NMR data for both diastereomers matched those reported in the literature.[11]

6a: ^1H NMR (D_2O, 600 MHz): δ 4.41 – 4.54 (m, 5H), 4.33 – 4.40 (m, 2H), 4.29 (s, 5H), 2.58 (d, *J* = 13.2 Hz, 6H), 1.70 (d, *J* = 6.9 Hz, 3H).

6b: ^1H NMR (D_2O, 600 MHz): δ 4.47 – 4.60 (m, 5H), 4.43 (d, *J* = 2.3 Hz, 2H), 4.31 (s, 5H), 2.63 (d, *J* = 11.4 Hz, 6H), 1.74 (d, *J* = 6.9 Hz, 3H).

General Procedure A. Free basing Ugi's amine tartrate salt. In a round-bottomed flask equipped with a stir bar, the tartrate salt (**6a**/**6b**, 1 equiv), NaOH (1 equiv), and H_2O **([6a/6b]** = 0.5 M) were combined and stirred at room temperature for 1 h, becoming heterogeneous. DCM was added and the biphasic mixture was transferred to a separation funnel. The aqueous solution was then extracted with DCM (3x 20mL). The combined organic layers were dried with K_2CO_3, filtered through glass wool, and the volatiles removed under vacuum.

Free basing of (S,S)-Ugi's amine tartrate salt ((S)-1). Prepared using General Procedure A, with (*S*,*S*)-Ugi's amine tartrate salt (**6a**, 4.76 g, 1.0 equiv, 11.70 mmol), NaOH (0.94 g, 2.0 equiv, 23.40 mmol), in H_2O (25 mL, [**6a**] = 0.5 M), affording (*S*)-Ugi's amine (**(*S*)-1**, 2.43 g, 9.44 mmol, 81%) as a red oil.

^{1}H NMR ($CDCl_3$, 600 MHz) δ 4.17 – 4.02 (m, 9H), 3.59 (q, *J* = 6.9 Hz, 1H), 2.08 (s, 4H), 1.45 (d, *J* = 6.9 Hz, 1H).

α_D^{23} (c = 0.01, $CHCl_3$) -8.8

Free basing of (R,S)-Ugi's amine tartrate salt ((R)-1). Prepared using General Procedure A, with (*R*,*S*)-Ugi's amine tartrate salt (**6b**, 5.30 g, 1.0 equiv, 13.01 mmol), NaOH (1.04 g, 2.0 equiv, 26.02 mmol), in H_2O (30 mL, [**6b**] = 0.5 M), affording (*R*)-Ugi's amine (**(*R*)-3**, 2.70 g, 10.5 mmol, 81%) as a red oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 3.97 – 4.19 (m, 9H), 3.59 (q, *J* = 6.9 Hz, 1H), 2.08 (s, 6H), 1.44 (d, *J* = 6.9 Hz, 3H).

α_D^{23} (c = 0.01, $CHCl_3$) 10.8

General Procedure B. Preparation of Ugi's amine mandelate salt. (*S*)- or (*R*)-Ugi's amine (**(*S*)/(*R*)-3**, 0.024 g, 1.0 equiv, 0.093 mmol) was dissolved in $CDCl_3$ (0.5 mL). *L*-mandelic acid (0.014 g, 1.0 equiv, 0.093 mmol) was then added and the solution was sonicated until all solid was dissolved.

***(S,S)-Ugi's amine mandelate salt (7a*).** Prepared using General Procedure B. The diastereomeric ratio was determined by ^{1}H NMR analysis by integration of peaks at 1.62 ppm (major) and 1.59 ppm (minor) and was determined to be >100:1. ^{1}H NMR data matched those reported in the literature.[12]

^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.47 – 7.53 (m, 2H), 7.30 (t, J = 7.5 Hz, 2H), 7.24 – 7.19 (m, 1H), 4.97 (s, 1H), 4.25 (s, 2H), 4.21 – 4.23 (m, 1H), 4.19 – 4.21 (m, 1H), 4.14 – 4.16 (m, 1H), 4.14 (s, 5H), 2.35 (s, 6H), 1.61 (d, J = 6.8 Hz, 3H).

^{13}C NMR ($CDCl_3$, 151 MHz): δ 142.7, 128.4, 127.3, 126.9, 80.0, 70.8, 69.6, 69.6, 69.5, 67.7, 60.8, 15.5.

α_D^{23} (c = 0.01, $CHCl_3$) 42.2

(R,S)-Ugi's amine mandelate salt (7b). Prepared using General Procedure B. The diastereomeric ratio was determined by ^{1}H NMR analysis by integration of peaks at 1.58 ppm (major) and 1.61 ppm (minor) and was determined to be >100:1. ^{1}H NMR data matched those reported in the literature.[12]

^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.45 – 7.61 (m, 2H), 7.30 (t, J = 7.5 Hz, 2H), 7.15 – 7.24 (m, 1H), 4.95 (s, 1H), 4.22 – 4.24 (m, 1H), 4.21 (t, J = 1.6 Hz, 2H), 4.13 – 4.18 (m, 2H), 4.13 (s, 5H), 2.32 (s, 6H), 1.57 (d, J = 6.8 Hz, 3H).

^{13}C NMR ($CDCl_3$, 151 MHz): δ 178.7, 142.7, 128.1, 127.0, 126.7, 70.5, 69.3, 69.2, 67.5, 60.5, 15.4.

α_D^{23} (c = 0.01, $CHCl_3$) 45.6

Dimethyl{(S)-1-[(R)-2-(diphenylphosphanyl)ferrocenyl]ethyl}amine ((R,S)-8, (R,S)-PPFA). In a flame-dried 25-mL round-bottomed flask equipped with a stir bar, (*R*)-Ugi's amine (**(*R*)-3),** 1.00 g, 1 equiv, 3.89 mmol) was dissolved in dry Et_2O (7.0 mL, [**(*R*)-3)**] = 0.55 M) under N_2. ^{n}BuLi (2.5 M in hexanes, 2.10 mL, 1.2 equiv, 4.67 mmol) was added dropwise via syringe and the solution was stirred at room temperature for 1.5 h. Chlorodiphenylphosphine (1.72 g, 1.42 mL, 2 equiv, 7.78 mmol) was added dropwise via syringe, and the reaction was heated at reflux at 50 °C for 2 h. After cooling to room temperature, sat. aq. $NaHCO_3$ (5 mL) was added dropwise under N_2. The biphasic mixture was transferred to a separation funnel and the aqueous layer was extracted with Et_2O (3x25 mL), dried over $MgSO_4$, filtered through glass wool and the volatiles removed under vacuum. The resulting orange solid was recrystallized in EtOH to yield (*R*,*S*)-PPFA (**(*R*,*S*)-8**, 0.731 g, 1.66 mmol, 43% yield) as an orange crystal. ^{1}H NMR data matched those reported in the literature.[7]

^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.57 – 7.60 (m, 2H), 7.33 – 7.41 (m, 3H), 7.17 – 7.20 (m, 5H), 4.37 (br s, 1H), 4.24 (br s, 1H), 4.13 – 4.15 (m, 1H), 3.94 (s, 5H), 3.85 (br s, 1H), 1.76 (s, 6H), 1.25 – 1.27 (m, 3H).

(S)-l-[(R)-2-(diphenylphosphino)ferrocenyl]ethyldicyclohexyl-phosphine ((R,S,)-9, CuBr-(R,S)-J001). In a flamed-dried 25-mL two-necked round-bottomed flask equipped with a stir bar and a reflux condenser, (*R*,*S*)-PPFA (**(*R*,*S*)-8**, 0.730 g, 1.0 equiv, 1.65 mmol) was dissolved in degassed, glacial acetic acid (3.6 mL, 0.5 M) under Ar. Dicyclohexylphosphine (10% w/w in hexanes, 3.61 g, 3.99 mL, 1.1 equiv, 1.82 mmol) was added dropwise via syringe. The reaction was heated at reflux at 80 °C for 4 h. The volatiles were removed under vacuum, and the resulting oil dissolved in DCM (25 mL, [**(*R*,*S*)-8**] = 0.07 M). CuBr dimethylsulfide complex (0.340 g, 1.0 equiv, 1.65 mmol) was added in one portion and the reaction was stirred at room temperature for 2 h. The DCM was removed under reduced pressure and the resulting solid was recrystallized in MeOH to afford CuBr-(*R*,*S*)-J001 (**(*R*,*S*,)-9**, 0.725 g, 0.982 mmol, 59% yield) as an orange solid. ^{1}H NMR data matched those reported in the literature.[16]

^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.02 (ddd, J = 10.8, 6.5, 2.8 Hz, 2H), 7.48 (q, J = 2.4 Hz, 3H), 7.28 (s, 1H), 4.52 (d, J = 1.7 Hz, 1H), 4.44 (t, J = 2.6 Hz, 1H), 4.23 – 4.43 (m, 1H), 3.79 (s, 5H), 3.52 – 3.37 (m, 1H), 0.87 – 1.81 (m, 25H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 135.2 (d, *J* = 17.6 Hz), 132.7 (d, *J* = 14.1 Hz), 130.5 (d, *J* = 1.8 Hz), 129.0, 128.5 (d, *J* = 10.4 Hz), 128.4 (d, *J* = 8.5 Hz), 77.4, 74.0, 73.2 (d, *J* = 31.2 Hz), 70.7 – 70.9 (m), 70.5, 70.4, 69.8 (d, *J* = 4.3 Hz), 32.7 (d, *J* = 9.4 Hz), 32.1 (d, *J* = 9.1 Hz), 30.0, 29.8, 29.2 (d, *J* = 7.2 Hz), 28.9 (d, *J* = 5.4 Hz), 27.7 (d, *J* = 13.6 Hz), 27.4 (d, *J* = 8.4 Hz), 27.1, 26.8 (d, *J* = 12.5 Hz), 25.9, 16.5.

^{31}P NMR ($CDCl_3$, 101 MHz): δ 8.02 (d, *J* = 195.0 Hz), -22.85 (d, *J* = 195.1 Hz).

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Supporting Information

YES

Primary Data

NO.

Conflict of Interest

The authors declare no conflict of interest.

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